National Institute for Health and Care Excellence

Final

Multiple sclerosis in adults: management

[C1] Appendices for non-pharmacological management of fatigue

NICE guideline NG220

Evidence reviews underpinning recommendations 1.5.2 to 1.5.11 and research recommendations in the NICE guideline

June 2022

Final

National Institute for Health and Care Excellence

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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1 Appendices

2 Appendix A – Review protocols

A3 1 Review protocol for non-pharmacological management of fatigue

ID	Field	Content
0.	PROSPERO registration number	CRD42021229703
1.	Review title	Non-pharmacological management of fatigue
2.	Review question	For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of non-pharmacological interventions for fatigue?
3.	Objective	To determine the effectiveness of non-pharmacological treatments for fatigue in patients with MS.
4.	Searches	Key paper: Exercise therapy for fatigue in multiple sclerosis Heine M, van de Port I, Rietberg MB, van Wegen EEH, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD009956. The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		• CINAHL • Epistemonikos Searches will be restricted by: • Date limitations: databased will be searched from 2014 onwards (last search conducted for CG186) • English language studies • Human studies • Validated study filters for systematic reviews and RCTs The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Multiple sclerosis
6.	Population	Inclusion: Adults (≥18 years) with MS, including people receiving palliative care, who are experiencing fatigue. Exclusion: Children and young people (≤18 years).

7.	Intervention	Any non-pharmacological intervention for fatigue, for example: • Multidisciplinary rehabilitation/programmes including progressive resistance training • Energy conservation programs • Mindfulness based training • Exercise including aerobic exercise training • Resistance training – (distinguish it from balance and vestibular rehab) • Vestibular rehab • Getting To Grips • Gym prescription • Self-management programmes • Fatigue management programmes • FACETS (Fatigue: Applying Cognitive behavioural and Energy effectiveness Techniques to lifeStyle) • FatiMa (Fatigue management in MS– patient education programme) • Diet (ketogenic, intermittent fasting and George Jelinek* which is plant based, wholefood diet, excluding dairy and minimising saturated fat intake) • Yoga, • Tai chi • Pilates • Relaxation • Cognitive behavioural therapy • Hyperbaric oxygen Combinations may be included if relevant to clinical practice (to be checked with GC if unsure)

		*This may also be known as 'Overcoming MS' lifestyle programme which includes
8.	Comparator	Interventions will be compared to each other placebo/sham, usual care or no treatment.
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion if they have an appropriate washout period. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. We consider RCT data to be the best evidence for reviews of interventions. In addition, the surveillance review and GC have highlighted the existence of relevant RCTs in this area. Therefore, if no RCT data is available observational data will not be considered due to the risk of confounding variables influencing the study results, reducing our confidence in the overall results of the review. Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	This review will inform the update of the following recommendations in CG 186: 1.5.5 Consider mindfulness-based training, cognitive behavioural therapy or fatigue management for treating MS-related fatigue. 1.5.6 Advise people that aerobic, balance and stretching exercises including yoga may be helpful in treating MS-related fatigue.

		1.5.8 Consider a comprehensive programme of aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for fatigue in people with MS with moderately impaired mobility (an EDSS [Expanded Disability Status Scale] score of greater than or equal to 4). It may also inform the update of recommendations 1.5.11-1.5.15
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical. • Patient-reported outcome measures to assess MS fatigue, including MFIS Fatigue Severity Scale (FSS), National Fatigue Index (NFI), MS-specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS), and Visual Analogue Scale (VAS) • Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale. • Impact on carers. • Functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), or the Functional Assessment of Multiple Sclerosis (FAMS). • Cognitive functions, such as memory and concentration • Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments. • Adverse effects of treatment for example: o Incidence of adverse events o Adverse events leading to withdrawal

		• Outcomes measuring how acceptable to intervention was. These may be measured in terms of how acceptable it was to patients, completion rates, response to follow up, adherence, engagement or disengagement. **Follow up:** • 3-6 months (minimum of 3 months but can include 1-3 months and downgrade) • >6 months – 1 year (can include > 2years for diet, include >12 months but downgrade)
13.	Secondary outcomes (important outcomes)	n/a see comments above
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments

		Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. The following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. To maximise the amount of data for meta-analysis, where multiple scales have been used for an outcome such as mobility, fatigue or spasticity, the most commonly reported ones across studies will be extracted and meta-analysed with priority given to those included in CG 186. Where available, outcome data from new studies will be meta-analysed with corresponding data included in CG 186. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the

		heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available, meta-regression or NMA-meta-regression will be conducted. WinBUGS will be used for network meta-analysis, if possible given the data identified	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) • According to disability (EDSS <6 and EDSS ≥6) • Disease modifying treatment status (currently using and not currently using) • Group vs individual • Delivered remotely vs in person	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	October 2020	
22.	Anticipated completion date	July 2022	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		Preliminary searches	x / ☐
		Piloting of the study selection process	☐ / ☐
		Formal screening of search results against eligibility criteria	☐ / ☐
		Data extraction	☐ / ☐
		Risk of bias (quality) assessment	☐ / ☐
		Data analysis	☐ / ☐
24.	Named contact	5a. Named contact	

		National Guideline Centre 5b Named contact e-mail MultipleSclerosisUpdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	 From the National Guideline Centre: From the National Guideline Centre: Dr Sharon Swain [Guideline lead] Dr Saoussen Ftouh [Senior systematic reviewer] Nicole Downes [Systematic reviewer] Sophia Kemmis Betty [Senior health economist] Lina Gulhane [Information specialist] Emma Clegg [Information specialist] Kate Ashmore [Project Manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	
33.	Details of existing review of same topic by same authors	

34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

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2 **Table 1: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from 2014, which was the cut-off date for the searches conducted for NICE guideline CG186.

Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2005 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[4] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2005 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'. • Studies published before 2005 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

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Appendix B – Literature search strategies

This literature search strategy was used for the following review:

- Clinical and cost effectiveness of non-pharmacological interventions for fatigue for adults with MS, including people receiving palliative care.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[4]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 2: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2014 – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, children)
Embase (OVID)	01 January 2014 – 08 September 2021	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, conference abstracts, children)
The Cochrane Library (Wiley)	Cochrane Reviews 2014 to 2021 Issue 9 of 12 CENTRAL 2014 to 2021 Issue 9 of 12	None Exclusions (conference abstracts & clinical trials)
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	01 January 2014 – 08 September 2021	Human; Clinical Queries: Therapy - High Sensitivity, Review - High Sensitivity, Qualitative - High Sensitivity; Age Groups: All Adult; Language: English Exclusions (Medline Records)
Epistemonikos (The Epistemonikos Foundation)	01 January 2014 – 08 September 2021	Systematic Reviews Exclusions (Cochrane Reviews)

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or rodent* or mouse or mice).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
29.	27 not 28
30.	fatigue/ or mental fatigue/ or muscle fatigue/
31.	(fatigue* or exhaust* or tired* or weary or weariness or weak* or letharg* or langour* or lassitude or drowsiness or overtired* or sluggish* or debillitat* or enervat* or burn* out or burnout).ti,ab.
32.	((deplet* or low* or lack* or limit* or loss or lost or drain* or down or dull* or diminish* or reduce*) adj2 (energy or strength or stamina)).ti,ab.
33.	or/30-32
34.	29 and 33
35.	exp Rehabilitation/
36.	"Activities of Daily Living"/
37.	exp Physical Therapy Modalities/
38.	Self care/
39.	Self-Management/

40.	self efficacy/
41.	patient care team/
42.	Patient Education as Topic/
43.	Ambulatory care/
44.	Dependent Ambulation/
45.	exp orthotic devices/
46.	Self-Help Devices/
47.	(interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or non pharmacological or non pharma or nonpharmacological).ti,ab.
48.	(rehab* or neurorehab*).ti,ab.
49.	((self* or own or personal* or alone or tailor* or individual* or specific) adj3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or device* or aid*)).ti,ab.
50.	((patient* or health) adj2 (teach* or educat* or program* or train*)).ti,ab.
51.	(orthotic* or orthos*).ti,ab.
52.	((treatment* or therap* or intervention* or energy) adj2 (strateg* or method* or programme* or program* or technique* or manag* or train*)).ti,ab.
53.	((lifestyle* or life) adj2 (choice* or program*)).ti,ab.
54.	((energy or fatigue) adj2 (effectiv* or conserv*)).ti,ab.
55.	Transcutaneous Electrical Nerve Stimulation/
56.	Transcranial Magnetic Stimulation/
57.	Transcranial Direct Current Stimulation/
58.	(TENS or electroanalgesi* or electro analgesi*).ti,ab.
59.	(electric* nerve adj2 stimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
60.	(electrostimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
61.	((transcranial or non-invasive or noninvasive) adj3 stimulation).ti,ab.
62.	FACETS.ti,ab.
63.	(fatima or "overcom* MS" or "get* adj2 gri*").ti,ab.
64.	(("whole body" or local*) adj vibration*).ti,ab.
65.	((vibration or WBV) adj therap*).ti,ab.
66.	"hyperbaric oxygen".ti,ab.
67.	exp Complementary therapies/
68.	((complementary or alternative or homeopath* or naturopath* or holistic) adj3 (therap* or treat* or care or caring or practic* or medicine* or intervention*)).ti,ab.
69.	(psychotherap* or hypnosis or hypnotherap* or hydrotherap* or ai chi or acupunctur* or reflexo* or massage).ti,ab.
70.	Mindfulness/
71.	Relaxation/
72.	Cognitive Behavioral Therapy/
73.	Executive function/
74.	(mindfulness or relax* or meditat* or cognit* or CBT or dual task).ti,ab.
75.	((executive or cognitive) adj function*).ti,ab.
76.	exp Exercise therapy/

77.	Postural Balance/
78.	exercise/ or gymnastics/ or muscle stretching exercises/ or exp physical conditioning, human/ or exp running/ or swimming/ or exp walking/
79.	exp Physical fitness/
80.	((vestibular or balanc*) adj2 therap*).ti,ab.
81.	(exercising or exercise* or aerobic* or fitness).ti,ab.
82.	((physical* or muscle* or muscular or core or postur* or cardio*) adj2 (endurance or exertion or stretch* or stand* or splinting or stability or strength* or balanc* or control or activ* or train* or condition*)).ti,ab.
83.	((resistance or weight or gait or ambulat* or balanc*) adj2 (technics or techniques or train* or workout* or routine* or intervention*)).ti,ab.
84.	(tai ji or tai chi or taichi or taiji or taijiquan).ti,ab.
85.	(gym* or calisthenics or pilates or yoga or swim* or run* or walk* or danc* or sport*).ti,ab.
86.	exp Diet/
87.	(diet* or nutrition*).ti,ab.
88.	(Mediterranean or keto* or fast* or paleo* or Jelinek or wholefood* or "plant-based" or vegan or vegetarian or healthy eat*).ti,ab.
89.	((dairy or gluten or meat or fats or fat) adj2 (free or remov* or restrict* or reduc* or "cut* out" or minimis* or lower* or control*)).ti,ab.
90.	Computer-Assisted Instruction/ or Virtual Reality/ or Computer Simulation/
91.	video games/
92.	telemedicine/ or telerehabilitation/
93.	(exergam* or "exer gam*" or "fitness gam*" or gamercis* or "virtual reality" or video* or online or internet* or computer* or wiifit or gaming technology or web* or e*health or tele*).ti,ab.
94.	(robot* or "robot assist*" or exoskeleton* or exosuit*).ti,ab.
95.	Clothing/
96.	lycra.ti,ab.
97.	(cooling adj2 (device* or clothing or clothes or cloth or garment*)).ti,ab.
98.	or/35-97
99.	34 and 98
100.	randomized controlled trial.pt.
101.	controlled clinical trial.pt.
102.	randomi#ed.ti,ab.
103.	placebo.ab.
104.	randomly.ti,ab.
105.	Clinical Trials as topic.sh.
106.	trial.ti.
107.	or/100-106
108.	Meta-Analysis/
109.	exp Meta-Analysis as Topic/
110.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
111.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
112.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

113.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
114.	(search* adj4 literature).ab.
115.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
116.	cochrane.jw.
117.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
118.	or/108-117
119.	99 and (107 or 118)

Embase (Ovid) search terms

1.	exp *Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or rodent* or mouse or mice).ti.
24.	or/16-23
25.	7 not 24
26.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
27.	25 not 26
28.	limit 27 to English language
29.	fatigue/ or exhaustion/ or lassitude/ or muscle fatigue/
30.	dysthymia/
31.	(fatigue* or exhaust* or tired* or weary or weariness or weak* or letharg* or langour* or lassitude or drowsiness or overtired* or sluggish* or debillitat* or enervat* or burn* out or burnout).ti,ab.

32.	((deplet* or low* or lack* or limit* or loss or lost or drain* or down or dull* or diminish* or reduce*) adj2 (energy or strength or stamina)).ti,ab.
33.	or/29-32
34.	exp rehabilitation/
35.	daily life activity/
36.	exp physiotherapy/
37.	self care/
38.	self concept/
39.	patient care/
40.	patient education/
41.	ambulatory care/
42.	walking difficulty/
43.	exp orthosis/
44.	self help device/
45.	(interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or non pharmacological or non pharma or nonpharmacological).ti,ab.
46.	(rehab* or neurorehab*).ti,ab.
47.	((self* or own or personal* or alone or tailor* or individual* or specific) adj3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or device* or aid*)).ti,ab.
48.	((patient* or health) adj2 (teach* or educat* or program* or train*)).ti,ab.
49.	(orthotic* or orthos*).ti,ab.
50.	((treatment* or therap* or intervention* or energy) adj2 (strateg* or method* or programme* or program* or technique* or manag* or train*)).ti,ab.
51.	((lifestyle* or life) adj2 (choice* or program*)).ti,ab.
52.	((energy or fatigue) adj2 (effectiv* or conserv*)).ti,ab.
53.	transcutaneous electrical nerve stimulation/
54.	transcranial magnetic stimulation/
55.	transcranial direct current stimulation/
56.	(TENS or electroanalgesi* or electro analgesi*).ti,ab.
57.	(electric* nerve adj2 stimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
58.	(electrostimulation adj2 (transcutaneous or percutaneous or analgesi*)).ti,ab.
59.	((transcranial or non-invasive or noninvasive) adj3 stimulation).ti,ab.
60.	FACETS.ti,ab.
61.	(fatima or "overcom* MS" or "get* adj2 gri*").ti,ab.
62.	(("whole body" or local*) adj vibration*).ti,ab.
63.	((vibration or WBV) adj therap*).ti,ab.
64.	"hyperbaric oxygen".ti,ab.
65.	exp alternative medicine/
66.	((complementary or alternative or homeopath* or naturopath* or holistic) adj3 (therap* or treat* or care or caring or practic* or medicine* or intervention*)).ti,ab.
67.	(psychotherap* or hypnosis or hypnotherap* or hydrotherap* or ai chi or acupunctur* or reflexo* or massage).ti,ab.

68.	mindfulness/
69.	leisure/
70.	cognitive behavioral therapy/
71.	executive function/
72.	(mindfulness or relax* or meditat* or cognit* or dual task or CBT).ti,ab.
73.	((executive or cognitive) adj function*).ti,ab.
74.	exp kinesiotherapy/
75.	body equilibrium/
76.	exp "physical activity, capacity and performance"/
77.	physical education/
78.	stretching exercise/
79.	fitness/
80.	((vestibular or balanc*) adj2 therap*).ti,ab.
81.	(exercising or exercise* or aerobic* or fitness).ti,ab.
82.	((physical* or muscle* or muscular or core or postur* or cardio*) adj2 (endurance or exertion or stretch* or stand* or splinting or stability or strength* or balanc* or control or activ* or train* or condition*)).ti,ab.
83.	((resistance or weight or gait or ambulat* or balanc*) adj2 (technics or techniques or train* or workout* or routine* or intervention*)).ti,ab.
84.	(tai ji or tai chi or taichi or taiji or taijiquan).ti,ab.
85.	(gym* or calisthenics or pilates or yoga or swim* or run* or walk* or sport*).ti,ab.
86.	exp diet/
87.	(diet* or nutrition*).ti,ab.
88.	(Mediterranean or keto* or fast* or paleo* or Jelinek or wholefood* or "plant-based" or vegan or vegetarian or healthy eat*).ti,ab.
89.	((dairy or gluten or meat or fats or fat) adj2 (free or remov* or restrict* or reduc* or "cut* out" or minimis* or lower* or control*)).ti,ab.
90.	teaching/
91.	exp computer simulation/
92.	video game/
93.	telemedicine/ or telerehabilitation/
94.	(exergam* or "exer gam*" or "fitness gam*" or gamercis* or "virtual reality" or video* or online or internet* or computer* or wiifit or gaming technology or web* or e*health or tele*).ti,ab.
95.	(robot* or "robot assist*" or exoskeleton* or exosuit*).ti,ab.
96.	clothing/
97.	lycra.ti,ab.
98.	(cooling adj2 (device* or clothing or clothes or cloth or garment*)).ti,ab.
99.	or/34-98
100.	28 and 33 and 99
101.	random*.ti,ab.
102.	factorial*.ti,ab.
103.	(crossover* or cross over*).ti,ab.
104.	((doubl* or singl*) adj blind*).ti,ab.
105.	(assign* or allocat* or volunteer* or placebo*).ti,ab.

106.	crossover procedure/
107.	single blind procedure/
108.	randomized controlled trial/
109.	double blind procedure/
110.	or/101-109
111.	systematic review/
112.	meta-analysis/
113.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
114.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
115.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
116.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
117.	(search* adj4 literature).ab.
118.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
119.	cochrane.jw.
120.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
121.	or/111-120
122.	100 and (110 or 121)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Multiple Sclerosis] explode all trees
#2.	((multiple or disseminated) NEAR/2 scleros*):ti,ab
#3.	(encephalomyelitis disseminata):ti,ab
#4.	MS:ti
#5.	MeSH descriptor: [Myelitis, Transverse] this term only
#6.	transverse myelitis:ti,ab
#7.	(OR #1-#6)
#8.	MeSH descriptor: [Fatigue] this term only
#9.	MeSH descriptor: [Mental Fatigue] this term only
#10.	MeSH descriptor: [Muscle Fatigue] this term only
#11.	(fatigue* or exhaust* or tired* or weary or weariness or weak* or letharg* or langour* or lassitude or drowsiness or overtired* or sluggish* or debillitat* or enervat* or burn* out or burnout):ti,ab
#12.	((deplet* or low* or lack* or limit* or loss or lost or drain* or down or dull* or diminish* or reduce*) NEAR/2 (energy or strength or stamina)):ti,ab
#13.	(OR #8-#12)
#14.	MeSH descriptor: [Rehabilitation] explode all trees
#15.	MeSH descriptor: [Activities of Daily Living] this term only
#16.	MeSH descriptor: [Physical Therapy Modalities] explode all trees
#17.	MeSH descriptor: [Self Care] this term only
#18.	MeSH descriptor: [Self-Management] this term only
#19.	MeSH descriptor: [Self Efficacy] this term only
#20.	MeSH descriptor: [Patient Care Team] this term only

#21.	MeSH descriptor: [Patient Education as Topic] this term only
#22.	MeSH descriptor: [Ambulatory Care] this term only
#23.	MeSH descriptor: [Dependent Ambulation] this term only
#24.	MeSH descriptor: [Orthotic Devices] explode all trees
#25.	MeSH descriptor: [Self-Help Devices] this term only
#26.	(interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or non pharmacological or non pharma or nonpharmacological):ti,ab
#27.	(rehab* or neurorehab*):ti,ab
#28.	((self* or own or personal* or alone or tailor* or individual* or specific) NEAR/3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or device* or aid*)):ti,ab
#29.	((patient* or health) NEAR/2 (teach* or educat* or program* or train*)):ti,ab
#30.	(orthotic* or orthos*):ti,ab
#31.	((treatment* or therap* or intervention* or energy) NEAR/2 (strateg* or method* or programme* or program* or technique* or manag* or train*)):ti,ab
#32.	(lifestyle* or life) NEAR/2 (choice* or program*):ti,ab
#33.	((energy or fatigue) NEAR/2 (effectiv* or conserv*)):ti,ab
#34.	MeSH descriptor: [Transcutaneous Electric Nerve Stimulation] this term only
#35.	MeSH descriptor: [Transcranial Magnetic Stimulation] this term only
#36.	MeSH descriptor: [Transcranial Direct Current Stimulation] this term only
#37.	(TENS or electroanalgesi* or electro analgesi*):ti,ab
#38.	((electric* NEXT nerve) NEAR/2 stimulation NEAR/2 (transcutaneous or percutaneous or analgesi*)):ti,ab
#39.	(electrostimulation NEAR/2 (transcutaneous or percutaneous or analgesi*)):ti,ab
#40.	((transcranial or non-invasive or noninvasive) NEAR/3 stimulation):ti,ab
#41.	FACETS:ti,ab
#42.	(fatima or "overcom* MS" or "get* NEAR/2 gri*"):ti,ab
#43.	(("whole body" or local*) NEAR vibration*):ti,ab
#44.	((vibration or WBV) NEAR therap*):ti,ab
#45.	hyperbaric oxygen:ti,ab
#46.	MeSH descriptor: [Complementary Therapies] explode all trees
#47.	((complementary or alternative or homeopath* or naturopath* or holistic) NEAR/3 (therap* or treat* or care or caring or practic* or medicine* or intervention*)):ti,ab
#48.	(psychotherap* or hypnosis or hypnotherap* or hydrotherap* or ai chi or acupunctur* or reflexo* or massage):ti,ab
#49.	MeSH descriptor: [Mindfulness] this term only
#50.	MeSH descriptor: [Relaxation] this term only
#51.	MeSH descriptor: [Cognitive Behavioral Therapy] this term only
#52.	MeSH descriptor: [Executive Function] this term only
#53.	(mindfulness or relax* or meditat* or cognit* or "dual task" or CBT):ti,ab
#54.	((executive or cognitive) NEAR function*):ti,ab
#55.	MeSH descriptor: [Exercise Therapy] explode all trees
#56.	MeSH descriptor: [Postural Balance] this term only
#57.	MeSH descriptor: [Exercise] this term only

#58.	MeSH descriptor: [Gymnastics] this term only
#59.	MeSH descriptor: [Muscle Stretching Exercises] this term only
#60.	MeSH descriptor: [Physical Conditioning, Human] explode all trees
#61.	MeSH descriptor: [Running] explode all trees
#62.	MeSH descriptor: [Swimming] this term only
#63.	MeSH descriptor: [Walking] explode all trees
#64.	MeSH descriptor: [Physical Fitness] explode all trees
#65.	((vestibular or balanc*) NEAR/2 (therap*)):ti,ab
#66.	(exercising or exercise* or aerobic* or fitness):ti,ab
#67.	((physical* or muscle* or muscular or core or postur* or cardio*) NEAR/2 (endurance or exertion or stretch* or stand* or splinting or stability or strength* or balanc* or control or activ* or train* or condition*)):ti,ab
#68.	((resistance or weight or gait or ambulat* or balanc*) NEAR/2 (technics or techniques or train* or workout* or routine* or intervention*)):ti,ab
#69.	(tai ji or tai chi or taichi or taiji or taijiquan):ti,ab
#70.	(gym* or calisthenics or pilates or yoga or swim* or run* or walk* or sport*):ti,ab
#71.	MeSH descriptor: [Diet] explode all trees
#72.	(diet* or nutrition*):ti,ab
#73.	(Mediterranean or keto* or fast* or paleo* or Jelinek or wholefood* or "plant-based" or vegan or vegetarian or healthy eat*):ti,ab
#74.	((dairy or gluten or meat or fats or fat) NEAR/2 (free or remov* or restrict* or reduc* or "cut* out" or minimis* or lower* or control*)):ti,ab
#75.	MeSH descriptor: [Computer-Assisted Instruction] this term only
#76.	MeSH descriptor: [Virtual Reality] this term only
#77.	MeSH descriptor: [Computer Simulation] this term only
#78.	MeSH descriptor: [Video Games] this term only
#79.	MeSH descriptor: [Telemedicine] this term only
#80.	MeSH descriptor: [Telerehabilitation] this term only
#81.	(exergam* or "exer gam*" or "fitness gam*" or gamercis* or "virtual reality" or video* or online or internet* or computer* or wiifit or gaming technology or web* or e*health or tele*):ti,ab
#82.	(robot* or "robot assist*" or exoskeleton* or exosuit*):ti,ab
#83.	MeSH descriptor: [Clothing] this term only
#84.	lycra:ti,ab
#85.	(cooling NEAR/2 (device* or clothing or clothes or cloth or garment*)):ti,ab
#86.	(OR #14-#85)
#87.	#7 AND #13 AND #86
#88.	conference:pt or (clinicaltrials or trialsearch):so
#89.	#87 NOT #88

CINAHL (EBSCO) search terms

S1.	(MH "Multiple Sclerosis+")
S2.	TI ((multiple or disseminated) n2 scleros*) OR AB ((multiple or disseminated) n2 scleros*)
S3.	TI (encephalomyelitis disseminata or disseminated encephalomyelitistis or ADEM) OR AB (encephalomyelitis disseminata or disseminated encephalomyelitistis or ADEM)

S4.	TI MS
S5.	(MH "Myelitis, Transverse")
S6.	TI transverse myelitis OR AB transverse myelitis
S7.	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8.	(MH "Fatigue") OR (MH "Mental Fatigue") OR (MH "Muscle Fatigue")
S9.	TI ((fatigue* or exhaust* or tired* or weary or weariness or weak* or letharg* or langour* or lassitude or drowsiness or overtired* or sluggish* or debillitat* or enervat* or burn* out or burnout)) OR AB ((fatigue* or exhaust* or tired* or weary or weariness or weak* or letharg* or langour* or lassitude or drowsiness or overtired* or sluggish* or debillitat* or enervat* or burn* out or burnout))
S10.	TI (((deplet* or low* or lack* or limit* or loss or lost or drain* or down or dull* or diminish* or reduce*) N2 (energy or strength or stamina))) OR AB (((deplet* or low* or lack* or limit* or loss or lost or drain* or down or dull* or diminish* or reduce*) N2 (energy or strength or stamina)))
S11.	S8 OR S9 OR S10
S12.	(MH "Rehabilitation+")
S13.	(MH "Activities of Daily Living")
S14.	(MH "Physical Therapy+")
S15.	(MH "Self Care") OR (MH "Self-Management")
S16.	(MH "Self-Efficacy")
S17.	(MH "Multidisciplinary Care Team") OR (MH "Nutritional Support Team")
S18.	(MH "Patient Education")
S19.	(MH "Ambulatory Care")
S20.	(MH "Orthoses+")
S21.	(MH "Assistive Technology Devices") OR (MH "Ambulation Aids+")
S22.	TI ((interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or non pharmacological or non pharma or nonpharmacological)) OR AB ((interdisciplinary or multidisciplinary or inter disciplinary or multi disciplinary or MDT or home based or non pharmacological or non pharma or nonpharmacological))
S23.	TI ((rehab* or neurorehab*)) OR AB ((rehab* or neurorehab*))
S24.	TI (((self* or own or personal* or alone or tailor* or individual* or specific) N3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or device* or aid*))) OR AB (((self* or own or personal* or alone or tailor* or individual* or specific) N3 (efficacy or treatment* or programme* or program* or technique* or manag* or intervention* or therap* or train* or strateg* or method* or counsel* or care* or caring or device* or aid*)))
S25.	TI (((patient* or health) N2 (teach* or educat* or program* or train*))) OR AB (((patient* or health) N2 (teach* or educat* or program* or train*)))
S26.	TI ((orthotic* or orthos*)) OR AB ((orthotic* or orthos*))
S27.	TI (((treatment* or therap* or intervention* or energy) N2 (strateg* or method* or programme* or program* or technique* or manag* or train*))) OR AB (((treatment* or therap* or intervention* or energy) N2 (strateg* or method* or programme* or program* or technique* or manag* or train*)))
S28.	TI (((lifestyle* or life) N2 (choice* or program*))) OR AB (((lifestyle* or life) N2 (choice* or program*)))
S29.	TI (((energy or fatigue) N2 (effectiv* or conserv*))) OR AB (((energy or fatigue) N2 (effectiv* or conserv*)))
S30.	(MH "Transcutaneous Electric Nerve Stimulation")

S31.	(MH "Transcranial Magnetic Stimulation")
S32.	(MH "Transcranial Direct Current Stimulation")
S33.	TI ((TENS or electroanalgesi* or electro analgesi*)) OR AB ((TENS or electroanalgesi* or electro analgesi*))
S34.	TI ((electric* nerve N2 stimulation N2 (transcutaneous or percutaneous or analgesi*))) OR AB ((electric* nerve N2 stimulation N2 (transcutaneous or percutaneous or analgesi*)))
S35.	TI ((electrostimulation N2 (transcutaneous or percutaneous or analgesi*))) OR AB ((electrostimulation N2 (transcutaneous or percutaneous or analgesi*)))
S36.	TI (((transcranial or non-invasive or noninvasive) N3 stimulation)) OR AB (((transcranial or non-invasive or noninvasive) N3 stimulation))
S37.	TI FACETS OR AB FACETS
S38.	TI ((fatima or "overcom* MS" or "get* N2 gri*")) OR AB ((fatima or "overcom* MS" or "get* N2 gri*"))
S39.	TI ((("whole body" or local*) N1 vibration*)) OR AB ((("whole body" or local*) N1 vibration*))
S40.	TI (((vibration or WBV) N1 therap*)) OR AB (((vibration or WBV) N1 therap*))
S41.	TI "hyperbaric oxygen" OR AB "hyperbaric oxygen"
S42.	(MH "Alternative Therapies+")
S43.	TI (((complementary or alternative or homeopath* or naturopath* or holistic) N3 (therap* or treat* or care or caring or practic* or medicine* or intervention*))) OR AB (((complementary or alternative or homeopath* or naturopath* or holistic) N3 (therap* or treat* or care or caring or practic* or medicine* or intervention*)))
S44.	TI ((psychotherap* or hypnosis or hypnotherap* or hydrotherap* or ai chi or acupunctur* or reflexo* or massage)) OR AB ((psychotherap* or hypnosis or hypnotherap* or hydrotherap* or ai chi or acupunctur* or reflexo* or massage))
S45.	(MH "Mindfulness")
S46.	(MH "Relaxation") OR (MH "Relaxation Techniques+")
S47.	(MH "Cognitive Therapy")
S48.	(MH "Executive Function")
S49.	TI ((mindfulness or relax* or meditat* or cognit* or CBT or dual task)) OR AB ((mindfulness or relax* or meditat* or cognit* or CBT or dual task))
S50.	TI (((executive or cognitive) N1 function*)) OR AB (((executive or cognitive) N1 function*))
S51.	(MH "Therapeutic Exercise+")
S52.	(MH "Balance, Postural")
S53.	(MH "Exercise+")
S54.	(MH "Muscle Strengthening+")
S55.	(MH "Physical Fitness+")
S56.	TI (((vestibular or balanc*) N2 therap*)) OR AB (((vestibular or balanc*) N2 therap*))
S57.	TI ((exercising or exercise* or aerobic* or fitness)) OR AB ((exercising or exercise* or aerobic* or fitness))
S58.	TI (((physical* or muscle* or muscular or core or postur* or cardio*) N2 (endurance or exertion or stretch* or stand* or splinting or stability or strength* or balanc* or control or activ* or train* or condition*))) OR AB (((physical* or muscle* or muscular or core or postur* or cardio*) N2 (endurance or exertion or stretch* or stand* or splinting or stability or strength* or balanc* or control or activ* or train* or condition*)))
S59.	TI (((resistance or weight or gait or ambulat* or balanc*) N2 (technics or techniques or train* or workout* or routine* or intervention*))) OR AB (((resistance or weight or gait

	or ambulat* or balanc*) N2 (technics or techniques or train* or workout* or routine* or intervention*)))
S60.	TI ((tai ji or tai chi or taichi or taiji or taijiquan)) OR AB ((tai ji or tai chi or taichi or taiji or taijiquan))
S61.	TI ((gym* or calisthenics or pilates or yoga or swim* or run* or walk* or danc* or sport*)) OR AB ((gym* or calisthenics or pilates or yoga or swim* or run* or walk* or danc* or sport*))
S62.	(MH "Diet+")
S63.	TI ((diet* or nutrition*)) OR AB ((diet* or nutrition*))
S64.	TI ((Mediterranean or keto* or fast* or paleo* or Jelinek or wholefood* or "plant-based" or vegan or vegetarian or healthy eat*)) OR AB ((Mediterranean or keto* or fast* or paleo* or Jelinek or wholefood* or "plant-based" or vegan or vegetarian or healthy eat*))
S65.	TI (((dairy or gluten or meat or fats or fat) N2 (free or remov* or restrict* or reduc* or "cut* out" or minimis* or lower* or control*))) OR AB (((dairy or gluten or meat or fats or fat) N2 (free or remov* or restrict* or reduc* or "cut* out" or minimis* or lower* or control*)))
S66.	(MH "Computer Assisted Instruction")
S67.	(MH "Virtual Reality")
S68.	(MH "Computer Simulation")
S69.	(MH "Video Games+")
S70.	(MH "Telemedicine") OR (MH "Telerehabilitation")
S71.	TI ((exergam* or "exer gam*" or "fitness gam*" or gamercis* or "virtual reality" or video* or online or internet* or computer* or wiifit or gaming technology or web* or e*health or tele*)) OR AB ((exergam* or "exer gam*" or "fitness gam*" or gamercis* or "virtual reality" or video* or online or internet* or computer* or wiifit or gaming technology or web* or e*health or tele*))
S72.	TI ((robot* or "robot assist*" or exoskeleton* or exosuit*)) OR AB ((robot* or "robot assist*" or exoskeleton* or exosuit*))
S73.	(MH "Clothing")
S74.	TI lycra OR AB lycra
S75.	TI ((cooling N2 (device* or clothing or clothes or cloth or garment*))) OR AB ((cooling N2 (device* or clothing or clothes or cloth or garment*)))
S76.	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR 265 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75
S77.	S7 AND S11 AND S76

Epistemonikos search terms

1.	(((advanced_title_en:(multiple sclerosis) OR advanced_abstract_en:(multiple sclerosis)) AND (advanced_title_en:((fatigue* OR exhaust* OR tired* OR weary OR weariness OR weak* OR letharg* OR langour* OR lassitude OR drowsiness OR overtired* OR sluggish* OR debillitat* OR enervat* OR burn* out OR burnout)) OR advanced_abstract_en:((fatigue* OR exhaust* OR tired* OR weary OR weariness OR weak* OR letharg* OR langour* OR lassitude OR drowsiness OR overtired* OR sluggish* OR debillitat* OR enervat* OR burn* out OR burnout)))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search with the Multiple Sclerosis population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics. Searches for quality of life studies were run for general information.

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, children)
Embase	01 January 2014 – 07 September 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, conference abstracts, children)
Centre for Research and Dissemination (CRD)	HTA – 01 January 2014 – 31 March 2018 NHSEED – 01 January 2014 – March 2015	None
The International Network of Agencies for Health Technology Assessment (INAHTA)	01 January 2018 – 07 September 2021	None

Medline (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	Myelitis, Transverse/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	*Demyelinating Diseases/
9.	*Demyelinating Autoimmune Diseases, CNS/
10.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
11.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
12.	Venous Insufficiency/cf, co, di, dg, et [Cerebrospinal Fluid, Complications, Diagnosis, Diagnostic Imaging, Etiology]
13.	(Devic* adj (disease or syndrome)).ti,ab.

14.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
15.	exp Optic Neuritis/
16.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
17.	(NMO or NMOSD).ti,ab.
18.	or/1-17
19.	letter/
20.	editorial/
21.	news/
22.	exp historical article/
23.	Anecdotes as Topic/
24.	comment/
25.	case report/
26.	(letter or comment*).ti.
27.	or/19-26
28.	randomized controlled trial/ or random*.ti,ab.
29.	27 not 28
30.	animals/ not humans/
31.	exp Animals, Laboratory/
32.	exp Animal Experimentation/
33.	exp Models, Animal/
34.	exp Rodentia/
35.	(rat or rats or rodent* or mouse or mice).ti.
36.	or/29-35
37.	18 not 36
38.	limit 37 to English language
39.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
40.	38 not 39
41.	Economics/
42.	Value of life/
43.	exp "Costs and Cost Analysis"/
44.	exp Economics, Hospital/
45.	exp Economics, Medical/
46.	Economics, Nursing/
47.	Economics, Pharmaceutical/
48.	exp "Fees and Charges"/
49.	exp Budgets/
50.	budget*.ti,ab.
51.	cost*.ti.
52.	(economic* or pharmaco?economic*).ti.
53.	(price* or pricing*).ti,ab.

54.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
55.	(financ* or fee or fees).ti,ab.
56.	(value adj2 (money or monetary)).ti,ab.
57.	or/41-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	40 and 57
79.	40 and 77
80.	78 or 79

Embase (Ovid) search terms

1.	exp Multiple Sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	MS.ti.
5.	myelitis/
6.	transverse myelitis.ti,ab.
7.	or/1-6
8.	demyelinating disease/
9.	(Demyelinat* adj2 (syndrome* or disease* or autoimmun*)).ti,ab.
10.	(Chronic Cerebrospinal Venous Insufficiency or CCSVI).ti,ab.
11.	vein insufficiency/co, di, et [Complication, Diagnosis, Etiology]

12.	(Devic* adj (disease or syndrome)).ti,ab.
13.	((clinical* isolat* or radiological* isolat*) adj2 syndrome*).ti,ab.
14.	exp optic neuritis/
15.	((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*)).ti,ab.
16.	(NMO or NMOSD).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	(conference abstract or conference paper).pt.
22.	case report/ or case study/
23.	(letter or comment*).ti.
24.	or/18-23
25.	randomized controlled trial/ or random*.ti,ab.
26.	24 not 25
27.	animal/ not human/
28.	nonhuman/
29.	exp Animal Experiment/
30.	exp Experimental Animal/
31.	animal model/
32.	exp Rodent/
33.	(rat or rats or rodent* or mouse or mice).ti.
34.	or/26-33
35.	17 not 34
36.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
37.	35 not 36
38.	limit 37 to English language
39.	health economics/
40.	exp economic evaluation/
41.	exp health care cost/
42.	exp fee/
43.	budget/
44.	funding/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/39-51
53.	quality adjusted life year/

54.	"quality of life index"/
55.	short form 12/ or short form 20/ or short form 36/ or short form 8/
56.	sickness impact profile/
57.	(quality adj2 (wellbeing or well being)).ti,ab.
58.	sickness impact profile.ti,ab.
59.	disability adjusted life.ti,ab.
60.	(qal* or qtime* or qwb* or daly*).ti,ab.
61.	(euroqol* or eq5d* or eq 5*).ti,ab.
62.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
63.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
64.	(hui or hui1 or hui2 or hui3).ti,ab.
65.	(health* year* equivalent* or hye or hyes).ti,ab.
66.	discrete choice*.ti,ab.
67.	rosser.ti,ab.
68.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
69.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
70.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
71.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
72.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
73.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
74.	or/53-73
75.	38 and 52
76.	38 and 74
77.	75 or 76

NHS EED and HTA (CRD) search terms

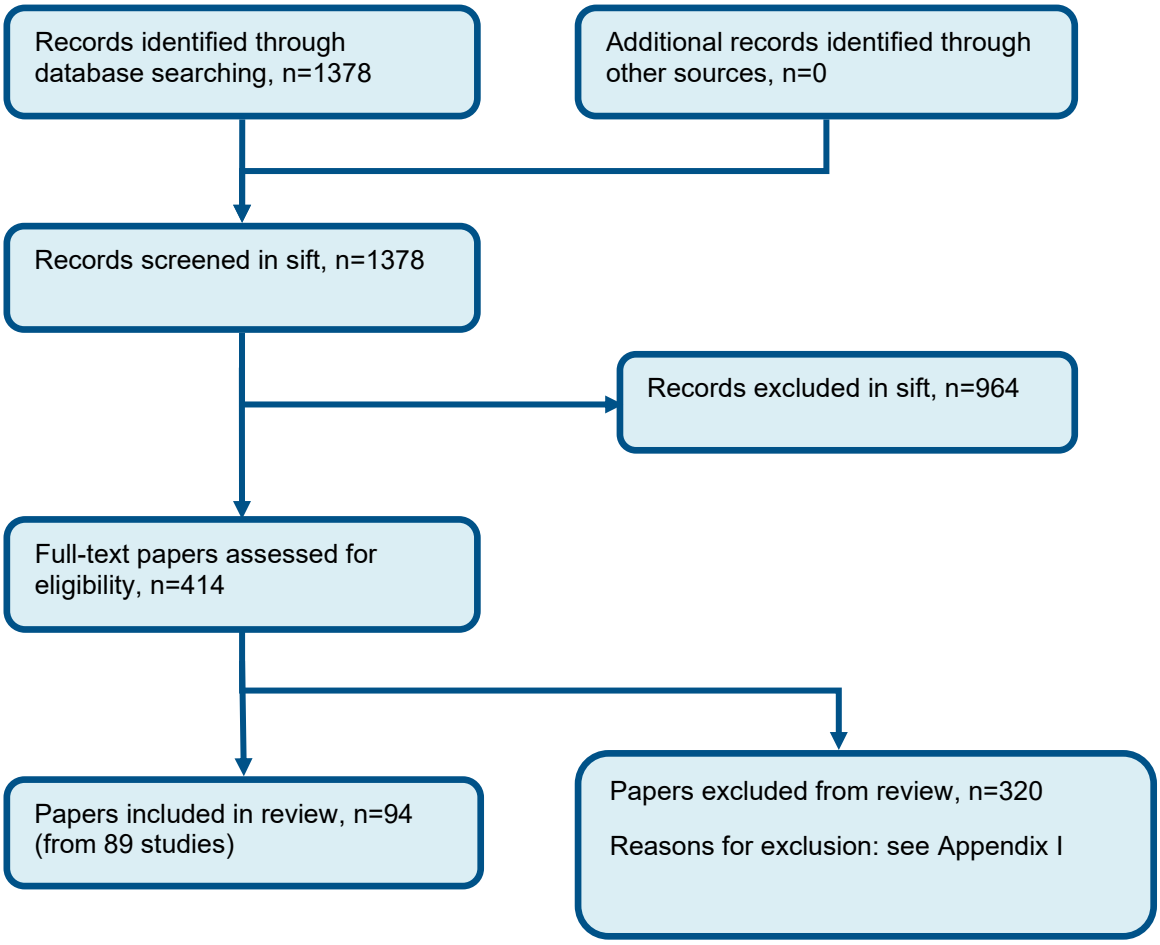
#1.	MeSH DESCRIPTOR Multiple Sclerosis EXPLODE ALL TREES
#2.	(((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	(MS)
#5.	MeSH DESCRIPTOR Myelitis, Transverse EXPLODE ALL TREES
#6.	(transverse myelitis)
#7.	MeSH DESCRIPTOR Demyelinating Diseases EXPLODE ALL TREES
#8.	((Demyelinat* adj2 (syndrome or disease)))
#9.	(Chronic Cerebrospinal Venous Insufficiency)
#10.	MeSH DESCRIPTOR Venous Insufficiency
#11.	(((Devic or "devic's") adj (disease or syndrome)))
#12.	(((clinically isolated or radiologically isolated) adj syndrome))
#13.	MeSH DESCRIPTOR Optic Neuritis EXPLODE ALL TREES
#14.	(Neuromyelitis Optica)
#15.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14

INAHTA search terms

1.	(multiple sclerosis)[mh] OR (((multiple or disseminated) adj2 scleros*)) OR (encephalomyelitis disseminata) OR (MS)[Title] OR (Myelitis, Transverse)[mh] OR (transverse myelitis) OR (Demyelinating Diseases)[mh] OR (Demyelinating Autoimmune Diseases, CNS)[mh] OR ((Demyelinat* adj2 (syndrome* or disease* or autoimmun*))) OR ((Chronic Cerebrospinal Venous Insufficiency or CCSVI)) OR (venous insufficiency)[mh] OR ((Devic* adj (disease or syndrome))) OR (((clinical* isolat* or radiological* isolat*) adj2 syndrome*)) OR (optic neuritis)[mh] OR (((neuromyelitis or neuritis or neuropapillitis) adj2 (retrobulbar or optic*))) OR ((NMO or NMOSD))

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of non-pharmacological management of fatigue



Appendix D – Effectiveness evidence

D.1 Studies extracted using EPPI reviewer (new studies identified in current update)

Abonie, 2020

Bibliographic Reference	**Abonie, U. S.; Hettinga, F. J.; Effect of a Tailored Activity Pacing Intervention on Fatigue and Physical Activity Behaviours in Adults with Multiple Sclerosis; International Journal of Environmental Research & Public Health [Electronic Resource]; 2020; vol. 18 (no. 1); 22**

Study details

Trial name / registration number	Not reported.
Study location	UK
Study setting	Outpatient
Study dates	Recruitment was between July 2017 and December 2017
Sources of funding	No external funding was received. No conflicts of interest reported.
Inclusion criteria	aged ≥18 years; definite diagnosis of MS; relapse-free for previous 30 days; ambulatory (with or without an assistive device); could reliably wear an accelerometer; and English-speaking
Exclusion criteria	Non-ambulatory; had experienced a relapse in previous month; changed medications with previous 2 weeks that could interfere with fatigue ratings or accelerometer data; and currently or recently (within past 12 months) received a physical activity programme with or without activity management instruction

Recruitment / selection of participants	Community-dwelling adults recruited from MS-UK centre and MS Society focus group through public advertisements (online and e-posters) in Colchester, Essex. Interested participants were contacted by researchers to answer questions and assess against inclusion criteria.
Intervention(s)	Tailored activity pacing intervention (fatigue management programme). Prior to randomisation, participants wore an accelerometer on their waist at all times other than when showering or swimming, and were told not to alter their activity behaviour and to keep an accompanying logbook to record daily fatigue, activity pacing behaviours and activities, in addition to wake-up and bedtimes, during a 7-day home monitoring period. After the home monitoring period, participants returned the accelerometer and logbook, were stratified by age and gender, and randomised into an intervention or control group. Participants blindly selected a folded paper which had either 'intervention' or 'control' on to assign to groups. Intervention began the week after baseline assessment. The pacing intervention involved tailored activity pacing based on data from the accelerometer and logbook. Those reporting activity avoidance as a response to fatigue or who were limiting their activities in fear of a relapse identified as generally very low activity levels and moderate-severe fatigue ratings were given information about perceptions and expectations relating to activity-related symptoms and given strategies to develop graded consistent physical activity to increase their physical activity levels and fitness. Those whose report indicated overdoing activities when they felt better, leading to worsened fatigue and the need to rest for prolonged periods to recover (low fatigue preceding high activity level clusters followed by severe fatigue and prolonged inactivity periods), were given information about developing a consistent pattern of paced activity and rest followed by a gradual increase in physical activity. The intervention sessions was ~30 min long depending on the participant. Outcomes were assessed at 4-week follow-up.
Population subgroups	Not reported
Comparator	Control group. Prior to randomisation, participants wore an accelerometer on their waist at all times other than when showering or swimming, and were told not to alter their activity behaviour and to keep an accompanying logbook to record daily fatigue, activity pacing behaviours and activities, in addition to wake-up and bedtimes, during a 7-day home monitoring period. After the home monitoring period, participants returned the accelerometer and logbook, were stratified by age and gender, and randomised into an intervention or control group. Participants blindly selected a folded paper which had either 'intervention' or 'control' on to assign to groups. Treatment in control group not defined. Presumably continued usual lifestyle? Outcomes were assessed at 4-week follow-up.

Number of participants	24 randomised (n=21 analysed in intention to treat).
Duration of follow-up	4 weeks - indirectness as specified minimum of 3 months follow-up ideally in the protocol
Indirectness	Follow-up - 4 weeks whereas specified a minimum of 3 months ideally in the protocol
Method of analysis	Intention to treat - those randomised and that had adequate baseline measures
Additional comments	Of the 24 randomised, 21 were included in intention to treat analyses (n=11 in intervention group and n=10 in control group). The three participants not included in intention to treat analyses did not complete baseline assessment (n=1 in intervention due to lack of time and n=2 in control due to not feeling well enough). One further participant in the control group was lost to follow-up but included in intention to treat analyses as baseline data had been collected.

Study arms

Tailored activity pacing intervention (N = 12)
Activity pacing tailored based on accelerometer and logbook data that generated personalised reports summarising each person's symptom-activity relationship based on physical activity, fatigue and physical activity patterns. Fatigue management programme as discusses the intervention in relation to reducing fatigue.

Control (N = 12)
Control group not defined. Presumably continued usual lifestyle?

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Clinically significant fatigue at baseline FSS score of 4 or higher used to define clinically significant fatigue. Number (%)	16 (76%)

Arm-level characteristics

Characteristic	Tailored activity pacing intervention (N = 12)	Control (N = 12)
% Female Nominal	27	30
Mean age (SD) Mean (SD)	57.9 (8)	60.9 (9.5)
Ethnicity Text	NR	NR
Comorbidities Text	*empty data*	NR

Characteristic	Tailored activity pacing intervention (N = 12)	Control (N = 12)
Number analysed (intention to treat population) Those randomised with adequate baseline measures Nominal	11	10
Body mass index (kg/m²) Median (IQR)	25.2 (3.9)	25.1 (7.6)
Relapsing-remitting MS Number (%)	6 (54.5%)	4 (40%)
Primary progressive MS Number (%)	1 (9.1%)	1 (10%)
Secondary progressive MS Number (%)	4 (36.4%)	5 (50%)
Disease duration (years) Median (IQR)	12.0 (24.0)	9.5 (19.5)
PDSS disability scale Patient Determined Disease Steps. Scale 0-8. Higher indicates increased disability. Median (IQR)	2.0 (2.0)	3.5 (2.0)

Characteristic	Tailored activity pacing intervention (N = 12)	Control (N = 12)
FSS Fatigue severity scale. Scale 1-7. Higher indicates worse fatigue. Mean (SD)	4.7 (2)	4.8 (1.2)
Activity level (counts per minute) Measured by accelerometer. Median (IQR)	296.5 (149.2)	195.2 (131.7)
Activity variability Amount of physical activity during peak activity hour for each day divided by the mean amount of physical activity on that day and averaged over 7 days. Higher scores indicated high activity variability and a stronger concentration of physical activity. Low scores suggested low variability and evenly spread physical activity throughout the day. Mean (SD)	4 (0.9)	3.9 (0.5)
Health-related quality of life Unclear which instrument used. Mean (SD)	43 (8.6)	42.3 (8)
Engagement in pacing Measured using 'Engagement in Pacing' subscale of the Activity Pacing and Risk of Overactivity Questionnaire. Evaluated how and based on what aspects participants modified their physical activity behaviour over the day. Scale 1-5. Higher scores indicated increased activity pacing. Mean (SD)	3.2 (0.8)	3.2 (0.7)

Characteristic	Tailored activity pacing intervention (N = 12)	Control (N = 12)
Perceived risk of overactivity Measured using 'Perceived Risk of Overactivity' subscale of the Activity Pacing and Risk of Overactivity Questionnaire. Scale 1-5. Higher score indicates increased risk of overactivity. Mean (SD)	3.5 (1.3)	3.2 (0.7)

Note that n reported in heading refers to the number randomised whereas characteristics are given for the intention to treat population (randomised with adequate baseline measures), as indicated in the table under 'number analysed' (n=11 for intervention group and n=10 for control group).

Outcomes

Study timepoints

- Baseline
- 4 week (Follow-up assessments performed at 4 weeks. Indirect relative to protocol as specified minimum of 3 months follow-up ideally.)

Results - raw data

Outcome	Tailored activity pacing intervention, Baseline, N = 11	Tailored activity pacing intervention, 4 week, N = 11	Control, Baseline, N = 10	Control, 4 week, N = 10
FSS - final value Fatigue Severity Scale. Scale 1-7. Mean (SD)	4.7 (2)	4.6 (1.9)	4.8 (1.2)	5.1 (1.1)

Outcome	Tailored activity pacing intervention, Baseline, N = 11	Tailored activity pacing intervention, 4 week, N = 11	Control, Baseline, N = 10	Control, 4 week, N = 10
Clinically significant improvement in fatigue Defined as a 0.5 point reduction on Fatigue Severity Scale compared to baseline No of events	n = NA ; % = NA	n = 2 ; % = 18.2	n = NA ; % = NA	n = 1 ; % = 11.1
Clinically significant improvement in fatigue Defined as a 0.5 point reduction on Fatigue Severity Scale compared to baseline Sample size	n = NA ; % = NA	n = 11	n = NA ; % = NA	n = 9

FSS - final value - Polarity - Lower values are better

Available case analyses extracted for the dichotomous FSS outcome based on information provided in the report.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS final value 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point of 4 weeks rather than the minimum of 3 months specified in the protocol as ideal)*

Results clinically significant improvement in FSS 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point of 4 weeks rather than the minimum of 3 months specified in the protocol as ideal)*

Afrasiabifar, 2016

Bibliographic Reference	**Afrasiabifar, A.; Mehri, Z.; Javad Sadat, S.; Ghaffarian Shirazi, H. R.; The Effect of Orem's Self-Care Model on Fatigue in Patients With Multiple Sclerosis: A Single Blind Randomized Clinical Trial Study; Iranian Red Crescent Medical Journal; 2016; vol. 18 (no. 8); e31955**

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	Iranian Registry of Clinical Trials: IRCT2015012020313N2.
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Unclear. Initially inpatient then community setting. Notes gathered at a university medical centre.
Study dates	Recruitment began at 07/23/2014 and lasted for 2 months.
Sources of funding	They received a grant from the deputy of research and technology of Yasuj university of Medical Sciences, Iran.
Inclusion criteria	The inclusion criteria included confirmation of diagnosis of MS disease by a neurologist, being under treatment and having medical records at reliable medical centers, conscious willingness to participate in the research.
Exclusion criteria	Known cognitive disorders.

Recruitment / selection of participants	People with MS under treatment who had medical records at the society of special diseases of the vice-chancellor in treatment affairs of Yasuj University of Medical Sciences, Iran, in 2014.
Intervention(s)	The nursing process of Orem's self-care model based on: a) Assessment of self-care needs (including universal, developmental and health deviation needs) and self-care agency; b) nursing diagnosis or self-care deficit; c) goal setting; a) nursing system design (including wholly compensatory, partially compensatory, and supportive-educative nursing systems) and methods of helping (including acting, guiding, teaching, supporting and providing an environment); b) planning; a) implementation; b) follow-up; c) evaluation. In those included, 4 were included in the partially compensatory and 28 were included in the supportive-educative nursing system. Orem's self-care model was applied during six sessions of 45-60 minutes in length (3 weeks) by 09/23/2014. After the sessions were over, the self-care model was applied for 4 weeks at home, terminating on 12/13/2014. In the follow-up stage, people completed the checklist of self-care self-reporting on a daily basis over 4 weeks and their level of obligation to Orem's model was controlled. Concomitant therapy: No additional information. Group vs. individual: Individual Delivered remotely vs. in person: In person? Unclear.
Population subgroups	According to type: See participant characteristics table. Majority relapsing-remitting. According to disability (EDSS): Not stated/unclear. Disease modifying treatment status: Not stated/unclear.
Comparator	No intervention was conducted, and the participants received only care and training routines. At the end of the research, nursing interventions were made available to them based on the supportive-educative nursing system. Including 5 people in the partially compensatory and 26 people in the supportive-educative nursing system groups.

	Concomitant therapy: No additional information.
Number of participants	63
Duration of follow-up	3 weeks of treatment, 4 weeks of self-care at home, 4 weeks of additional follow up
Indirectness	No indirectness.
Additional comments	No additional information.

Study arms

Self-management programme (Orem's self-care model) (N = 32)
The nursing process of Orem's self-care model based on: a) Assessment of self-care needs (including universal, developmental and health deviation needs) and self-care agency; b) nursing diagnosis or self-care deficit; c) goal setting; a) nursing system design (including wholly compensatory, partially compensatory, and supportive-educative nursing systems) and methods of helping (including acting, guiding, teaching, supporting and providing an environment); b) planning; a) implementation; b) follow-up; c) evaluation. In those included, 4 were included in the partially compensatory and 28 were included in the supportive-educative nursing system. Orem's self-care model was applied during six sessions of 45-60 minutes in length (3 weeks) by 09/23/2014. After the sessions were over, the self-care model was applied for 4 weeks at home, terminating on 12/13/2014. In the follow-up stage, people completed the checklist of self-care self-reporting on a daily basis over 4 weeks and their level of obligation to Orem's model was controlled.

Usual care (N = 31)

No intervention was conducted, and the participants received only care and training routines. At the end of the research, nursing interventions were made available to them based on the supportive-educative nursing system. Including 5 people in the partially compensatory and 26 people in the supportive-educative nursing system groups.

Characteristics

Arm-level characteristics

Characteristic	Self-management programme (Orem's self-care model) (N = 32)	Usual care (N = 31)
% Female Sample size	n = 26 ; % = 81.3	n = 21 ; % = 67.8
Mean age (SD) Mean (SD)	29 (6.5)	30.7 (8.44)
Ethnicity Nominal	NR	NR
Comorbidities Background of other diseases - yes Nominal	4	3
Duration of suffering from MS (Units not stated, ?months) Mean (SD)	52.3 (31.9)	42.8 (27.1)
Relapsing-remitting Sample size	n = 29 ; % = 90.6	n = 29 ; % = 93.5

Characteristic	Self-management programme (Orem's self-care model) (N = 32)	Usual care (N = 31)
Primary and secondary progressive Sample size	n = 3 ; % = 9.4	n = 2 ; % = 6.5

Outcomes

Study timepoints

- Baseline
- 11 week (This is close to 3 months and therefore has not been downgraded for indirectness. This will be included in the time period for 3-6 months.)

Self care management compared to usual care at 3-6 months - continuous outcomes (change score)

Outcome	Self-management programme (Orem's self-care model), Baseline, N = 32	Self-management programme (Orem's self-care model), 11 week, N = 32	Usual care, Baseline, N = 31	Usual care, 11 week, N = 31
Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) Scale range: 1-7, lower values are better Mean (SD)	6.22 (0.37)	-5.45 (0.52)	6.04 (0.4)	0.41 (0.38)

Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) - Polarity - Lower values are better

Self care management compared to usual care at 3-6 months - dichotomous outcomes

Outcome	Self-management programme (Orem's self-care model), Baseline, N = 32	Self-management programme (Orem's self-care model), 11 week, N = 32	Usual care, Baseline, N = 31	Usual care, 11 week, N = 31
Adverse events leading to withdrawal Nominal	NA	0	NA	0

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

- Self care management compared to usual care at 3-6months - continuous outcomes (change score) –
- Patient-reported outcome measures to assess MS fatigue (FatigueSeverityScale)-MeanSD
- Self-management programme (Orem's self-care model)-
- Usual care-t11

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Self-care management compared to usual care at 3-6months – dichotomous outcomes – Adverse events leading to withdrawal - Nominal-Self-management programme (Orem's self-care model)-Usual care-t11

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ahmadi, 2010

Bibliographic Reference	**Ahmadi, A.; Arastoo, A. A.; Nikbakht, M.; The effects of a treadmill training programme on balance, speed and endurance walking, fatigue and quality of life in people with multiple sclerosis; International sportmed journal; 2010; vol. 11 (no. 4); 389-397**

Study details

Secondary publication of another included study- see primary study for details	Ahmadi, A., Arastoo, A. A., Nikbakht, M. et al. (2013) Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients. Iranian red crescent medical journal 15(6): 449-454
Other publications associated with this study included in review	Ahmadi, Nikbakh, Arastoo, A et al. (2010) The Effects of a Yoga Intervention on Balance, Speed and Endurance of Walking, Fatigue and Quality of Life in People with Multiple Sclerosis. Journal of Human Kinetics 23(1): 71-78

Ahmadi, 2013

Bibliographic Reference	**Ahmadi, A.; Arastoo, A. A.; Nikbakht, M.; Zahednejad, S.; Rajabpour, M.; Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients; Iranian red crescent medical journal; 2013; vol. 15 (no. 6); 449-454**

Study details

Secondary publication of another included	

study- see primary study for details	
Other publications associated with this study included in review	Ahmadi, Nikbakh, Arastoo, A et al. (2010) The Effects of a Yoga Intervention on Balance, Speed and Endurance of Walking, Fatigue and Quality of Life in People with Multiple Sclerosis. Journal of Human Kinetics 23(1): 71-78 Ahmadi, A.; Arastoo, A. A.; Nikbakht, M. (2010) The effects of a treadmill training programme on balance, speed and endurance walking, fatigue and quality of life in people with multiple sclerosis. International sportmed journal 11(4): 389-397 These originally appeared to be separate studies on top of the 2013 paper, but upon review the baseline characteristics for the yoga and treadmill groups are almost identical for all of the reported values and the control groups across all three papers are again almost identical for most reported baseline characteristics, as well as the number in each group being identical across the papers for each group. Therefore, this paper was re-extracted with the 2013 paper as the main paper and any additional outcomes reported in the 2010 papers added to the extraction table.
Trial name / registration number	Not reported.
Study location	Iran
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Reports funding in one of the 2010 papers from Ahvaz Shahid Chamran University and Ahwaz Jundishapour University of Medical Sciences, Iran.
Inclusion criteria	Physician diagnosed MS with a self-assessed EDSS score between 1.0 and 4.0; ability to walk on the treadmill with or without hand support (without human assistance) and to be able to walk at a constant speed on a treadmill for 5 min; and

	no participation in any physical activity for at least three months prior to the study. Use of disease-modifying drugs was allowed.
Exclusion criteria	Cardiovascular disease, liver or kidney failure; symptomatic lung disease; diabetes; thyroid disorders; gout or orthopedic limitations; pregnant women; and cigarette smokers or drug addicts.
Recruitment / selection of participants	Screened from a waiting list for a rehabilitation program in Physiotherapy Clinic of the Jundishapour University of Medical Sciences, Iran.
Intervention(s)	Yoga - 8 weeks: Hatha yoga classes were 60 - 70 minutes in duration and there were three sessions per week. Hatha yoga has three basic components, postures (asanas), breathing techniques (pranayama) and meditation (dhyana). The postures started with stretching techniques followed by standing, supine and prone-lying and sitting postures. The yoga teacher was familiar with problems common to people with MS and used this to develop the programme. Each pose was held for approximately 10 - 30 seconds (even eight seconds for subjects who were unable to maintain some techniques) with resting periods between poses lasting 30 seconds to one minute. Patients were supported for the majority of poses, with a chair, Swiss ball or wall. Usually, classes began with a calmative music. The yoga class was set up in a physiotherapy clinic and supervised by a neurologist and a physiotherapist. Temperature was maintained at about 23-26 degrees C in the room during training to avoid problems with overheating. Treadmill training (aerobic exercise) - 8 weeks: supervised treadmill training (three times weekly) exercises for eight consecutive weeks. Each training session consisted of 30 minutes of treadmill exercise. The exercise class began and ended with about 10 minutes of stretching of muscles and flexion and rotation movements of the trunk and the lower limb. Training intensity was 40-75% age predicted maximal heart rate. Initial speed was based on baseline comfortable walking speed and was increased as directed by participants.
Population subgroups	None reported.
Comparator	Control: waitlist control group. Not well defined but assume continued usual lifestyle.

Number of participants	N=31 randomised, N=31 analysed
Duration of follow-up	Up to 8 weeks - end of treatment period
Indirectness	Outcome follow-up - 8 weeks is less than 3 months minimum specified in protocol
Method of analysis	Intention to treat - all randomised

Study arms

Yoga (N = 11)

Treadmill training - aerobic exercise (N = 10)

Control - routine treatment (N = 10)

Characteristics

Arm-level characteristics

Characteristic	Yoga (N = 11)	Treadmill training - aerobic exercise (N = 10)	Control - routine treatment (N = 10)
% Female Sample size	n = 11 ; % = 100	n = 10 ; % = 100	n = 10 ; % = 100
Mean age (SD)	32.27 (8.68)	36.8 (9.17)	36.7 (9.32)

Characteristic	Yoga (N = 11)	Treadmill training - aerobic exercise (N = 10)	Control - routine treatment (N = 10)
Mean (SD)			
Ethnicity Custom value	NR	NR	NR
Comorbidities Custom value	NR	NR	NR
Disease duration (years) Mean (SD)	4.72 (5.62)	5.6 (3.3)	5 (3.05)
EDSS score Scale 0-10. Higher indicates increased disability. Mean (SD)	2 (1.09)	2.4 (1.24)	2.25 (1.25)

Outcomes

Study timepoints

- Baseline
- 8 week (8 weeks - end of treatment period)

Results - raw data

Outcome	Yoga, Baseline, N = 11	Yoga, 8 week, N = 11	Treadmill training - aerobic exercise, Baseline, N = 10	Treadmill training - aerobic exercise, 8 week, N = 10	Control - routine treatment, Baseline, N = 10	Control - routine treatment, 8 week, N = 10
Fatigue Severity Score Scale possibly 1-7. Mean (SD)	3.98 (0.99)	2.44 (1.5)	3.46 (1.77)	1.9 (0.73)	4.17 (1.28)	4.23 (1.04)
MSQOL-54 physical health composite Scale usually 0-100. Mean (SD)	58.95 (13)	65.7 (11.5)	56.62 (12.3)	71.19 (10.1)	67.24 (12.87)	66.64 (12.3)
MSQOL-54 - mental health composite Scale usually 0-100. Mean (SD)	56.12 (9.7)	74.3 (15.34)	57.98 (13.88)	64.62 (15.12)	60.48 (15.53)	65.54 (14.89)
MSQOL-54 - change in health domain Scale usually 0-100. Mean (SD)	40.9 (34.45)	52.27 (23.59)	40 (37.63)	52.5 (27.51)	50 (23.57)	52.5 (27.51)

Outcome	Yoga, Baseline, N = 11	Yoga, 8 week, N = 11	Treadmill training - aerobic exercise, Baseline, N = 10	Treadmill training - aerobic exercise, 8 week, N = 10	Control - routine treatment, Baseline, N = 10	Control - routine treatment, 8 week, N = 10
Beck Depression Inventory Scale usually 0-63. Mean (SD)	17.36 (12.42)	11.09 (12.46)	8.5 (3.06)	5.6 (3.4)	11.9 (9.39)	12.5 (8.12)
Beck Anxiety Inventory Scale usually 0-63. Mean (SD)	12.45 (4.54)	6.45 (3.61)	7.9 (5.91)	6.1 (4.95)	7.5 (6.77)	8.2 (7.39)

Fatigue Severity Score - Polarity - Lower values are better

MSQOL-54 physical health composite - Polarity - Higher values are better

MSQOL-54 - mental health composite - Polarity - Higher values are better

MSQOL-54 - change in health domain - Polarity - Higher values are better

Beck Depression Inventory - Polarity - Lower values are better

Beck Anxiety Inventory - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 physical composite 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 mental health composite 8 weeks

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 change in health domain 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results Beck Depression Inventory 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results Beck Anxiety Inventory 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results FSS 8 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results FSS 8 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 physical composite 8 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 physical composite 8 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 mental health composite 8 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 mental health composite 8 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 change in health domain 8 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results MSQOL-54 change in health domain 8 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results Beck Depression Inventory 8 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results Beck Depression Inventory 8 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results Beck Anxiety Inventory 8 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Results Beck Anxiety Inventory 8 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 months specified in the protocol)*

Ahmadi, 2010

Bibliographic Reference	**Ahmadi; Nikbakh; Arastoo, A; .; Habibi, A-H.; The Effects of a Yoga Intervention on Balance, Speed and Endurance of Walking, Fatigue and Quality of Life in People with Multiple Sclerosis.; Journal of Human Kinetics; 2010; vol. 23 (no. 1); 71-78**

Study details

Secondary publication of another included study- see primary study for details	Ahmadi, A., Arastoo, A. A., Nikbakht, M. et al. (2013) Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients. Iranian red crescent medical journal 15(6): 449-454
Other publications associated with	Ahmadi, A.; Arastoo, A. A.; Nikbakht, M. (2010) The effects of a treadmill training programme on balance, speed and endurance walking, fatigue and quality of life in people with multiple sclerosis. International sportmed journal 11(4): 389-397

this study included in review	

Arab, 2019

Bibliographic Reference	**Arab, Mansour; Radfar, Ali; Madadizadeh, Naser; Pour, Zaynab Sadat Afsharian; Karzari, Zahra; The effect of massage therapy on fatigue of patients with multiple sclerosis; J Adv Pharm Educ Res; 2019; vol. 9; 45**

Study details

Trial name / registration number	11IRCT201611217844N
Study location	Iran
Study setting	likely outpatient
Study dates	Not reported
Sources of funding	Reported to be no support
Inclusion criteria	No history of using massage therapy; reading and writing and speaking literacy; not using fatigue-reducing medicines; fatigue severity score of 36 and above; affected by the disease for more than 6 months; not in the acute phase of the disease; having first-degree members of the family for home massage; non-pregnancy (pregnancy intention) in women; lack of physical injury in the organs and spinal cord; and no history of recent seizure, asthma and allergy.
Exclusion criteria	Affected by other physical and mental diseases; increase in the severity of disease leading to hospitalization of the patient or meaning it was not possible to perform the massage therapy program; unwillingness to cooperate; non-continuation of

	the massage program for any reason by patient or family (less than 10 sessions); being affected by acute diseases, infection, cold and pain during the study; and having ulcer, redness and any lesions in the neck, spinal cord and organs during the study, which prevents the intervention.
Recruitment / selection of participants	Recruited from those referred to a treatment centre.
Intervention(s)	Massage intervention: three techniques used for massage therapy (four techniques for feet massage, three techniques for back, two techniques for neck and four techniques for hand). Family member taking responsibility for delivering the home massage were completely trained by physiotherapist at a one-hour session. Each patient in the intervention group received the massage therapy programme three days per week for 4 weeks and 20 min per session. The massage time was planned with consent of the patient before bedtime. The minimum number of massage therapy sessions to enter the information in the data analysis stage included 10 sessions. Moreover, an SMS was sent to patients and a weekly massage table was provided to them as a reminder of planned sessions.
Population subgroups	None
Comparator	Control: routine medical care only for 4 weeks.
Number of participants	80 randomised, 80 analysed
Duration of follow-up	4 weeks - end of intervention period
Indirectness	Outcome - time-point reported at <3-month minimum specified in the protocol
Additional comments	Appears to be intention to treat but missing data not mentioned

Study arms

Massage (N = 40)

Control - routine medical care (N = 40)

Characteristics

Arm-level characteristics

Characteristic	Massage (N = 40)	Control - routine medical care (N = 40)
% Female Sample size	n = 33 ; % = 82.5	n = 27 ; % = 67.5
Mean age (SD) Mean (SD)	33.88 (8.28)	32.88 (8.69)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	7.73 (6.1)	5.55 (5.79)

Outcomes

Study timepoints

- Baseline
- 4 week (4-weeks - end of intervention period)

Results - raw data

Outcome	Massage, Baseline, N = 40	Massage, 4 week, N = 40	Control - routine medical care, Baseline, N = 40	Control - routine medical care, 4 week, N = 40
Fatigue Severity Scale Scale 9-63. Values at baseline appear to be quite low suggesting limited fatigue at baseline. Mean (SD)	48.3 (9.78)	43.89 (8.33)	47.72 (10.25)	46.91 (7.07)
Fatigue relief and effectiveness of fatigue reduction - VAS scale Scale 0-10. Mean (SD)	4.15 (2.52)	6.85 (2.33)	5.15 (3.17)	5.55 (3.07)

Fatigue Severity Scale - Polarity - Lower values are better

Fatigue relief and effectiveness of fatigue reduction - VAS scale - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Results fatigue relief/effectiveness of fatigue reduction VAS 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3-month minimum specified in protocol)*

Atashi, 2014

Bibliographic Reference	**Atashi, Vajihe; The effect of SSBM massage on anxiety and fatigue of patients with multiple sclerosis; journal of applied environmental and biological sciences; 2014; vol. 4 (no. 8); 217-223**

Study details

Trial name / registration number	Not reported

Study location	Iran
Study setting	Likely outpatient
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	20-45 years old; interested in taking part in the study; length of the disease over 6 months; no history of back massage in the past 6 months prior to the study; lack of any complication as a prohibition to administrate the intervention (not being in acute phase of the disease, no back or spinal cord injury, no pregnancy, no back wound or inflammation); and the ability to communicate for data collection and attending the study.
Exclusion criteria	Loss of patients' motivation to remain in study and a disturbance in patients' health due to any reasons.
Recruitment / selection of participants	Subjects were selected by purposive sampling based on inclusion criteria. Sampling was continued during 2 months to achieve the sufficient sample size for study and participants were randomly assigned to study and control groups (alternation)
Intervention(s)	Slow stroke back massage: massage was administrated in a room in MS association building with conventional conditions for massage therapy (quiet with mild light and room temperature of 27°C and with no environmental stimulations) for seven 10-min sessions by the researcher and a co-researcher. Unclear whether sessions were delivered weekly or twice weekly for example. Massage therapy was administrated by the researcher with the patient sat on massage chair with his/her head on a pillow. Small circular massage was conducted on patients' neck by researcher's thumb. Slow stroke back massage was administrated from neck area to sacrum by the researcher's palm and repetition of the action by her other palm on the other side of spine in a reverse direction simultaneously (toward neck). It also included slow stroke with thumb in both sides of spine from shoulder to waist and sweep stroke from neck nearly down to sacrum by two palms.
Population subgroups	None
Comparator	Control - not defined, assume no intervention.

Number of participants	62 randomised, 62 assumed analysed as no missing data reported
Duration of follow-up	Unclear - seven massage sessions but unclear over how many weeks these were delivered
Indirectness	Outcome - unclear if time-point of at least 3 months, unlikely given only seven sessions which are 10 min duration (even if one session weekly wouldn't add up to 3 months)
Additional comments	Assume intention to treat as no missing data/switching mentioned

Study arms

Slow Stroke Back Massage (N = 32)

Control (N = 30)

Not defined - assume no intervention

Characteristics

Arm-level characteristics

Characteristic	Slow Stroke Back Massage (N = 32)	Control (N = 30)
% Female Sample size	n = 28 ; % = 87.5	n = 22 ; % = 73.3

Characteristic	Slow Stroke Back Massage (N = 32)	Control (N = 30)
Mean age (SD) Custom value	NR	NR
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
No recurrence Sample size	n = 19 ; % = 59.4	n = 12 ; % = 40
Once or twice per year Sample size	n = 10 ; % = 31.3	n = 12 ; % = 40
At least three times per year Sample size	n = 3 ; % = 9.4	n = 6 ; % = 20
<1 year Sample size	n = 7 ; % = 21.9	n = 7 ; % = 23.3
1-4 years Sample size	n = 16 ; % = 50	n = 13 ; % = 43.3
5-9 years	n = 5 ; % = 15.6	n = 6 ; % = 20

Characteristic	Slow Stroke Back Massage (N = 32)	Control (N = 30)
Sample size		
10-14 years Sample size	n = 2 ; % = 6.3	n = 3 ; % = 10
15-19 years Sample size	n = 2 ; % = 6.3	n = 1 ; % = 3.4

Outcomes

Study timepoints

- Baseline
- 7 week (Unclear intervention length - 7 sessions but unclear if this was once weekly or multiple times a week, in which case the time-point would be <7 weeks)

Results - raw data

Outcome	Slow Stroke Back Massage, Baseline, N = 32	Slow Stroke Back Massage, 7 week, N = 30	Control, Baseline, N = 32	Control, 7 week, N = 30
Fatigue Severity Scale Scale 9-63. Mean (SD)	48.31 (6.94)	33.12 (7.16)	48.86 (7.25)	53.2 (7.52)
Spielberger Overt Anxiety Questionnaire	51.53 (4.51)	38.65 (5.11)	51.63 (4.96)	52.13 (4.71)

Outcome	Slow Stroke Back Massage, Baseline, N = 32	Slow Stroke Back Massage, 7 week, N = 30	Control, Baseline, N = 32	Control, 7 week, N = 30
State-Trait anxiety measured. Scale 20-80. Mean (SD)				

Fatigue Severity Scale - Polarity - Lower values are better

Spielberger Overt Anxiety Questionnaire - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS end of intervention

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(duration of intervention and time-point reported at unclear, but likely <3-month minimum specified in the protocol)*

Results Spielberger anxiety end of intervention

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(duration of intervention and time-point reported at unclear, but likely <3-month minimum specified in the protocol)*

Backus, 2020

Bibliographic Reference	**Backus, D.; Moldavskiy, M.; Sweatman, W. M.; Effects of Functional Electrical Stimulation Cycling on Fatigue and Quality of Life in People with Multiple Sclerosis Who Are Nonambulatory; International Journal of Ms Care; 2020; vol. 22 (no. 4); 193-200**

Study details

Trial name / registration number	Not reported.
Study location	USA
Study setting	Outpatient
Study dates	Not reported.

Sources of funding	Funded by National Multiple Sclerosis Society and supplemented by private donations to Shepherd Center.
Inclusion criteria	≥18 years of age; physician diagnosed as having MS; non-ambulatory (used a wheelchair for indoor and outdoor mobility, with EDSS score >6.5); and experiencing fatigue as indicated on the Fatigue Severity Scale (mean score >2.3, the mean in healthy adults).
Exclusion criteria	Any neuromuscular, musculoskeletal or cardiovascular injury or disease; any condition that prevented them from safely exercising on the functional electrical stimulation cycle, such as an existing pacemaker, defibrillator or other implanted electronic or metallic device (other than a Baclofen pump); had unstable long bone fractures of the lower limb or trunk; had allergy to surface electrodes or conductive gel; could not tolerate sitting for at least 1 h; experienced a diagnosed relapse in the past 6 months; and if electrical stimulation could not elicit a muscle contraction.
Recruitment / selection of participants	Recruited via flyers, referrals from providers in the MS clinic and at local MS-related events (e.g. National MS Society walks or support group activities).
Intervention(s)	Functional electrical stimulation cycling. 12-week training intervention, with three sessions per week. Performed while seated in wheelchair. Trained exercise staff assisted each participant in applying the surface electrodes over the muscle bellies of the gluteus maximus, hamstrings, and quadriceps bilaterally and safely positioning the participant's lower limbs on the pedals of the RT300 device. Participants cycled volitionally with assistance from the electrical stimulation as needed and with oversight for safety by the exercise staff. Each session consisted of 2 min passive warm-up phase (no volitional cycling or electrical stimulation), followed by 30 min of volitional cycling or assisted with electrical stimulation and ended with a 2 min passive cycling cool-down phase. During the passive phases, the ergometer propelled the pedals at 35 rpm and the goal during the active phase was to reach a target cycling speed of 35 to 50 rpm. Stimulation parameters were a pulse width of 200 microseconds and frequency of 50 Hz. Stimulation intensity varied based on patient tolerance and amount of stimulation required to achieve target cycling speed. Resistance was added in 0.14 Nm increments once they could pedal actively (with or without stimulation) for 30 min at 35-50 rpm for three consecutive sessions without defaulting to passive mode.
Population subgroups	None reported.

Comparator	Waitlist control group. Encouraged to keep activities and medications constant and completed same data collection procedures as training group.
Number of participants	N=21 randomised (n=12 completed and were analysed)
Duration of follow-up	Up to 12 weeks - end of treatment period
Indirectness	None.
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Functional electrical stimulation cycling (N = 12)

Performed functional electrical stimulation cycling while seated in wheelchair.

Control (N = 9)

Waitlist control group.

Characteristics

Arm-level characteristics

Characteristic	Functional electrical stimulation cycling (N = 12)	Control (N = 9)
% Female Sample size	n = 3 ; % = 50	n = 4 ; % = 67
Mean age (SD) Mean (SD)	56.17 (10.01)	54.67 (11.55)
White Sample size	n = 2 ; % = 33	n = 3 ; % = 50
Black Sample size	n = 4 ; % = 67	n = 3 ; % = 50
Comorbidities Text	NR	NR
Relapsing-remitting MS Sample size	n = 2 ; % = 33	n = 1 ; % = 17
Secondary progressive MS Sample size	n = 3 ; % = 50	n = 1 ; % = 17
Not specified Sample size	n = 1 ; % = 17	n = 4 ; % = 67

Characteristic	Functional electrical stimulation cycling (N = 12)	Control (N = 9)
FSS Fatigue Severity Scale. Scale not reported but likely 1-7. Higher score indicates worse fatigue. Mean (SD)	3.9 (0.98)	4.98 (1.51)
Medical Outcomes Study Pain Effects Scale score Scale possibly 6-30. Higher indicates worse impact of pain. Mean (SD)	12.17 (8.23)	14.67 (4.63)
Median EDSS score Expanded Disability Status Scale score. Scale 0-10. Higher indicates increased disability. Median	7.0	7.5
7.0 Sample size	n = 3 ; % = 50	n = 3 ; % = 50
7.5 Sample size	n = 2 ; % = 33	n = 1 ; % = 17
8.0 Sample size	n = 1 ; % = 17	n = 0 ; % = 0
8.5 Sample size	n = 0 ; % = 0	n = 2 ; % = 33

Study provides results for only those that were analysed, meaning the sample size was n=6 in each of the two groups for the characteristics listed in the table below.

Outcomes

Study timepoints

- Baseline
- 12 week (Time-point unclear but appears to report results at the end of the treatment period (12 weeks).)

Results - change scores at end of treatment

Outcome	Functional electrical stimulation cycling, 12 week vs Baseline, N = 6	Control, 12 week vs Baseline, N = 6
5-Item MFIS score. Modified Fatigue Impact Scale. Scale not reported in paper, based on information from elsewhere likely to be 0-20. Baseline values not reported. Mean (SD)	-2.5 (4.55)	0.17 (4.36)
Fatigue Scale of Motor and Cognitive Functions - Total score Scale not reported but information from elsewhere suggests it is usually 20-100. Baseline values not reported. Mean (SD)	-4.67 (4.13)	-2.17 (8.54)
Fatigue Scale of Motor and Cognitive Functions - Cognitive score Scale not reported but information from elsewhere suggests it is usually 10-50. Baseline values not reported. Mean (SD)	-2.5 (3.39)	-1.5 (3.39)

Outcome	Functional electrical stimulation cycling, 12 week vs Baseline, N = 6	Control, 12 week vs Baseline, N = 6
Fatigue Scale of Motor and Cognitive Functions - Motor score Scale not reported but information from elsewhere suggests it is usually 10-50. Baseline values not reported. Mean (SD)	-2.17 (3.54)	-0.67 (5.82)
MSQOL-54 - physical health composite MS Quality of Life-54. Scale not reported but usually 0-100 based on information from elsewhere. Baseline values not reported. Mean (SD)	6.77 (5.25)	-2.18 (6.77)
MSQOL-54 - mental health composite MS Quality of Life-54. Scale not reported but usually 0-100 based on information from elsewhere. Baseline values not reported. Mean (SD)	1.77 (14.11)	1.05 (9.64)
MSQOL-54 - change in health domain MS Quality of Life-54. Scale not reported but usually 0-100 based on information from elsewhere. Baseline values not reported. Mean (SD)	-4.17 (10.21)	0 (15.81)
PHQ-9 - depression Patient Health Questionnaire-9. Scale not reported but based on information from elsewhere is usually 0-27. Mean (SD)	0.33 (2.42)	-2.5 (5.47)

5-Item MFIS score. - Polarity - Lower values are better

Fatigue Scale of Motor and Cognitive Functions - Total score - Polarity - Lower values are better

Fatigue Scale of Motor and Cognitive Functions - Cognitive score - Polarity - Lower values are better

Fatigue Scale of Motor and Cognitive Functions - Motor score - Polarity - Lower values are better

MSQOL-54 - physical health composite - Polarity - Higher values are better

MSQOL-54 - mental health composite - Polarity - Higher values are better

MSQOL-54 - change in health domain - Polarity - Higher values are better

PHQ-9 - depression - Polarity - Lower values are better

N= 6 in each group completed the training and were analysed.

Results - raw data

Outcome	Functional electrical stimulation cycling, Baseline, N = NA	Functional electrical stimulation cycling, 12 week, N = 12	Control, Baseline, N = NA	Control, 12 week, N = 9
Adverse events (all led to withdrawal) Intervention: wound on foot (n=1), pressure sore reopened (n=1), knee pain (n=1), unhealed wound (n=1) and pseudo relapse (n=1); control: change in medication/relapse (n=1). All reported not to be related to intervention. No of events	n = NA ; % = NA	n = 5 ; % = 46	n = NA ; % = NA	n = 1 ; % = 14
Adverse events (all led to withdrawal) Intervention: wound on foot (n=1), pressure sore reopened (n=1), knee pain (n=1), unhealed wound (n=1) and pseudo relapse (n=1); control: change in medication/relapse (n=1). All reported not to be related to intervention.	NA	11	NA	7

Outcome	Functional electrical stimulation cycling, Baseline, N = NA	Functional electrical stimulation cycling, 12 week, N = 12	Control, Baseline, N = NA	Control, 12 week, N = 9
Number analysed				
Completion of all 36 training sessions Limited information given. No formal asssesment of patient satisfaction/acceptability. Text	NA	Reported that all but one (presumably 5/6 analysed in this group) completed all of the 36 sessions.	NA	NR
Decrease in fatigue on MFIS Could be any decrease and not a certain threshold for reduction No of events	n = NA ; % = NA	n = 4 ; % = 67	n = NA ; % = NA	n = 3 ; % = 50
Decrease in fatigue on MFIS Could be any decrease and not a certain threshold for reduction Number analysed	NA	6	NA	6
Decrease in fatigue on FMSC total score Could be any decrease and not a certain threshold for reduction No of events	n = NA ; % = NA	n = 5 ; % = 83	n = NA ; % = NA	n = 4 ; % = 67
Decrease in fatigue on FMSC total score Could be any decrease and not a certain threshold for reduction Number analysed	NA	6	NA	6

For adverse events, an available case analysis could be extracted (n=11 in intervention group and n=7 in control group). N=6 in each group analysed for fatigue reduction outcome.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS 5-item change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results FSMC total score change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results FSMC cognitive scale change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results FSMC motor scale change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 physical health composite change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 mental health composite change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 change in health subdomain change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results PHQ-9 depression change from baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events (all led to withdrawal) at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results completion of all 36 sessions 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results reduction in fatigue on MFIS vs. baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results reduction in fatigue on MFSC total score vs. baseline at 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Barlow, 2009

Bibliographic Reference	**Barlow, J.; Turner, A.; Edwards, R.; Gilchrist, M.; A randomised controlled trial of lay-led self-management for people with multiple sclerosis; Patient Educ Couns; 2009; vol. 77 (no. 1); 81-9**

Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	Not reported
Study location	UK
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Funded by a grant from the MS Society.
Inclusion criteria	aged ≥18 years; diagnosis of MS; ability to communicate in and understand English; and ability to complete the questionnaire
Exclusion criteria	inability to understand and participate in a programme delivered in English.

Recruitment / selection of participants	Patients identified through databases held by the MS Society with additional recruitment conduced via MS Society website and local media. Those that registered an interest in the study were sent letters inviting participation. Following completion of written consent and completion of baseline questionnaires, the group that expressed interest in attending the Chronic Disease Self-Management Course were randomly allocated to intervention or waitlist control groups.
Intervention(s)	Chronic Disease Self-Management Course (CDSMC). Not disease-specific and designed for participants with any chronic disease. Aims to promote the ability of each individual to select the self-management tool that will meet their needs at a given time. Despite not being MS-specific, the programme was pioneered by voluntary organisations including the MS Society. Includes 6 weekly sessions that are delivered in the community setting by pairs of tutors trained in course delivery, each of which last ~2 h. Each session guided by a manual to ensure consistency of content. Course utilises principles of self-efficacy theory as it provides mastery experience, role modelling, persuasion and reinterpretation of physiological and affective states to aid participants in making changes. It covers general topics including: overview of self-management principles, exercise, pain and fatigue management, relaxation techniques (e.g. guided imagery and breathing), dealing with depression, nutrition, communicating with family and health professionals, solving problems and setting goals. Goals were set weekly and should be personally relevant, realistic but challenging, have proximal outcomes and depend largely on the person's own efforts. Reporting of goals achieved was performed at the next session. Course is largely interactive with short lectures to introduce topics, group discussion, problem solving, role plays and experience of trying out skills highlighted on the course.
Population subgroups	None reported
Comparator	Waitlist control group. Continued usual lifestyle and given the opportunity to attend the course after the 12 month follow-up.
Number of participants	142 in randomised groups (further 74 were part of a control group not randomised that did not wish to take part in the trial). 56/78 and 43/78 had data available at 4 and 12 months, respectively, in the intervention group. 49/64 and 32/64 had data available at 4 and 12 months, respectively, in the waitlist control group.
Duration of follow-up	Up to 12 months, with 4 and 12 month time-points reported
Indirectness	None

Method of analysis	Intention to treat - last observation carried forward for missing data

Study arms

Chronic Disease Self-Management Course (N = 78)

Lay-led self-management intervention. Not disease-specific and aims to promote individual ability to select the self-management tool that will meet their individual needs. Self-management as defined in the study and although it contains a fatigue management element it is not limited to fatigue.

Waitlist control (N = 64)

Waitlist control group. Given the opportunity to take part in the course after 12 month follow-up.

Characteristics

Arm-level characteristics

Characteristic	Chronic Disease Self-Management Course (N = 78)	Waitlist control (N = 64)
% Female Sample size	n = 57 ; % = 73	n = 44 ; % = 69
Mean age (SD) Mean (SD)	48.2 (10.1)	50.7 (11.7)
White Sample size	n = 77 ; % = 99	n = 57 ; % = 89

Characteristic	Chronic Disease Self-Management Course (N = 78)	Waitlist control (N = 64)
Other health problems Such as arthritis, asthma and high blood pressure Sample size	n = 28 ; % = 36	n = 18 ; % = 28
Time since diagnosis (years) Mean (SD)	9.6 (8.3)	12.1 (7.4)
Self-management self-efficacy Scale 10-70. Higher is better. Mean (SD)	42.8 (11.6)	45.4 (12.5)
MS self-efficacy Scale 11-44. Higher is better. Mean (SD)	28.2 (5.6)	29.4 (5.7)
MSIS-29 PHYS score Multiple Sclerosis Impact Scale Physical subscale. Scale 0-100. Lower is better. Mean (SD)	50.4 (25.4)	44 (27.3)
MSIS-29 PSYCH score Multiple Sclerosis Impact Scale Psychological subscale. Scale 0-100. Lower is better. Reported to be significantly different at baseline. Mean (SD)	46.3 (23.7)	36.1 (23)

Characteristic	Chronic Disease Self-Management Course (N = 78)	Waitlist control (N = 64)
Pain VAS Scale 0-10. Lower is better. Mean (SD)	3.2 (2.8)	2.9 (2.7)
Fatigue VAS Scale 0-10. Lower is better. Mean (SD)	5.7 (2.8)	4.8 (2.8)
HADS - anxiety Hospital Anxiety and Depression Scale. Scale 0-21. Lower is better. Mean (SD)	8.5 (4.3)	7.2 (4.3)
HADS - depression Hospital Anxiety and Depression Scale. Scale 0-21. Lower is better. Mean (SD)	6.7 (3.8)	6.3 (4.2)
Cognitive symptom management Measured on Cognitive Symptom Management Scale with 5 items. Scale 0-25. Higher is better. Mean (SD)	7.2 (5.1)	5.9 (4.3)
Communication with physician Measured using Communication With Physician Scale. Scale 0-25. Higher is better. Mean (SD)	12.8 (5.6)	13.5 (6.1)

Outcomes

Study timepoints

Baseline

- 4 month (4 month follow-up.)
- 12 month (12 month-follow-up.)

Results - change from baseline

Outcome	Chronic Disease Self-Management Course, 4 month vs Baseline, N = 78	Chronic Disease Self-Management Course, 12 month vs 4 month, N = 78	Waitlist control, 4 month vs Baseline, N = 64	Waitlist control, 12 month vs 4 month, N = 64
Fatigue VAS Scale 0-10. Mean (99% CI)	-0.3 (-1.0 to 0.4)	0.3 (-0.8 to 1.4)	-0.8 (-1.6 to 0.0)	1.5 (0.3 to 2.8)
MSIS-29 PHYS score Multiple Sclerosis Impact Scale Physical subscale. Scale 0-100. Mean (99% CI)	-3.3 (-7.3 to 0.7)	1.9 (-3.1 to 6.9)	3.3 (-1.1 to 7.8)	1.2 (-4.4 to 6.8)
MSIS-29 PSYCH score Multiple Sclerosis Impact Scale Psychological subscale. Scale 0-100. Mean (99% CI)	-5.9 (-12.2 to 0.4)	1.0 (-5.9 to 7.7)	-2.3 (-9.0 to 4.4)	-1.1 (-8.9 to 6.8)

Outcome	Chronic Disease Self-Management Course, 4 month vs Baseline, N = 78	Chronic Disease Self-Management Course, 12 month vs 4 month, N = 78	Waitlist control, 4 month vs Baseline, N = 64	Waitlist control, 12 month vs 4 month, N = 64
HADS - anxiety Hospital Anxiety and Depression Scale. Scale 0-21. Mean (99% CI)	-0.7 (-1.6 to 0.1)	0.2 (-0.8 to 1.2)	-0.2 (-1.2 to 0.7)	-0.4 (-1.3 to 0.5)
HADS - depression Hospital Anxiety and Depression Scale. Scale 0-21. Mean (99% CI)	-0.9 (-1.6 to 0.1)	0.6 (-0.2 to 1.5)	0.0 (-0.8 to 0.8)	-0.4 (-1.3 to 0.5)

Fatigue VAS - Polarity - Lower values are better

MSIS-29 PHYS score - Polarity - Lower values are better

MSIS-29 PSYCH score - Polarity - Lower values are better

HADS - anxiety - Polarity - Lower values are better

HADS - depression - Polarity - Lower values are better

Results adjusted using ANCOVA for following covariates: baseline measures of the specific outcome and MSIS-29 psychological subscale at baseline for 4 month time-point and baseline value of MSIS-29 psychological subscale only for 12 month time-point. 4-month results given relative to baseline and 12-month results relative to 4-month time-point.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results fatigue change from baseline at 4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results fatigue change from 4 months to 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 Physical change from baseline at 4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 Physical change from 4 months to 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 Psychological change from baseline at 4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 Psychological change from 4 months to 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results HADS anxiety change from baseline at 4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results HADS anxiety change from 4 months to 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results HADS depression change from baseline at 4 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results HADS depression change from 4 months to 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Bastani, 2015

Bibliographic Reference	**Bastani, F.; Sobhani, M.; Emamzadeh Ghasemi, H. S.; Effect of acupressure on fatigue in women with multiple sclerosis; Global Journal of Health Science; 2015; vol. 7 (no. 4); 375-81**

Study details

Trial name / registration number	None reported
Study location	Iran
Study setting	Community
Study dates	Not reported
Sources of funding	Tehran University of Medical Sciences
Inclusion criteria	(a) age at least 18 years, (b) stable vital signs, (c) no scar, lesion, scratch or deformities on the skin of selected areas (d) being literate, (e) complaining of fatigue (assessed by the Fatigue Severity Scale [FSS] with the score of 5 and over, (f) no history of smoking, substance or sedatives use and (g) not pregnant.
Exclusion criteria	Lack of the subjects' willingness to continue participation in the trial for any reason, such as complications, or known serious physical or mental diseases during the trial. Also, the women who had not feeling of warmth, heaviness, or numbness during applying acupressure on the points LI4, ST36, and SP6 for any reason were excluded from the study
Recruitment / selection of participants	Women with MS at Tehran Multiple Sclerosis (MS) Association
Intervention(s)	The experimental group were received acupressure, at the acupoints (ST36, SP6, LI4) and the placebo group, were received touching at the same points in the first session. The duration of each session of the intervention was 3 minutes

	bilaterally, for each group. In other words, the acupressure intervention, i.e. pressure on the acupoints, was conducted for three minutes (several cycles including 10 seconds consecutive pressure and 2 seconds rest) on each of the mentioned points, and then this was repeated for the opposite side of the body. This procedure took 18 minutes for each intervention per day. During training session the researcher demonstrated the procedure in one part of the patient's body, and asked her to do the same herself on the other side of the body. The training was over when the correct practice by the patients was ensured. It was explained to the patients that the accuracy of the points or channels are confirmed by the client feeling warmth, heaviness, or numbness in that special areas.
Population subgroups	None
Comparator	The experimental group were received acupressure, at the acupoints (ST36, SP6, LI4) and the placebo group, were received touching at the same points in the first session. The duration of each session of the intervention was 3 minutes bilaterally, for each group. In other words, the acupressure intervention, i.e. pressure on the acupoints, was conducted for three minutes (several cycles including 10 seconds consecutive pressure and 2 seconds rest) on each of the mentioned points, and then this was repeated for the opposite side of the body. This procedure took 18 minutes for each intervention per day. During training session the researcher demonstrated the procedure in one part of the patient's body, and asked her to do the same herself on the other side of the body. The training was over when the correct practice by the patients was ensured. It was explained to the patients that the accuracy of the points or channels are confirmed by the client feeling warmth, heaviness, or numbness in that special areas. These procedures were also performed in the placebo group but by touching rather than pressing the required three points that were similar to the experimental group. Also the placebo group was not given the pamphlet.
Number of participants	100
Duration of follow-up	4 weeks after the intervention
Indirectness	Outcome indirectness due to short duration of follow-up

Study arms

Acupressure (N = 50)

Acupressure at the acupoints (ST36, SP6, LI4)

Control (N = 50)

Touching at the same points in the first session

Characteristics

Study-level characteristics

Characteristic	Study (N = 100)
Ethnicity Custom value	Iranian

Arm-level characteristics

Characteristic	Acupressure (N = 50)	Control (N = 50)
% Female Sample size	n = 50 ; % = 100	n = 50 ; % = 100
Mean age (SD) Mean (SD)	31.88 (6.21)	31.9 (6.33)

Characteristic	Acupressure (N = 50)	Control (N = 50)
Duration of MS (years) Mean (SD)	2.86 (1.27)	3.16 (1.18)

Outcomes

Study timepoints

Baseline

4 week (End of treatment)

Fatigue Severity Scale

Outcome	Acupressure, Baseline, N = 50	Acupressure, 4 week, N = 50	Control, Baseline, N = 50	Control, 4 week, N = 50
Fatigue Severity Scale Mean (SD)	88.5 (55)	65.5 (83)	82.5 (54)	95.5 (59)

Fatigue Severity Scale - Polarity - Lower values are better

The fatigue severity scale (FSS) measures the patient’s ability to function with nine statements each of which are scored from 1-7 in Likert scale, by classifying them as 1 (completely disagree) to 7 (completely agree). The final score is calculated by averaging the sum of responses divided by nine. Therefore, the mean score was used to compare the severity of fatigue in the two groups

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Fatigue Severity Scale 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up is less than minimum of three months in protocol)*

Blikman, 2017

Bibliographic Reference	**Blikman, L. J.; van Meeteren, J.; Twisk, J. W.; de Laat, F. A.; de Groot, V.; Beckerman, H.; Stam, H. J.; Bussmann, J. B.; group, Trefams-Ace study; Effectiveness of energy conservation management on fatigue and participation in multiple sclerosis: A randomized controlled trial; Multiple Sclerosis; 2017; vol. 23 (no. 11); 1527-1541**

Study details

Trial name / registration number	Part of the TREFAMS-ACE programme consisting of multiple trials (Treating Fatigue in MS with Aerobic Training, Cognitive Behavioural Therapy and Energy Conservation Management). Trial registration number: ISRCTN82353628.
Study location	The Netherlands
Study setting	Outpatient
Study dates	Patients recruited between November 2011 and March 2014
Sources of funding	Financially supported by Fonds NutsOhra grant. Funder had no role in design or conduct of the study, data collection, data management, data analysis, data interpretation, preparation and writing of the manuscript nor the approval of the manuscript and decision to submit for publication. No conflicts of interest reported.
Inclusion criteria	Definitive diagnosis of MS; severe fatigue (≥35 on fatigue subscale of Checklist Individual Strength - CIS20r); aged between 18 and 70 years; ambulant (EDSS ≤6.0); no evident signs of an MS exacerbation or corticosteroid treatment within previous 3 months; and no infections, anaemia or thyroid dysfunction.
Exclusion criteria	Depression (HADS-depression score >11); severe comorbidity (Cumulative Illness Rating Scale item scores ≥3); primary sleep disorders; current pregnancy or having given birth within last 3 months; and newly initiated pharmacological (e.g. amantadine) or non-pharmacological treatment for fatigue (e.g. energy conservation management, aerobic training, cognitive behavioural therapy or other) within the last 3 months.
Recruitment / selection of participants	Potentially eligible people with MS initially recruited and informed by MS teams (rehabilitation, physicians, MS nurses and neurologists) at two participating outpatient clinics. Rehabilitation physician checked the inclusion and exclusion criteria.
Intervention(s)	Individual energy conservation management. Aim to promote positive attitude aimed at active decision-making and the optimum use of available energy to fit unique needs of each individual. Also intends to reduce the impact and severity of fatigue, to increase patients' use of energy-conserving strategies and to improve their confidence in their management of fatigue. Original content of a group course 'Managing Fatigue' by Packer et al. was adapted to fit 12 one-on-one 45 min

	sessions over a 4 month intervention period. Content of the energy conservation management programme given in the form of a booklet to participants. Attention was given to individual learning and approaching style to produce the programme contents. Motivational interviewing used as a communication technique to assist in exploring and resolving ambivalence to change. Energy conservation strategies were an important part of each session. Various teaching methods used including giving information, discussions, long- and short-term goal setting, practice activities and homework activities, all of which aimed to assist integration of energy conservation principles into everyday tasks. Sessions were delivered by trained occupational therapists that were already familier with MS, energy conservation strategies and the Packer group course 'Managing Fatigue'. Had to be qualified in motivational interviewing techniques. All sessions were performed by the same therapist for each participant.
Population subgroups	None reported
Comparator	Information-only control group. Three MS nurse consultations of 45 min each by experienced nurses over 4 months. Nurses trained to avoid providing treatment or treatment advice but instead gave standardised information about MS-related fatigue. The aim of this control group was to control for attention and information about fatigue. Nurses were trained in how to deliver this information without providing advice about treatment and informed of the restrictions about referral of patients to other first or second line healthcare professionals within the hospital. Participants also provided with a brochure to provide standardised information about MS-related fatigue. Each patient saw the same MS nurse at each of the sessions. In some cases face-to-face sessions were replaced with phone sessions.
Number of participants	86 randomised (n=76 analysed in modified intention to treat analysis - those randomised with at least one follow-up measurement).
Duration of follow-up	Up to 12 months follow-up with outcomes reported at 8, 16, 26 and 52 weeks after starting the treatment. Time-points 26 and 52 were considered to best match the two follow-up time-points specified in the protocol and were therefore extracted.
Indirectness	None
Method of analysis	Modified intention to treat - those randomised with at least one follow-up measurement

Study arms

Energy conservation management (N = 42)

Individual energy conservation management programme. Developed based on the group programme developed by Packer et al. Consisted of 12 sessions with an occupational therapist over 4 months.

Information only control (N = 44)

Three MS nurse consultations lasting 45 min each performed by experienced nurses over 4 months.

Characteristics

Arm-level characteristics

Characteristic	Energy conservation management (N = 42)	Information only control (N = 44)
% Female number (%)	34 (81.0%)	30 (68.2%)
Mean age (SD) Mean (SD)	47.7 (11)	46.6 (11.5)
Ethnicity Text	NR	NR
Comorbidities Text	NR	NR
Relapsing remitting MS	n = 32 ; % = 76.2	n = 32 ; % = 72.7

Characteristic	Energy conservation management (N = 42)	Information only control (N = 44)
Sample size		
Primary progressive MS Sample size	n = 2 ; % = 4.8	n = 4 ; % = 9.1
Secondary progressive MS Sample size	n = 7 ; % = 16.7	n = 7 ; % = 15.9
Unknown Sample size	n = 1 ; % = 2.4	n = 1 ; % = 2.3
Years since diagnosis (years) Median (IQR)	6.5 (3.7 to 17.3)	7.5 (3 to 14)
EDSS score Expanded Disability Status Scale. Scale 0-10. Higher indicates worse disability. Median (IQR)	2.5 (2 to 4)	1.8 (1 to 4)

Outcomes

Study timepoints

Baseline

- 26 week (Performed at 26 weeks after starting treatment, meaning this time-point is 2 months following the last session of the intervention. Fits into the 3-6 month time-point in protocol as is 6 month follow-up.)
- 52 week (Performed at 52 weeks after starting treatment, meaning this time-point is 8 months following the last session of the intervention. Fits into the 6-12 month time-point in protocol as is 12 month follow-up.)

Results - energy conservation management group relative to control group

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
CIS20r fatigue Checklist Individual Strength fatigue subscale. Scale 8-56. Baseline values, mean (SD): 44.3 (7.9) vs. 43.6 (7.1) P-value	NR	0.08	0.48
CIS20r fatigue Checklist Individual Strength fatigue subscale. Scale 8-56. Baseline values, mean (SD): 44.3 (7.9) vs. 43.6 (7.1) Mean (95% CI)	NR (NR to NR)	-3.55 (-7.52 to 0.42)	-1.45 (-5.46 to 2.56)
MFIS total score Modified Fatigue Impact scale. Scale 0-84. Baseline values, mean (SD): 45.1 (11.7) vs. 42.7 (14.4) P-value	NR	0.71	0.97

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
MFIS total score Modified Fatigue Impact scale. Scale 0-84. Baseline values, mean (SD): 45.1 (11.7) vs. 42.7 (14.4) Mean (95% CI)	NR (NR to NR)	1.03 (-4.48 to 6.54)	0.1 (-5.46 to 5.65)
MFIS physical subscale Modified Fatigue Impact Scale - physical subscale. Scale 0-36. Baseline values, mean (SD): 21.2 (4.8) vs. 20.5 (5.7) P-value	NR	0.58	0.96
MFIS physical subscale Modified Fatigue Impact Scale - physical subscale. Scale 0-36. Baseline values, mean (SD): 21.2 (4.8) vs. 20.5 (5.7) Mean (95% CI)	NR (NR to NR)	0.74 (-1.87 to 3.34)	0.07 (-2.56 to 2.7)
MFIS cognitive subscale Modified Fatigue Impact Scale - cognitive subscale. Scale 0-40. Baseline values, mean (SD): 19.9 (7.6) vs. 18.2 (8.8) P-value	NR	0.97	0.89

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
MFIS cognitive subscale Modified Fatigue Impact Scale - cognitive subscale. Scale 0-40. Baseline values, mean (SD): 19.9 (7.6) vs. 18.2 (8.8) Mean (95% CI)	NR (NR to NR)	0.05 (-2.79 to 2.89)	0.2 (-3.07 to 2.66)
MFIS psychosocial subscale Modified Fatigue Impact Scale - psychosocial subscale. Scale 0-8. Baseline values, mean (SD): 4.0 (1.8) vs. 4.0 (1.9) P-value	NR	0.48	0.53
MFIS psychosocial subscale Modified Fatigue Impact Scale - psychosocial subscale. Scale 0-8. Baseline values, mean (SD): 4.0 (1.8) vs. 4.0 (1.9) Mean (95% CI)	NR (NR to NR)	0.25 (-0.45 to 0.95)	0.22 (-0.48 to 0.93)
FSS Fatigue Severity Scale. Scale 1-7. Baseline values, mean (SD): 5.3 (0.8) vs. 5.1 (0.9)	NR	0.72	0.89

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
P-value			
FSS Fatigue Severity Scale. Scale 1-7. Baseline values, mean (SD): 5.3 (0.8) vs. 5.1 (0.9) Mean (95% CI)	NR (NR to NR)	0.06 (-0.28 to 0.4)	-0.02 (-0.37 to 0.32)
SF-36 Physical Function Scale 0-100. Baseline values, mean (SD): 53.9 (24.8) vs. 59.2 (26.4) P-value	NR	0.37	0.05
SF-36 Physical Function Scale 0-100. Baseline values, mean (SD): 53.9 (24.8) vs. 59.2 (26.4) Mean (95% CI)	NR (NR to NR)	2.91 (-3.45 to 9.27)	6.5 (0.1 to 12.9)
SF-36 Role Physical Scale 0-100. Baseline values, mean (SD): 24.4 (33.8) vs. 34.1 (37.4) P-value	NR	0.31	0.66

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
SF-36 Role Physical Scale 0-100. Baseline values, mean (SD): 24.4 (33.8) vs. 34.1 (37.4) Mean (95% CI)	NR (NR to NR)	-8.83 (-26.06 to 8.41)	3.88 (-13.53 to 21.29)
SF-36 Body Pain Scale 0-100. Baseline values, mean (SD): 65.3 (21.3) vs. 67.3 (21.9) P-value	NR	0.85	0.20
SF-36 Body Pain Scale 0-100. Baseline values, mean (SD): 65.3 (21.3) vs. 67.3 (21.9) Mean (95% CI)	NR (NR to NR)	0.8 (-7.37 to 8.97)	-5.37 (-13.62 to 2.87)
SF-36 general health Scale 0-100. Baseline values, mean (SD): 49.4 (14.0) vs. 50.7 (13.1) P-value	NR	0.24	0.49
SF-36 general health Scale 0-100. Baseline values, mean (SD): 49.4 (14.0) vs. 50.7 (13.1) Mean (95% CI)	NR (NR to NR)	3.22 (-2.14 to 8.57)	1.88 (-3.52 to 7.28)

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
SF-36 vitality Scale 0-100. Baseline values, mean (SD): 41.1 (15.3) vs. 44.0 (18.5) P-value	NR	0.91	0.41
SF-36 vitality Scale 0-100. Baseline values, mean (SD): 41.1 (15.3) vs. 44.0 (18.5) Mean (95% CI)	NR (NR to NR)	-0.38 (-7.16 to 6.4)	2.87 (-3.98 to 9.73)
SF-36 Social Function Scale 0-100. Baseline values, mean (SD): 62.2 (16.9) vs. 60.5 (22.5) P-value	NR	0.89	0.79
SF-36 Social Function Scale 0-100. Baseline values, mean (SD): 62.2 (16.9) vs. 60.5 (22.5) Mean (95% CI)	NR (NR to NR)	-0.56 (-8.79 to 7.68)	-1.14 (-9.48 to 7.2)
SF-36 Role Emotional Scale 0-100. Baseline values, mean (SD): 68.3 (41.0) vs. 62.1 (39.7) P-value	NR	0.36	0.41

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
SF-36 Role Emotional Scale 0-100. Baseline values, mean (SD): 68.3 (41.0) vs. 62.1 (39.7) Mean (95% CI)	NR (NR to NR)	-8.05 (-25.15 to 9.05)	7.3 (-9.98 to 24.58)
SF-36 Mental Health Scale 0-100. Baseline values, mean (SD): 67.7 (15.5) vs. 68.8 (14.7) P-value	NR	0.58	0.86
SF-36 Mental Health Scale 0-100. Baseline values, mean (SD): 67.7 (15.5) vs. 68.8 (14.7) Mean (95% CI)	NR (NR to NR)	1.81 (-4.61 to 8.23)	0.56 (-5.92 to 7.05)
CIS20r concentration subscale Checklist Individual Strength - concentration subscale. Scale 5-35. Baseline values, mean (SD): 20.9 (7.4) vs. 20.0 (7.8) P-value	NR	0.79	0.86
CIS20r concentration subscale Checklist Individual Strength - concentration subscale. Scale 5-35.	NR (NR to NR)	0.4 (-2.54 to 3.35)	-0.26 (-3.23 to 2.71)

Outcome	Energy conservation management vs Information only control, Baseline, N2 = 44, N1 = 42	Energy conservation management vs Information only control, 26 week, N2 = 37, N1 = 34	Energy conservation management vs Information only control, 52 week, N2 = 35, N1 = 34
Baseline values, mean (SD): 20.9 (7.4) vs. 20.0 (7.8) Mean (95% CI)			

CIS20r fatigue - Polarity - Lower values are better

MFIS total score - Polarity - Lower values are better

MFIS physical subscale - Polarity - Lower values are better

MFIS cognitive subscale - Polarity - Lower values are better

MFIS psychosocial subscale - Polarity - Lower values are better

FSS - Polarity - Lower values are better

SF-36 Physical Function - Polarity - Higher values are better

SF-36 Role Physical - Polarity - Higher values are better

SF-36 Body Pain - Polarity - Higher values are better

SF-36 general health - Polarity - Higher values are better

SF-36 vitality - Polarity - Higher values are better

SF-36 Social Function - Polarity - Higher values are better

SF-36 Role Emotional - Polarity - Higher values are better

SF-36 Mental Health - Polarity - Higher values are better

CIS20r concentration subscale - Polarity - Lower values are better

Difference between the two groups at specific time-points

Adjusted model was adjusted for centre, gender, exacerbations and time since diagnosis. Unclear whether also adjusted for baseline value of outcome but is possible as mentioned for the crude model but not clear if also included in the adjusted model.

Results - raw data

Outcome	Energy conservation management, Baseline, N = 42	Energy conservation management, 26 week, N = NA	Energy conservation management, 52 week, N = 36	Information only control, Baseline, N = 44	Information only control, 26 week, N = NA	Information only control, 52 week, N = 40
Serious adverse events Includes relapse (n=1 in ECM group) and ischaemic bone disease (n=1 control group) during treatment period, as well as a further 6 events (n=3 in each group) during follow-up. Events were determined not to be directly associated with intervention. No of events	n = NA ; % = NA	n = NR ; % = NR	n = 4 ; % = 11.1	n = NA ; % = NA	n = NR ; % = NR	n = 4 ; % = 10
Serious adverse events Includes relapse (n=1 in ECM group) and ischaemic bone disease (n=1 control group) during treatment period, as well as a further 6 events (n=3 in each group) during follow-up. Events were determined not to be directly associated with intervention.	NA	NA	36	NA	NA	40

Outcome	Energy conservation management, Baseline, N = 42	Energy conservation management, 26 week, N = NA	Energy conservation management, 52 week, N = 36	Information only control, Baseline, N = 44	Information only control, 26 week, N = NA	Information only control, 52 week, N = 40
Number analysed						
Adverse events leading to withdrawal No of events	n = NA ; % = NA	n = NR ; % = NR	n = 0 ; % = 0	n = NA ; % = NA	n = NR ; % = NR	*empty data*
Adverse events leading to withdrawal Number analysed	NA	NA	34	NA	NA	35
Treatment adherence Assessed by occupational therapists and MS nurses by completing checklist to confrim whether each participant adhered to the programme. Sample size	n = NA ; % = NA	n = NA ; % = NA	n = 35 ; % = 83	n = NA ; % = NA	n = NA ; % = NA	n = 38 ; % = 86
Treatment adherence Assessed by occupational therapists and MS nurses by completing checklist to confrim whether each participant adhered to the programme.	NA	NA	42	NA	NA	44

Outcome	Energy conservation management, Baseline, N = 42	Energy conservation management, 26 week, N = NA	Energy conservation management, 52 week, N = 36	Information only control, Baseline, N = 44	Information only control, 26 week, N = NA	Information only control, 52 week, N = 40
Number analysed						

For the treatment adherence outcome, this was measured at the end of the treatment period (4 months) in terms of how many adhered to the complete programme. Available case analysis extracted for adverse events leading to withdrawal as sufficient information provided.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results CIS20r fatigue mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS20r fatigue mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS total score mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS total score mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical subscale mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical subscale mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive subscale mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive subscale mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial subscale mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial subscale mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results FSS mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results FSS mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Physical Function mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Physical Function mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Role Physical mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Role Physical mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Body Pain mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Body Pain mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 General Health mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 General Health mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Vitality mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Vitality mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Social Function mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Social Function mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Role Emotional mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Role Emotional mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Mental Health mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 Mental Health mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS20r Concentration mean difference ECM relative to control 26 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS20r Concentration mean difference ECM relative to control 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Serious Adverse Events during follow-up 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events leading to withdrawal during follow-up 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results treatment adherence during follow-up 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Bohlouli, 2021

Bibliographic Reference	**Bohlouli, J.; Namjoo, I.; Borzoo-Isfahani, M.; Poorbaferani, F.; Moravejolahkami, A. R.; Clark, C. C. T.; Hojjati Kermani, M. A.; Modified Mediterranean Diet VS. Traditional Iranian Diet: Efficacy of Dietary Interventions on Dietary Inflammatory Index Score, Fatigue Severity and Disability in Multiple Sclerosis Patients; British Journal of Nutrition; 2021; 1-35**

Study details

Trial name / registration number	IRCT20181113041641N1
Study location	Iran
Study setting	Outpatient
Study dates	Interventions performed between July 2018 and February 2019
Sources of funding	No support from any commercial organisation
Inclusion criteria	Mild-moderate relapsing remitting MS (EDSS up to 3, and receiving dimethyl fumarate 240 mg twice daily in last year); aged 20-60 years; ability to write or recall dietary history.
Exclusion criteria	Other forms of MS; disease duration of less than one year with active relapses; viral infections such as Epstein Barr; major medical illnesses (such as cancer, allergy, other autoimmune diseases anticoagulant or antiplatelet use, and psychiatric

	disorders); current smokers (one or more per day); left >40% blank items on Food Frequency Questionnaire at baseline; and prescribed high dose corticosteroid therapy (>30 mg/day methylprednisolone).
Recruitment / selection of participants	Recruited using advertisements in local media outlets and clinicians' invitation
Intervention(s)	Modified Mediterranean diet: modified version of Mediterranean diet (17% protein, 51% carbohydrate and 32% fat) based on higher consumption of fresh fruits and and vegetables, whole grains, monounsaturated fatty acids, fish, and low to moderate consumption of dairy products, meat, and poultry. Prescribed diet was individualised based on cultural and personal preferences, and the elimination of any alcohol-containing foods and beverages.
Population subgroups	None
Comparator	Traditional Iranian diet: low in low-fat dairy products, whole grains; high in red meats, solid oils, refined grains, and moderate intakes of legumes, fruits and vegetables); based on prior investigations, this diet consisted of 13 % protein, 58 % carbohydrate and 29 % fat. This group did not continue their normal eating pattern - the original dietary principles in the control group were maintained, however, the traditional Iranian diet plan was adjusted for energy intake to avoid unexpected body weight changes. All the participants received an individualised diet plan.
Number of participants	180 randomised, 147 analysed at 6 months
Duration of follow-up	6 months (end of intervention)
Indirectness	None
Method of analysis	Per protocol - all apart from those with missing data

Additional comments	Subgroups: Type of MS: relapsing-remitting EDSS score: <6.0 Disease modifying treatment status: all using dimethyl fumarate Group vs individual: individual Delivered remotely vs in person: remotely based on nature of intervention (diet)

Study arms

Modified Mediterranean diet (N = 90)

Traditional Iranian diet (N = 90)

Characteristics

Arm-level characteristics

Characteristic	Modified Mediterranean diet (N = 90)	Traditional Iranian diet (N = 90)
% Female Sample size	n = 57 ; % = 83.8	n = 65 ; % = 82.3
Mean age (SD)	38.6 (8.6)	40 (9.6)

Characteristic	Modified Mediterranean diet (N = 90)	Traditional Iranian diet (N = 90)
Mean (SD)		
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	8.1 (5.7)	9.3 (6.9)
EDSS score Mean (SD)	1.7 (0.7)	2 (0.9)

Note that characteristics are given for the n=68 and n=79 analysed at 6 months, not those randomised

Outcomes

Study timepoints

Baseline

6 month (6 months - end of intervention)

Results - raw data

Outcome	Modified Mediterranean diet, Baseline, N = 68	Modified Mediterranean diet, 6 month, N = 68	Traditional Iranian diet, Baseline, N = 79	Traditional Iranian diet, 6 month, N = 79
MFIS - total score Modified Fatigue Impact Scale. Scale 0-84. Mean (SD)	72.4 (17.2)	63.9 (14.2)	69.5 (13.2)	75.9 (15.3)
MFIS - physical subscale Scale 0-36. Mean (SD)	31.2 (10.4)	28.5 (8.8)	32.9 (9.2)	33.7 (10.2)
MFIS - cognitive Scale 0-40. Mean (SD)	35.8 (11.1)	30.2 (8.5)	36.6 (9.9)	36.1 (7.1)
MFIS - psychosocial Scale 0-8 Mean (SD)	5.4 (3.1)	5.2 (2.6)	6 (2.9)	6.1 (3.4)
EDSS score Scale 0-10 Mean (SD)	1.7 (0.7)	1.7 (0.6)	2 (0.9)	2.1 (0.8)
Side effects (diarrhoea, abdomen pain, constipation and appetite changes) No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

MFIS - total score - Polarity - Lower values are better

MFIS - physical subscale - Polarity - Lower values are better

MFIS - cognitive - Polarity - Lower values are better

MFIS - psychosocial - Polarity - Lower values are better

EDSS score - Polarity - Lower values are better

Note, despite n=90 randomised to each group, baseline values given only for those analysed

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Result MFIS total score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results EDSS score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results side effects 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Borji, 2018

Bibliographic Reference	**Borji, M.; Taghinejad, H.; Salimi, A. H.; The effect of motivational interviewing on fatigue in patients with multiple sclerosis; Archives of Neuroscience; 2018; vol. 5 (no. 3)**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	Iran
Study setting	Shahid Mostafa Khomeini Teaching Hospital in the city of Ilam
Study dates	During the year 2017
Sources of funding	NR
Inclusion criteria	Confirmation of infliction with MS by a neurologist, reading and writing literacy, age range between 18 and 65 years, residence in the city of Ilam, ability to communicate verbally, lack of any depression and anxiety based on patient records

	and interviews, scores or 21 or higher on the scale of Mini - Mental State Examination, receiving no treatments disrupting mental ability, memory, or thinking, and having no trouble communicating.
Exclusion criteria	Relapses of the disease during the study, unwillingness to participate in the study, and absence in interventions for more than one training session
Recruitment / selection of participants	A total number of 70 patients with MS referring to Shahid Mostafa Khomeini Teaching Hospital in the city of Ilam (as the only centre providing care to MS patients) were placed in two experimental (intervention; 35 patients) and (control; 35 patients) groups
Intervention(s)	Motivational interviewing was conducted according to Miller and Rollnick's Model for the experimental (intervention) group. Since most effective interventions in healthcare centres are better provided in groups based on this model and implementation of this type of interview in a group and in small clinical groups is better justified, the intervention in the present study was also administered in a group. For this purpose, the patients were placed in seven groups of five individuals and motivational interviewing was conducted, lasting between 45 to 60 minutes in five sessions (a total of 35 sessions over five weeks for all patients in the experimental and intervention group), and on a weekly basis for each group. To track the interventions, a mobile or phone number was taken from the participants. The questionnaires were completed before the interventions and four weeks after the final training session by patients in the experimental (intervention) and control groups.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - not reported · According to disability (EDSS <6 and EDSS ≥6) - not reported · Disease modifying treatment status (currently using and not currently using) - not reported · Group vs individual - group · Delivered remotely vs in person - not clear
Comparator	No details provided of control group. Just did not receive the intervention.

Number of participants	70
Duration of follow-up	4 weeks post intervention. intervention was for 5 weeks so assuming it was at 9 weeks. downgraded for indirectness
Indirectness	downgraded for indirectness as FU less than 3 months
Additional comments	NR

Study arms

motivational interviewing (N = 35)

control group (N = 35)

Characteristics

Arm-level characteristics

Characteristic	motivational interviewing (N = 35)	control group (N = 35)
% Female Nominal	12	8
Age Mean (SD)	32.6 (5.57)	35 (6.7)

Outcomes

Study timepoints

9 week (study reports outcome measured at 4 weeks post intervention. intervention lasted 5 weeks.)

fatigue outcomes

Outcome	motivational interviewing, 9 week, N = 32	control group, 9 week, N = 28
FIS (fatigue impact scale) 84 max score Mean (SD)	41.75 (14.35)	62.13 (7.69)

FIS (fatigue impact scale) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Fatigue outcomes-FIS(fatigue impact scale)-Mean SD-motivational interviewing-control group-t9

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(7 missing in experimental group due to flare up of MS and 4 unwilling to continue. only 3 drop outs in control group)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(knowledge of intervention and subjective outcome measure)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down for indirectness due to <3 month FU)*

Bulguroglu, 2017

Bibliographic Reference	**Bulguroglu, I.; Guclu-Gunduz, A.; Yazici, G.; Ozkul, C.; Irkec, C.; Nazliel, B.; Batur-Caglayan, H. Z.; The effects of Mat Pilates and Reformer Pilates in patients with Multiple Sclerosis: A randomized controlled study; Neurorehabilitation; 2017; vol. 41 (no. 2); 413-422**

Study details

Trial name / registration number	Not reported.
Study location	Turkey
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Not reported.
Inclusion criteria	MS diagnosed by neurologist; EDSS score ≤4.0; aged >18 years; and no MS attack or any surgery in last 6 months.
Exclusion criteria	Any orthopaedic, vision, hearing or perception problems which could affect results; and BMI of 30 or higher
Recruitment / selection of participants	Recruited from Department of Physiotherapy and Rehabilitation, Gazi University, Turkey
Intervention(s)	Pilates - 8 weeks: two groups randomised were combined for the purpose of this review into a single Pilates group and compared with the control group. Mat Pilates and reformer Pilates sessions were held twice weekly for 60-90 min per session. Taught key elements of Pilates in first session. Each movement was first demonstrated by a physiotherapist and movements were controlled by a physiotherapist where needed with the necessary corrections made through tactile and verbal warnings and imagery. Sessions started with warm-up exercises. Exercises performed standing up and centring in the supine position. Continued with segmental upper and lower extremity movements. For cooling down, stretching exercises and posture exercises were performed. All were performed with 10 repetitions in the first 2 weeks and 20 repetitions after 2 weeks. Mat Pilates involved increasing difficulty using different positions and elastic bands. Reformer Pilates increased difficulty through different positions and increasing resistance of springs.
Population subgroups	None reported.

Comparator	Control: asked to follow home programme consisting of relaxation and respiration exercises for 8 weeks, two times weekly.
Number of participants	N=45 randomised (number in each group unclear but assuming 15 in each of the three original groups), n=38 analysed
Duration of follow-up	Up to 8 weeks - end of treatment period
Indirectness	Outcome - follow-up at 8 weeks is less than minimum of three months specified in the protocol
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Pilates (N = 30)

Two separate groups were randomised (mat and reformer Pilates), but combined for the purpose of this review and compared to the control group.

Control - relaxation and respiration exercises (N = 15)

Characteristics

Arm-level characteristics

Characteristic	Pilates (N = 30)	Control - relaxation and respiration exercises (N = 15)
% Female Custom value	NR	NR

Characteristic	Pilates (N = 30)	Control - relaxation and respiration exercises (N = 15)
Mean age (SD) Median (IQR)	45 (39.3-49.5) years for mat Pilates group and 37 (29.5-40.0) years for reformer Pilates group	40 (26.0-43.0) years
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Duration of illness (years) Median (IQR)	4.5 (3.0-13.3) years for mat Pilates group and 2.0 (1.0-3.0) years for reformer Pilates group	3.0 (1.0-8.5) years
EDSS score Scale 0-10. Higher indicates increased disability. Median (IQR)	1.8 (1.1-3.3) for mat Pilates group and 2.0 (1.0-3.0) for reformer Pilates group	1.0 (0.5-2.0)

Outcomes

Study timepoints

Baseline

8 week (8 weeks - end of treatment period)

Results - raw data

Outcome	Pilates, Baseline, N = 30	Pilates, 8 week, N = 25	Control - relaxation and respiration exercises, Baseline, N = 15	Control - relaxation and respiration exercises, 8 week, N = 13
Fatigue Severity Scale Scale usually 9-63. Median (IQR)	49 (33.25-54.25) for mat Pilates group (n=12) and 48 (40.5-51.0) for reformer Pilates group (n=13)	43.5 (26.75-50.50) for mat Pilates group (n=12) and 39 (32.5-48.0) for reformer Pilates group (n=13)	44 (18.0-53.5)	32 (19.5-47.0)
Fatigue Severity Scale Scale usually 9-63. P-value vs. baseline	NA	0.034 for mat Pilates and 0.008 for reformer Pilates	NA	0.221
MSQOL-54 mental health composite Scale usually 0-100. Median (IQR)	74.54 (65.43-83.41) for mat Pilates (n=12) and 69.2 (65.86-71.41) for reformer Pilates group (n=13)	77.23 (70.2-84.54) for mat Pilates (n=12) and 74.58 (70.39-80.58) for reformer Pilates (n=13)	75.65 (68.08-86.38)	78.52 (64.77-89.21)
MSQOL-54 mental health composite Scale usually 0-100.	NA	0.006 for mat Pilates and 0.002 for reformer PIlates	NA	0.249

Outcome	Pilates, Baseline, N = 30	Pilates, 8 week, N = 25	Control - relaxation and respiration exercises, Baseline, N = 15	Control - relaxation and respiration exercises, 8 week, N = 13
P-values vs. baseline				
MSQOL-54 physical health composite Scale usually 0-100. Median (IQR)	74.54 (65.43-83.41) for mat Pilates (n=12) and 71.14 (67.26-74.35) for reformer Pilates group (n=13)	75.8 (70.83-86.42) for mat Pilates (n=12) and 76.3 (74.39-83.37) for reformer Pilates group (n=13)	77.35 (68.17-88.31)	82.64 (66.77-91.27)
MSQOL-54 physical health composite Scale usually 0-100. P-value vs. baseline	NA	0.005 for mat Pilates and 0.002 for reformer Pilates	NA	0.023

Fatigue Severity Scale - Polarity - Lower values are better

MSQOL-54 mental health composite - Polarity - Higher values are better

MSQOL-54 physical health composite - Polarity - Higher values are better

Note that baseline values given are for those analysed (n=25 vs. n=13) rather than those randomised.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8 weeks follow-up does not reach minimum 3 months in protocol)*

Results MSQOL-54 mental health 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8 weeks follow-up does not reach minimum 3 months in protocol)*

Results MSQOL-54 physical health 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8 weeks follow-up does not reach minimum 3 months in protocol)*

Callesen, 2020

Bibliographic Reference	**Callesen, J.; Cattaneo, D.; Brincks, J.; Kjeldgaard Jorgensen, M. L.; Dalgas, U.; How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study; Multiple Sclerosis; 2020; vol. 26 (no. 11); 1420-1432**

Study details

Secondary publication of another included	No additional information.

study- see primary study for details	
Other publications associated with this study included in review	No additional information.
Trial name / registration number	NCT02870023
Study type	Cluster randomised controlled trial
Study location	Denmark
Study setting	Outpatient follow up
Study dates	September 2016 to October 2018
Sources of funding	The work was supported by the Danish foundation TrygFonden.
Inclusion criteria	Age >18, confirmed diagnosis of multiple sclerosis, Expanded Disability Status Scale: 2.0-6.5, Six Spot Step Test score >8 seconds or Timed 25-Foot Walk >5 seconds, relapse-free within the past 8 weeks, and no adjustment of disease -modifying medication or medication that affects gait performance and spasticity within the past 8 weeks.
Exclusion criteria	Co-morbidity in terms of cognitive disorders or alcohol abuse (based on clinical judgement), pathologies that did not allow systematic resistance training >1 session/week within the last 3 months.
Recruitment / selection of participants	People who were invited via seven multiple sclerosis clinics and targeted advertisements sent out via the Danish MS Society. Eligibility according to the criteria that concerned co-morbidity, disease activity, medication and EDSS score was

	provided by neurologists based on journal records. Furthermore, it was registered if participants changed disease modifying medication and/or started/terminated medical treatment affecting gait during the study.
Intervention(s)	Vestibular therapy and resistance training. Concomitant therapy: No additional information. Group vs. individual: Unclear/not stated. Delivered remotely vs. in person: In person.
Population subgroups	According to type: See participant characteristics table. Majority relapsing-remitting but mixed. EDSS: See participants characteristics table. EDSS <6. Disease modifying treatment status: Unclear. However, people were advised to not change their disease modifying treatment, so likely people were taking it.
Comparator	Compared to each other and compared to no treatment/usual care.
Number of participants	71
Duration of follow-up	10 weeks (results after 10 weeks are reported for the control group. As this group receives the intervention at this point this data is not included as it invalidates the comparison).
Indirectness	Outcome indirectness: The amount of follow up is <3 months and so will be downgraded for indirectness as per the protocol.

Additional comments	Analysis were carried out as intention-to-treat, where all participants who completed the baseline assessment were included regardless of their adherence to the allocated intervention. Carry forward imputations were not used to replace missing data in the primary intention to treat analysis.

Study arms

Vestibular rehab (balance and motor control training) (N = 28)

7 centers. Balance and motor control training consisting of 20 1-hour training sessions over 10 weeks (2 sessions/week). All sessions started with a 10 minute warm-up on a stationary bicycle or treadmill. The intervention was developed on previously published programs and according to the principle of the task-oriented approach, thus addressing salient tasks including sitting (5 minutes), standing (5 minutes), stepping (10 minutes), walking (2 x 10 minutes), an eye movement training (10 minutes). To ensure the exercises were sufficiently challenging, the relative complexity level of an exercise was maintained by variation and by progression obtained by alteration of geometry of the base of support, by changing movement speed, by adding sensory conditions to promote better use of proprioceptive and visuo-vestibular information, and by addition of segmental movement. Furthermore, as a means of progression, and to promote cognitive load related to divided attention, cognitive multitask challenges were added to some of the exercises. Exercise intensity was derived from the rate of failure, as this was interpreted as an indication of how challenging a given task was perceived. Visual displacement of the centre of mass and excessive corrective upper limb movements were considered failure. Physiotherapists with experience in providing the intervention managed the programs. The therapists were instructed to aim for a level of difficulty, where the participants experienced failure but still reached successful execution in more than 50% of attempts/time.

Resistance training (progressive resistance training) (N = 23)

7 centers. Training consisting of 21-hour training session over 10 weeks (2 sessions/week). Each session started with a 10-minute warm-up on a stationary bicycle or treadmill. The program predominantly targeted knee and hip flexion and extension where the exercises progressed from three sets of 10 repetition at 15RM toward four sets of 8 repetitions at 8RM. The exercises were conducted in machines that targeted the specified muscle groups, but type of machines could vary between centers. All training sessions were supervised by physiotherapists who were trained to deliver the intervention.

No treatment (N = 20)

6 weeks. People waiting for 10 weeks, where they were encouraged to maintain usual care and level of physical activity. Thereafter, they received an intervention with one weekly session of vestibular rehab and one weekly session of resistance training.

Characteristics

Arm-level characteristics

Characteristic	Vestibular rehab (balance and motor control training) (N = 28)	Resistance training (progressive resistance training) (N = 23)	No treatment (N = 20)
% Female Sample size	n = 23 ; % = 82	n = 16 ; % = 70	n = 16 ; % = 80
Mean age (SD) Median age (range) Median (IQR)	51 (31 to 75)	52 (38 to 64)	56 (30 to 73)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
EDSS (median [range]) Median (IQR)	4 (2 to 6.5)	4 (2 to 6.5)	3.5 (2 to 6.5)
Relapsing-remitting	n = NR ; % = 75	n = NR ; % = 70	n = NR ; % = 65

Characteristic	Vestibular rehab (balance and motor control training) (N = 28)	Resistance training (progressive resistance training) (N = 23)	No treatment (N = 20)
Sample size			
Secondary progressive Sample size	n = NR ; % = 14	n = NR ; % = 22	n = NR ; % = 15
Primary progressive Sample size	n = NR ; % = 11	n = NR ; % = 9	n = NR ; % = 20

Outcomes

Study timepoints

- Baseline
- 10 week (Outcomes at this time will be downgraded for indirectness due to short follow up period (<3 months).)

Vestibular rehab compared to resistance training compared to no treatment at 3-6 months - Continuous outcomes (change scores)

Outcome	Vestibular rehab (balance and motor control training), Baseline, N = 28	Vestibular rehab (balance and motor control training), 10 week, N = 28	Resistance training (progressive resistance training), Baseline, N = 23	Resistance training (progressive resistance training), 10 week, N = 23	No treatment, Baseline, N = 20	No treatment, 10 week, N = 20
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue	40.8 (11.1)	NR (NR)	43.9 (15.8)	NR (NR)	41.9 (15.3)	NR (NR)

Outcome	Vestibular rehab (balance and motor control training), Baseline, N = 28	Vestibular rehab (balance and motor control training), 10 week, N = 28	Resistance training (progressive resistance training), Baseline, N = 23	Resistance training (progressive resistance training), 10 week, N = 23	No treatment, Baseline, N = 20	No treatment, 10 week, N = 20
Impact Scale) Scale range: 0-84 Mean (SD)						
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) Scale range: 0-84 Mean (95% CI)	NR (NR to NR)	-11.1 (-15.3 to -6.9)	NR (NR to NR)	-12.8 (-17.7 to -7.8)	NR (NR to NR)	-1.8 (-6.8 to 3.2)

Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) - Polarity - Lower values are better

Outcomes at this time will be downgraded for indirectness due to short follow up period (<3 months).

Vestibular rehab compared to resistance training compared to no treatment at 3-6 months - Dichotomous outcomes

Outcome	Vestibular rehab (balance and motor control training), Baseline, N = 28	Vestibular rehab (balance and motor control training), 10 week, N = 28	Resistance training (progressive resistance training), Baseline, N = 23	Resistance training (progressive resistance training), 10 week, N = 23	No treatment, Baseline, N = 20	No treatment, 10 week, N = 20
Adverse events leading to withdrawal Resistance training. 1	NA	0	NA	5	NA	0

Outcome	Vestibular rehab (balance and motor control training), Baseline, N = 28	Vestibular rehab (balance and motor control training), 10 week, N = 28	Resistance training (progressive resistance training), Baseline, N = 23	Resistance training (progressive resistance training), 10 week, N = 23	No treatment, Baseline, N = 20	No treatment, 10 week, N = 20
intermittent low back pain, 1 fatigue following session, 3 falls unrelated to training sessions Nominal						

Outcomes at this time will be downgraded for indirectness due to short follow up period (<3 months).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cluster randomised trials

Vestibular rehab compared to resistance training compared to no treatment at 3-6months – Continuous outcomes (change scores)-Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale)-Mean Nine Five Percent CI -Vestibular rehab (balance and motor control training)-Resistance training (progressive resistance training)-No treatment-t10

Section	Question	Answer
1a. Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
1b. Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomisation	Risk of bias judgement for the timing of identification and recruitment of individual participants in relation to timing of randomisation	Low

Section	Question	Answer
2. Bias due to deviations from intended interventions (If your aim is to assess the effect of assignment to intervention, answer the following questions).	Risk of bias judgement for deviations from intended interventions	Some concerns
3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
5. Bias in selection of the reported result	Risk of bias for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to outcome indirectness (<3 months follow up duration))*

Vestibular rehab compared to resistance training compared to no treatment at 3-6 months – Dichotomous outcomes -Adverse events leading to withdrawal – Nominal - Vestibular rehab (balance and motor control training)-Resistance training (progressive resistance training)-No treatment-t10

Section	Question	Answer
1a. Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
1b. Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomisation	Risk of bias judgement for the timing of identification and recruitment of individual participants in relation to timing of randomisation	Low
2. Bias due to deviations from intended interventions (If your aim is to assess the effect of assignment to intervention, answer the following questions).	Risk of bias judgement for deviations from intended interventions	Some concerns
3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns
4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns
5. Bias in selection of the reported result	Risk of bias for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to outcome indirectness (<3 months follow up duration))*

Correale, 2021

Bibliographic Reference	**Correale, L.; Buzzachera, C. F.; Liberali, G.; Codrons, E.; Mallucci, G.; Vandoni, M.; Montomoli, C.; Bergamaschi, R.; Effects of Combined Endurance and Resistance Training in Women With Multiple Sclerosis: A Randomized Controlled Study; Frontiers in neurology [electronic resource].; 2021; vol. 12; 698460**

Study details

Trial name / registration number	Not reported
Study location	Italy
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Definite relapsing-remitting MS according to 2010 McDonald's criteria; Expanded Disability Status Scale score <4; pyramidal function between 1 to 3; independent ambulation without uses of unilateral assistance; age >18 and <60 years; and acceptance of treatment
Exclusion criteria	Neuropathic pain of the lower limbs; severe cognitive impairments; alcoholism; medical comorbidities and/or a medical condition contraindicating participation in the study; had experienced an MS attack within the past eight weeks; were pregnant; and engaged in regular exercise over the past six months.
Recruitment / selection of participants	All participants were recruited from those referred to the neurologist of the IRCCS Casimiro Mondino Foundation of Pavia for periodic clinical and electrophysiological evaluations.
Intervention(s)	Endurance and resistance training: attended training facility twice weekly on non-consecutive days for 12 weeks to take part in combination of endurance and resistance training, with sessions between 45 and 60 min. Each training session began with a 5 min warm-up, which involved moderate-intensity aerobic exercise (~50% heart rate reserve) on either a motorised treadmill or a cycle ergometer. Then asked to complete a 25-min aerobic training at a moderate to-vigorous exercise intensity (50–70% heart rate reserve), with heart rate monitored continuously throughout each session. Exercise intensity was progressively increased or decreased every 2 weeks based on heart rate responses. The endurance training was followed by resistance training, consisting of calisthenics, dumbbells, and elastic band exercises for the major muscle groups, with participants being instructed to complete three sets of 8–12 repetitions for each exercise. The rest period

	between sets and exercises was 60–90 s. The load was increased when three sets of 12 repetitions of an exercise could be easily completed. All sessions conducted at same time of day under similar environmental conditions and supervised by trained research staff member. Participants had to attend at least 90% of scheduled sessions to be considered compliant. Instructed to maintain usual daily activities and dietary patterns.
Population subgroups	None
Comparator	Control - no further details, assume no intervention.
Number of participants	27 randomised, 23 analysed (all dropouts were in control group)
Duration of follow-up	12 weeks - end of intervention
Indirectness	None
Method of analysis	Per protocol - all apart from those with missing data
Additional comments	Subgroups: Type of MS: relapsing-remitting EDSS score: <6.0 Disease modifying treatment status: unclear Group vs individual: unclear, possibly group Delivered remotely vs in person: in person sessions

Study arms

Endurance + resistance training (N = 14)

Control (N = 13)

Characteristics

Arm-level characteristics

Characteristic	Endurance + resistance training (N = 14)	Control (N = 13)
% Female Sample size	n = 14 ; % = 100	n = 9 ; % = 100
Mean age (SD) Mean (SD)	45.4 (7.2)	48.3 (6.1)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Note that characteristics are given for those analysed (n=14 and n=9, respectively), not those randomised (n=14 and n=13, respectively)

Outcomes

Study timepoints

Baseline

- 12 week (12 weeks - end of intervention)

Results - change from baseline at 12 weeks

Outcome	Endurance + resistance training, 12 week vs Baseline, N = 14	Control , 12 week vs Baseline, N = 9
MFIS - Italian version Modified Fatigue Impact Scale. Scale 0-84. Baseline values were 39.9 (15.0) and 44.8 (16.3) Mean (SD)	-16.3 (16.6)	-4.5 (5.8)
Beck Depression Inventory II - Italian version Scale 0-63. Baseline values were 16.6 (9.3) and 15.4 (7.2) Mean (SD)	-7 (5.6)	-2.3 (9.2)
MSQoL-54 mental composite (Italian version) Scale 0-100. Baseline values were 48.6 (19.3) and 51.5 (18.2) Mean (SD)	11.1 (18.9)	-5.2 (14.1)
MSQoL-54 physical composite (Italian version) Scale 0-100. Baseline values were 57.5 (22.4) and 55.4 (23.8) Mean (SD)	10 (15.5)	3.3 (27.7)

MFIS - Italian version - Polarity - Lower values are better

Beck Depression Inventory II - Italian version - Polarity - Lower values are better

MSQoL-54 mental composite (Italian version) - Polarity - Higher values are better

MSQoL-54 physical composite (Italian version) - Polarity - Higher values are better

Note number analysed at 12 weeks are reported, including for baseline values (n=14 and n=9, respectively)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total 12 weeks change

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Beck Depression Inventory 12 weeks change

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQoL-54 mental composite 12 weeks change

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQoL-54 physical composite 12 weeks change

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dilek Dogan, 2021

Bibliographic Reference	**Dilek Dogan, H.; Tan, M.; Effects of Reflexology on Pain, Fatigue, and Quality of Life in Multiple Sclerosis Patients: A Clinical Study; Alternative therapies in health and medicine.; 2021; vol. 31**

Study details

Study location	Turkey
Study setting	Outpatient
Study dates	Data collected between 20/05/2013 and 25/01/2015
Sources of funding	No funding
Inclusion criteria	diagnosed with MS for at least 6 months; aged ≥18 years; ≤5.5 on EDSS score (able to walk without aid or rest for 200 m); no visual or hearing impairment; not being in MS relapse period; not having used any complementary alternative therapy previously; had both right and left feet; and no vascular disease, ulcer infection, fracture, sprains or surgical intervention in left or right foot.
Exclusion criteria	No further criteria reported

Recruitment / selection of participants	Recruited from those diagnosed with MS at Neurology Clinic of Selcuk University Hospital and Neurology Clinic of Mevlana University Hospital. Data collected between 20/05/2013 and 25/01/2015.
Intervention(s)	Reflexology: 12-week reflexology intervention. Applied in ergonomic and adjustable therapy chair in a neurology clinic. Performed by considering sympathetic and parasympathetic nervous systems with more intense focus on certain points in line with expert opinion. Researcher took theoretical and practical reflexology courses in the Association of Reflexologists and Reflexology. Three sessions weekly using pure olive oil. Process involved warm up movements for 1 min using rotation, stretching of Achilles tendon, wrist release, running the toe on the soles of the feet and laundry ringing methods. Warm up methods completed by applying pressure to solar plexus. Brain area then massaged for 4 min. Epiphyseal, hypothalamus and pituitary gland points in the toes massaged. Reflexology also applied to spinal region, lymphatic system, shoulder, elbow, hip and knee regions, intestinal regions, reproductive organs, bladder region, mouth and jaw muscles. Foot loosening movements performed also. Session completed in 15-20 min by applying pressure to solar plexus. Repeated for each foot. Also received routine treatment.
Population subgroups	None
Comparator	Control: no intervention was performed for the 12-week trial period and patients continued their routine clinical treatment.
Number of participants	66 randomised, 60 analysed (n=3 dropping from each group)
Duration of follow-up	12-weeks - end of intervention
Indirectness	None
Additional comments	Analysed those that completed or were adherent to the intervention, per protocol? Excluded n=2 in reflexology group that did not attend regularly.

Study arms

Reflexology + routine treatment (N = 33)

Control (no intervention)l + routine treatment (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Reflexology + routine treatment (N = 33)	Control (no intervention)l + routine treatment (N = 33)
% Female Custom value	NR	NR
Mean age (SD) Mean (SD)	36.43 (8.53)	39.46 (10.43)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	7.33 (3.84)	6.15 (4.65)

Characteristic	Reflexology + routine treatment (N = 33)	Control (no intervention)l + routine treatment (N = 33)
EDSS score Mean (SD)	2.33 (1.49)	2.25 (1.41)
Relapsing-remitting Definition used in paper 'in form of attacks and healings' Sample size	n = 24 ; % = 80	n = 23 ; % = 76.7
Secondary progressive Definition used in paper 'beginning in form of attacks and healings, later worsening' Sample size	n = 5 ; % = 16.7	n = 6 ; % = 20
Primary progressive Definition used in paper 'exhibiting progressive, starting from the first attack or increasingly worsening with every attack' Sample size	n = 1 ; % = 3.3	n = 1 ; % = 3.3
MS drug use Sample size	n = 23 ; % = 76.7	n = 24 ; % = 80

Note that baseline characteristics are given for the n=30 analysed in each arm not the n=33 randomised to each arm

Outcomes

Study timepoints

Baseline

12 week (12-weeks - end of intervention period)

Results - raw data

Outcome	Reflexology + routine treatment, Baseline, N = 30	Reflexology + routine treatment, 12 week, N = 30	Control (no intervention)l + routine treatment, Baseline, N = 30	Control (no intervention)l + routine treatment, 12 week, N = 30
Fatigue Severity Scale Scale 1-7. Mean (SD)	5.33 (1.13)	2.62 (1.35)	4.91 (1.61)	4.97 (1.8)
MSQOL-54 - physical composite MS Quality of Life-54. Scale usually 0-100 but unclear. Mean (SD)	49.34 (15.51)	65.55 (14.31)	44.19 (17.93)	41.12 (19.89)
MSQOL-54 mental composite MS Quality of Life-54. Scale usually 0-100 but unclear. Mean (SD)	52.44 (16.37)	72.81 (16.56)	47.86 (19.88)	44.48 (20.67)
MSQOL-54 - health change MS Quality of Life-54. Scale usually 0-100 but unclear. Significant difference at baseline.	57.5 (19.85)	73.33 (17.28)	39.16 (24.28)	34.16 (23.19)

Outcome	Reflexology + routine treatment, Baseline, N = 30	Reflexology + routine treatment, 12 week, N = 30	Control (no intervention)l + routine treatment, Baseline, N = 30	Control (no intervention)l + routine treatment, 12 week, N = 30
Mean (SD)				

Fatigue Severity Scale - Polarity - Lower values are better

MSQOL-54 - physical composite - Polarity - Higher values are better

MSQOL-54 mental composite - Polarity - Higher values are better

MSQOL-54 - health change - Polarity - Higher values are better

Note that although n=33 were randomised to each group, the study only gives the results at baseline for the n=30 per group that were analysed at end of intervention

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 physical composite 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 mental composite 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 health change 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Eftekhari, 2018

Bibliographic Reference	**Eftekhari, E.; Etemadifar, M.; Impact of clinical mat pilates on body composition and functional indices in female patients with multiple sclerosis; Crescent Journal of Medical and Biological Sciences; 2018; vol. 5 (no. 4); 297-305**

Study details

Secondary publication of another included	No additional information.

study- see primary study for details	
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Iran.
Study setting	Community.
Study dates	April and June 2015.
Sources of funding	This study was financially supported by the Najafabad Branch.
Inclusion criteria	Females with multiple sclerosis and EDSS 2-6.
Exclusion criteria	Exercise during the last 3 months; back problems; pregnancy; epliepsy; cancer.
Recruitment / selection of participants	Volunteers who were enrolled at the Goldasht Multiple Sclerosis Center
Intervention(s)	Mat pilates for 8 consecutive weeks based on the progressive program. The protocol consisted of special exercises which were based on core stability with low to moderate intensity according to the ability of the patients participating in the study.

	The protocol of training was designed in a way to avoid exacerbation, hyperthermia, fatigue and to maintain balance during training. The duration of the protocol was 8 weeks which consisted of 3 days per week with 48 hours rest between each session. The training session began with 10 minutes of warm-up which consisted of 2 repetitions of breathing, imprint-release, supine spinal, head nodes, shoulder shrugs. The main exercise was done for 30 to 40 minutes and consisted of 1-2 sets of 10 repetitions of 100, 1-2 sets of 3-10 repetitions of roll up, roll down, single leg circle (consisting of 10 seconds of exercise and 10 seconds of rest for 10 repetitions, and 30 seconds between each movement) and 60 seconds of rest between each set (each exercise took nearly 7 minutes) and cool down was done with a 10-minute duration like a warm-up. Concomitant therapy: Not stated/unclear. Intervention subgroups: Group vs. individual: Unclear/not stated. Delivered remotely vs. in person: In person
Population subgroups	According to type: Relapsing-remitting MS According to disability: EDSS 2-6 (mixed). Disease modifying treatment status: Not stated/unclear.
Comparator	Usual care (Continued with their routine life)
Number of participants	30
Duration of follow-up	8 weeks (outcomes will be downgraded for indirectness due to short follow up duration [<3 months]).
Indirectness	Outcome indirectness: due to short follow up duration (<3 months).

Additional comments	Outcomes were assessed by available case analysis.

Study arms

Pilates (N = 15)

Mat pilates for 8 consecutive weeks based on the progressive program. The protocol consisted of special exercises which were based on core stability with low to moderate intensity according to the ability of the patients participating in the study. The protocol of training was designed in a way to avoid exacerbation, hyperthermia, fatigue and to maintain balance during training. The duration of the protocol was 8 weeks which consisted of 3 days per week with 48 hours rest between each session. The training session began with 10 minutes of warm-up which consisted of 2 repetitions of breathing, imprint-release, supine spinal, head nodes, shoulder shrugs. The main exercise was done for 30 to 40 minutes and consisted of 1-2 sets of 10 repetitions of 100, 1-2 sets of 3-10 repetitions of roll up, roll down, single leg circle (consisting of 10 seconds of exercise and 10 seconds of rest for 10 repetitions, and 30 seconds between each movement) and 60 seconds of rest between each set (each exercise took nearly 7 minutes) and cool down was done with a 10-minute duration like a warm-up.

Usual care (N = 15)

Continued with their routine life

Characteristics

Arm-level characteristics

Characteristic	Pilates (N = 15)	Usual care (N = 15)
% Female Nominal	15	15

Characteristic	Pilates (N = 15)	Usual care (N = 15)
Mean age (SD) Mean (SD)	34.46 (7.29)	31.41 (8.89)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 8 week (Outcomes will be downgraded for indirectness due to short follow up duration (<3 months))

Pilates compared to usual care at 3-6 months - Continuous outcomes (final value)

Outcome	Pilates, Baseline, N = 15	Pilates, 8 week, N = 13	Usual care, Baseline, N = 15	Usual care, 8 week, N = 12
Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) Scale range: 0-84 Mean (SD)	10 (2.54)	6.46 (3.35)	8.5 (4.29)	10.5 (4.18)

Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) - Polarity - Lower values are better

Outcomes will be downgraded for indirectness due to short follow up duration (<3 months)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pilates compared to usual care at 3-6 months – Continuous outcomes (final value) - Patient-reported outcome measures to assess MS fatigue (Modified Fatigue Impact Scale) – Mean SD – Pilates - Usual care - t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Downgraded due to short follow up duration (<3 months))*

Ehde, 2015

Bibliographic Reference	**Ehde, D. M.; Elzea, J. L.; Verrall, A. M.; Gibbons, L. E.; Smith, A. E.; Amtmann, D.; Efficacy of a Telephone-Delivered Self-Management Intervention for Persons With Multiple Sclerosis: A Randomized Controlled Trial With a One-Year Follow-Up; Archives of Physical Medicine & Rehabilitation; 2015; vol. 96 (no. 11); 1945-58.e2**

Study details

Trial name / registration number	NCT00944190
Study location	USA
Study setting	Outpatient
Study dates	Study conducted between April 2011 and September 2013
Sources of funding	StataCorp LP mentioned as a 'supplier'.
Inclusion criteria	aged ≥18 years; self-reported physician diagnosis of MS; and at least one of the following: moderate depressive symptoms (score 10-14 on PHQ-9), presence of chronic pain (average pain intensity ≥3 in past week on 0-10 numeric rating scale) or significant fatigue symptoms (score ≥10 on 5-item Modified Fatigue Impact Scale Short Form).
Exclusion criteria	significant cognitive impairment (≥1 error on 6-item Cognitive Screener); currently in psychotherapy more than once each month; participated in another study for fatigue, depression or pain; and exhibited moderate-severe or severe depressive symptoms (PHQ-9 score ≥15).
Recruitment / selection of participants	Recruited from mailings to individuals in University of Washington Department of Rehabilitation Medicine Research Registry, advertisements through national MS organistions, flyers/referrals from University of Washington MS Center, ClinicalTrials.gov and other active studies in the department.

Intervention(s)	Telephone-delivered self-management intervention. Evidence-based cognitive behavioural and positive psychological strategies to aid participants in the self-management of pain, depression and fatigue in daily life. At final session, therapist and participant created comprehensive personal self-management plan integrating their preferred skills and goals to use post-treatment. Both interventions used therapist manuals and participant workbooks informed by qualitative research. Piloted and revised based on feedback from 8 participants. Consisted of 8 weekly 45-60 min telephone sessions with 15-min follow-up calls at 4 and 8 weeks post-treatment. Interventions delivered by therapists that had received training and supervision from the principal investigator (psychologist with >20 years expertise in study population and interventions).
Population subgroups	None reported
Comparator	Control - telephone-delivered education intervention. Aimed to inform participants about fatigue, pain and depression and other common MS challenges without teaching, rehearsing or prescribing any specific self-management skills. Interactive discussion encouraged. Designed to be a credible comparator that controlled for natural history, measurement processes and common factors such as therapist attention, therapeutic relationship, treatment dosing and participation in a manualised intervention. Both interventions used therapist manuals and participant workbooks informed by qualitative research. Piloted and revised based on feedback from 8 participants. Consisted of 8 weekly 45-60 min telephone sessions with 15-min follow-up calls at 4 and 8 weeks post-treatment. Interventions delivered by therapists that had received training and supervision from the principal investigator (psychologist with >20 years expertise in study population and interventions).
Number of participants	163 randomised and included in intention to treat analysis
Duration of follow-up	Follow-up up to 12 months after starting intervention (10 months after the last session), with results reported at 6 and 12 month time-points relevant to the protocol
Indirectness	Serious - includes proportion where fatigue was not one of the reasons for inclusion in the study (81.6% met criteria for fatigue).
Method of analysis	Intention to treat - all randomised

	Per protocol - all apart from those with missing data
Additional comments	Patients could continue existing medical treatments for pain, depression of fatigue. Intention to treat used for some analyses but per protocol where missing data was too high to run model as intention to treat.

Study arms

Telephone-directed self-management intervention (N = 75)

Evidence-based cognitive behavioural and positive psychology strategies for helping self-manage pain, depression and fatigue in daily lives.

Control - telephone-delivered education intervention (N = 88)

Information about fatigue, pain, depression and other common MS challenges without teaching, rehearsing or prescribing any specific self-management skills.

Characteristics

Arm-level characteristics

Characteristic	Telephone-directed self-management intervention (N = 75)	Control - telephone-delivered education intervention (N = 88)
% Female Sample size	n = 67 ; % = 89.3	n = 75 ; % = 85.2
Mean age (SD) Mean (SD)	51 (10.1)	53.2 (10)

Characteristic	Telephone-directed self-management intervention (N = 75)	Control - telephone-delivered education intervention (N = 88)
Non-hispanic white Sample size	n = 62 ; % = 82.7	n = 74 ; % = 84.1
Non-hispanic black Sample size	n = 9 ; % = 12	n = 10 ; % = 11.4
Hispanic and >1 race Sample size	n = 2 ; % = 2.7	n = 1 ; % = 1.1
Non-Hispanic and >1 race Sample size	n = 2 ; % = 2.7	n = 3 ; % = 3.4
Comorbidities Text	NR	NR
Relapsing remitting MS Sample size	n = 46 ; % = 61.3	n = 45 ; % = 51.1
Progressive MS Sample size	n = 29 ; % = 38.7	n = 43 ; % = 48.9
Normal Sample size	n = 2 ; % = 2.7	n = 5 ; % = 5.8

Characteristic	Telephone-directed self-management intervention (N = 75)	Control - telephone-delivered education intervention (N = 88)
Mild disability Sample size	n = 10 ; % = 13.3	n = 17 ; % = 19.5
Moderate disability Sample size	n = 8 ; % = 10.7	n = 13 ; % = 14.9
Gait disability Sample size	n = 24 ; % = 32	n = 24 ; % = 27.6
Early cane Sample size	n = 13 ; % = 17.3	n = 12 ; % = 13.8
Late cane Sample size	n = 7 ; % = 9.3	n = 7 ; % = 8.1
Bilateral support Sample size	n = 4 ; % = 5.3	n = 3 ; % = 3.5
Wheelchair/scooter Sample size	n = 7 ; % = 9.3	n = 6 ; % = 6.9
5+ years Sample size	n = 21 ; % = 28	n = 21 ; % = 23.9

Characteristic	Telephone-directed self-management intervention (N = 75)	Control - telephone-delivered education intervention (N = 88)
5-9 years Sample size	n = 17 ; % = 22.7	n = 25 ; % = 28.4
10-19 years Sample size	n = 29 ; % = 38.7	n = 26 ; % = 29.6
20+ years Sample size	n = 8 ; % = 10.7	n = 16 ; % = 18.2
Met criteria for fatigue - MFIS score at least 10 Modified Fatigue Impact Scale. Sample size	n = 61 ; % = 81	n = 72 ; % = 82
Met criteria for pain - score of at least 3 in past week for pain intensity on 0-10 scale Sample size	n = 60 ; % = 80	n = 69 ; % = 78
Met criteria for depression - PHQ-9 score between 10 and 14 at screening Patient Health Questionnaire-9. Sample size	n = 29 ; % = 39	n = 43 ; % = 49
Met criteria for 2 out of the 3 symptoms Of fatigue, pain and depression Sample size	n = 31 ; % = 41.3	n = 29 ; % = 33.3

Characteristic	Telephone-directed self-management intervention (N = 75)	Control - telephone-delivered education intervention (N = 88)
Met criteria for all 3 symptoms Of fatigue, pain and depression Sample size	n = 22 ; % = 29.3	n = 34 ; % = 39.1
Fatigue was the only symptom meeting criteria for inclusion Sample size	n = 10 ; % = 13.3	n = 9 ; % = 10.3
Fatigue impact - MFIS Modified Fatigue Impact Scale total score. Scale 0-84. Higher indicates worse fatigue. Mean (SD)	48.8 (14.7)	51.2 (12.7)
Pain interference - modified BPI Modified Brief Pain Inventory. Scale 0-10. Higher indicates worse pain interference. Mean (SD)	3.7 (2.4)	3.7 (2.4)
Pain intensity Scale 0-10 using numeric rating scale Mean (SD)	3.7 (2.2)	3.7 (1.8)
Depression - PHQ-9 Patient Health Questionnaire-9. Scale 0-27. Higher indicates worse depression.	8.6 (4)	10.2 (4.3)

Characteristic	Telephone-directed self-management intervention (N = 75)	Control - telephone-delivered education intervention (N = 88)
Mean (SD)		

Outcomes

Study timepoints

- Baseline
- 6 month (6 months post-randomisation. ~4 months following the last session. Fits into the 3-6 months category in the protocol.)
- 12 month (12 months post-randomisation. ~10 months following the last session. Fits into >6 months - 1 year time-point in protocol.)

Results - effect size self-management vs. education

Outcome	Telephone-directed self-management intervention vs Control - telephone-delivered education intervention, Baseline, N2 = 88, N1 = 75	Telephone-directed self-management intervention vs Control - telephone-delivered education intervention, 6 month, N2 = 81, N1 = 64	Telephone-directed self-management intervention vs Control - telephone-delivered education intervention, 12 month, N2 = 81, N1 = 64
≥10-point reduction in fatigue compared to baseline Modified Fatigue Impact Scale. n=30 (63%) vs. n=32 (53%) at 6 months and n=26 (55%) vs. n=29 (45%) at 12 months. Odds ratio/95% CI	NA (NA to NA)	1.74 (0.78 to 3.87)	1.74 (0.79 to 3.84)

Outcome	Telephone-directed self-management intervention vs Control - telephone-delivered education intervention, Baseline, N2 = 88, N1 = 75	Telephone-directed self-management intervention vs Control - telephone-delivered education intervention, 6 month, N2 = 81, N1 = 64	Telephone-directed self-management intervention vs Control - telephone-delivered education intervention, 12 month, N2 = 81, N1 = 64
≥50% reduction in depression compared to baseline Patient Health Questionnaire-9. n=8 (35%) vs. n=10 (29%) at 6 months and 7 (32%) vs. n=14 (37%) at 12 months. Odds ratio/95% CI	NA (NA to NA)	1.41 (0.45 to 4.46)	1 (0.31 to 3.23)

Analysis adjusted for baseline PHQ-9 scores. Per protocol analyses used for these outcomes due to missing data being too high to use intention to treat. Values not imputed in per protocol analysis.

Results - raw data

Outcome	Telephone-directed self-management intervention, Baseline, N = 75	Telephone-directed self-management intervention, 6 month, N = 64	Telephone-directed self-management intervention, 12 month, N = 64	Control - telephone-delivered education intervention, Baseline, N = 88	Control - telephone-delivered education intervention, 6 month, N = 81	Control - telephone-delivered education intervention, 12 month, N = 81
Modified Fatigue Impact Scale - total score Scale 0-84. Final values.	48 (14.7)	37.3 (16)	40.2 (16.5)	51.2 (12.7)	41.7 (16.2)	43.3 (15.8)

Outcome	Telephone-directed self-management intervention, Baseline, N = 75	Telephone-directed self-management intervention, 6 month, N = 64	Telephone-directed self-management intervention, 12 month, N = 64	Control - telephone-delivered education intervention, Baseline, N = 88	Control - telephone-delivered education intervention, 6 month, N = 81	Control - telephone-delivered education intervention, 12 month, N = 81
Mean (SD)						
SF-8 Physical domain Health-related quality of life. Scale 0-100. Mean (SD)	37.3 (8.7)	40.3 (9.5)	38.6 (8.6)	38.9 (7.4)	40.4 (9.2)	40.3 (9.1)
SF-8 Mental Health domain Health-related quality of life. Scale 0-100. Mean (SD)	44.2 (9.3)	48.2 (9.8)	47.7 (9.2)	43.4 (9.2)	47 (9.5)	47.2 (10)
Depression - PHQ-9 Patient Health Questionnaire-9. Scale 0-27. Mean (SD)	8.6 (4)	5.7 (4.7)	6.3 (4.2)	10.2 (4.3)	6.7 (4.2)	7.3 (5)

Outcome	Telephone-directed self-management intervention, Baseline, N = 75	Telephone-directed self-management intervention, 6 month, N = 64	Telephone-directed self-management intervention, 12 month, N = 64	Control - telephone-delivered education intervention, Baseline, N = 88	Control - telephone-delivered education intervention, 6 month, N = 81	Control - telephone-delivered education intervention, 12 month, N = 81
Serious adverse events Reported to be no serious adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0	n = 0 ; % = 0
Serious adverse events Reported to be no serious adverse events Number analysed	NA	62	60	NA	79	80
Treatment satisfaction Unclear how this was measured. Scale unclear. Number analysed	NA	NA	Number analysed unclear	NA	NA	Number analysed unclear
Treatment satisfaction Unclear how this	NA (NA to NA)	NA (NA to NA)	9 (8 to 10)	NA (NA to NA)	NA (NA to NA)	8 (5 to 9)

Outcome	Telephone-directed self-management intervention, Baseline, N = 75	Telephone-directed self-management intervention, 6 month, N = 64	Telephone-directed self-management intervention, 12 month, N = 64	Control - telephone-delivered education intervention, Baseline, N = 88	Control - telephone-delivered education intervention, 6 month, N = 81	Control - telephone-delivered education intervention, 12 month, N = 81
was measured. Scale unclear. Median (IQR)						
Treatment adherence attending all 8 sessions No of events	n = NA ; % = NA	n = NA ; % = NA	n = 58 ; % = 77	n = NA ; % = NA	n = NA ; % = NA	n = 77 ; % = 88
Treatment adherence attending all 8 sessions Number analysed	NA	NA	75	NA	NA	88

Modified Fatigue Impact Scale - total score - Polarity - Lower values are better

SF-8 Physical domain - Polarity - Higher values are better

SF-8 Mental Health domain - Polarity - Higher values are better

Depression - PHQ-9 - Polarity - Lower values are better

Treatment satisfaction - Polarity - Higher values are better

Analyses performed in the per protocol population for most of the outcomes below, with no imputation for missing data. Available case analysis extracted for serious adverse events as sufficient information available.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results 10-point reduction in fatigue vs. baseline 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results 10-point reduction in fatigue vs baseline 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results 50% reduction in depression vs. baseline 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results 50% reduction in depression vs baseline 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results MFIS total score final value 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results MFIS total score final value 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results SF-8 physical domain final value 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results SF-8 physical domain final value 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results SF-8 mental health domain final value 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results SF-8 mental health domain final value 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results depression PHQ-9 final value 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results depression PHQ-9 final value 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results serious adverse events 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results serious adverse events 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results treatment satisfaction

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Results treatment adherence

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population consists of some where fatigue was not a*

Section	Question	Answer
		primary reason for inclusion, though >80% had significant fatigue as one of the reasons for inclusion)

Feys, 2019

Bibliographic Reference	**Feys, P.; Moumdjian, L.; Van Halewyck, F.; Wens, I.; Eijnde, B. O.; Van Wijmeersch, B.; Popescu, V.; Van Asch, P.; Effects of an individual 12-week community-located "start-to-run" program on physical capacity, walking, fatigue, cognitive function, brain volumes, and structures in persons with multiple sclerosis; Multiple Sclerosis; 2019; vol. 25 (no. 1); 92-103**

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)

Study location	Belgium.
Study setting	Community.
Study dates	From January 2015 to October 2015.
Sources of funding	The non-for-profit organization Move To Sport initiated the study. The authors acknowledge Prof. Dr P. Parizel (UZA Antwerp) for facilitation of neuroimaging at UZA Wilrijk and Novartis and the MS Network Limburg for funding-related occupational costs.
Inclusion criteria	Adults with MS were included based on the ability to walk 5km without rest or use of assistive device. Interested pwMS attended an information session and jointly walked 5km for verification of their ability.
Exclusion criteria	Reports to have run 5km in the preceding 6 months or a relapse occurring in the preceding 3 months.
Recruitment / selection of participants	Announcements at REVAL rehabilitation research institute (UHasselt), Flemish MS rehabilitation centers and MS Society, and Move-to-Sport.
Intervention(s)	A 12-week gradual "start-to-run" program with the aim of completing a 5km run during a public event on 26th April 2015 (Antwerp 10 miles). People received training instructions by email and were asked to train three times weekly according to a personalized training intensity schedule that was based on their baseline aerobic capacity. During the first weeks, training consisted of longer walking bouts, interspersed with 1' running bouts. The relative amount of running gradually increased until participants were able to run 5km without interruption at 12 weeks. They wore an activity tracker (Withings Pulse Ox) at the waist that registered the intensity of steps per minute. People were asked to weekly upload data to allow remote supervision of the training adherence by the research assistant. If a participant had been inactive, a phone call was made for enquiry. Besides, two group training sessions were organised (weeks 4 and 8) at a 400m outdoor running track at KULeuven. Participants performed their individual training sessions simultaneously, while being observed by the project dedicated researcher and master students. This allowed to monitor individual progress and discuss potential risk for injuries. In addition, the sessions included elements of education, individual knowledge acquisition also related to observing others, and communication within the context of shared experiences and social interactions.

	Concomitant therapy: No additional information. Intervention subgroups: Individual vs. group - Mixed (includes group component). Remote vs. in person - Mixed (mostly remote, but a couple of in person components).
Population subgroups	According to type: Not stated/unclear. According to disability: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.
Comparator	Waiting list control with the intervention being completed after 12 weeks with the participants completing a different 5km running event on 11 October 2015 (Dwars door Hasselt). Concomitant therapy: No additional information.
Number of participants	42
Duration of follow-up	12 weeks
Indirectness	No additional information.
Additional comments	Intention -to-treat analysis was performed (no additional information).

Study arms

Exercise including aerobic exercise training (N = 21)

A 12-week gradual "start-to-run" program with the aim of completing a 5km run during a public event on 26th April 2015 (Antwerp 10 miles). People received training instructions by email and were asked to train three times weekly according to a personalized training intensity schedule that was based on their baseline aerobic capacity. During the first weeks, training consisted of longer walking bouts, interspersed with 1' running bouts. The relative amount of running gradually increased until participants were able to run 5km without interruption at 12 weeks. They wore an activity tracker (Withings Pulse Ox) at the waist that registered the intensity of steps per minute. People were asked to weekly upload data to allow remote supervision of the training adherence by the research assistant. If a participant had been inactive, a phone call was made for enquiry. Besides, two group training sessions were organised (weeks 4 and 8) at a 400m outdoor running track at KULeuven. Participants performed their individual training sessions simultaneously, while being observed by the project dedicated researcher and master students. This allowed to monitor individual progress and discuss potential risk for injuries. In addition, the sessions included elements of education, individual knowledge acquisition also related to observing others, and communication within the context of shared experiences and social interactions.

Waiting list (N = 21)

Waiting list control with the intervention being completed after 12 weeks with the participants completing a different 5km running event on 11 October 2015 (Dwars door Hasselt).

Characteristics

Arm-level characteristics

Characteristic	Exercise including aerobic exercise training (N = 21)	Waiting list (N = 21)
% Female Sample size	n = 20 ; % = 95.2	n = 18 ; % = 85.7
Mean age (SD) (years) Mean (SD)	36.6 (8.5)	44.4 (8.5)

Characteristic	Exercise including aerobic exercise training (N = 21)	Waiting list (N = 21)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
Disease duration (years) Mean (SD)	8.1 (6.1)	9.2 (5.3)

Outcomes

Study timepoints

- Baseline
- 12 week

Exercise including aerobic exercise training compared to waiting list at 3-6 months - continuous outcomes (final values)

Outcome	Exercise including aerobic exercise training, Baseline, N = 21	Exercise including aerobic exercise training, 12 week, N = 21	Waiting list, Baseline, N = 21	Waiting list, 12 week, N = 21
Physical domain Mean (SD)	32.3 (8.8)	26.2 (10.2)	29.3 (9.4)	29.6 (8.2)
Cognitive domain	33.4 (10)	28 (12.6)	28.9 (10)	28.9 (10.1)

Outcome	Exercise including aerobic exercise training, Baseline, N = 21	Exercise including aerobic exercise training, 12 week, N = 21	Waiting list, Baseline, N = 21	Waiting list, 12 week, N = 21
Mean (SD)				
Physical subscale Mean (SD)	23.5 (14.4)	16.3 (12.6)	16.4 (13.3)	22.3 (18.9)
Psychological subscale Mean (SD)	30 (24.3)	23 (17.2)	21.3 (20.8)	23.7 (18)
Cognitive functions (Digit Symbol Substitution Test) (Number of digits) Mean (SD)	92 (15)	94.3 (15.9)	83.5 (13.8)	85.5 (12.2)
Cognitive functions (Word List Generation) (Number of words) Mean (SD)	30.6 (8.5)	32.5 (7.4)	80.9 (9.7)	31.4 (7.8)
Long-term storage Mean (SD)	50.5 (6.2)	47.2 (10.6)	49.2 (6.8)	50.8 (7.8)
Consistent long-term retrieval Mean (SD)	58.4 (7.2)	53.2 (10)	59.7 (8.2)	62 (9.3)
Cognitive functions (Spatial Recall Test) (Number of correct answers)	43.1 (6.8)	48 (5.8)	44.7 (5)	44.4 (6.4)

Outcome	Exercise including aerobic exercise training, Baseline, N = 21	Exercise including aerobic exercise training, 12 week, N = 21	Waiting list, Baseline, N = 21	Waiting list, 12 week, N = 21
Mean (SD)				
Cognitive Functions (Paced Auditory Serial Attention Test) (Number of correct answers) Mean (SD)	47.8 (7.7)	50.7 (8.3)	48 (11)	48.6 (7.2)

Patient-reported outcome measures to assess MS fatigue (fatigue scale for motor and cognitive challenge) - Polarity - Lower values are better

Health-related Quality of Life (Multiple Sclerosis Impact Scale-29) - Polarity - Lower values are better

Cognitive functions (Digit Symbol Substitution Test) - Polarity - Higher values are better

Cognitive functions (Word List Generation) - Polarity - Higher values are better

Cognitive functions (Selective reminding test) - Polarity - Higher values are better

Cognitive functions (Spatial Recall Test) - Polarity - Higher values are better

Cognitive Functions (Paced Auditory Serial Attention Test) - Polarity - Higher values are better

Exercise including aerobic exercise training compared to waiting list at 3-6 months - dichotomous outcomes

Outcome	**Exercise including aerobic exercise training, Baseline, N = 21**	**Exercise including aerobic exercise training, 12 week, N = 21**	**Waiting list, Baseline, N = 21**	**Waiting list, 12 week, N = 21**
Acceptability of the intervention (people missing training sessions)	NR	6	NR	0

Outcome	Exercise including aerobic exercise training, Baseline, N = 21	Exercise including aerobic exercise training, 12 week, N = 21	Waiting list, Baseline, N = 21	Waiting list, 12 week, N = 21
Nominal				
Incidence of adverse events Training: 2 repetitive strain injury, 2 training-related fatigue, 1 hip and groin pain, 1 calf muscle strain Nominal	NA	6	NR	0

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (fatigue scale for motor and cognitive challenge) – Physical domain – Mean SD - Exercise including aerobic exercise training - Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values) -Patient-reported outcome measures to assess MS fatigue (fatigue scale for motor and cognitive challenge) – Cognitive domain- Mean SD-Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exerciseincludingaerobicexercisetrainingcomparedtowaitinglistat3-6months-continuousoutcomes(finalvalues)-Health-relatedQualityofLife(MultipleSclerosisImpactScale-29)-PhysicalsubscaleMeanSD-Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values)-Health-related Quality of Life (Multiple Sclerosis Impact Scale -29) – Psychological subscale – Mean SD - Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values)-Cognitive functions (Digit Symbol Substitution Test)-Mean SD - Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values)-Cognitive functions (Word List Generation) - Mean SD - Exercise including aerobic exercise training - Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values)-Cognitive functions (Selective reminding test) - Long-term storage – Mean SD - Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values) -Cognitive functions (Selective reminding test) – Consistent long-term retrieval- Mean SD-Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values)-Cognitive functions (Spatial Recall Test) – Mean SD -Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – continuous outcomes (final values) -Cognitive Functions (Paced Auditory Serial Attention Test) – Mean SD - Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – dichotomous outcomes -Acceptability of the intervention (people missing training sessions) - Nominal-Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to waiting list at 3-6 months – dichotomous outcomes -Incidence of adverse events - Nominal-Exercise including aerobic exercise training-Waiting list-t12

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Flachenecker, 2020

Bibliographic Reference	**Flachenecker, P.; Bures, A. K.; Gawlik, A.; Weiland, A. C.; Kuld, S.; Gusowski, K.; Streber, R.; Pfeifer, K.; Tallner, A.; Efficacy of an Internet-Based Program to Promote Physical Activity and Exercise after Inpatient Rehabilitation in Persons with Multiple Sclerosis: A Randomized, Single-Blind, Controlled Study; International Journal of Environmental Research & Public Health [Electronic Resource]; 2020; vol. 17 (no. 12); 24**

Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	Not reported
Study location	Germany

Study setting	Outpatient intervention following initial inpatient rehabilitation
Study dates	Patients admitted between August 2015 and May 2016 were considered for inclusion
Sources of funding	Funded in part by Freundeskreis Quellenhof e.V, a non-profit organisation
Inclusion criteria	Diagnosis of MS according to 2005 McDonald criteria; age ≥ 18 years; EDSS score ≤ 6.0; presence of fatigue, as indicated by a Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS) score ≥ 32; willingness to undergo an outpatient visit after 3 months and to participate in a postal survey after 6 months; and internet access and basic computer knowledge
Exclusion criteria	Relapse and/or had received corticosteroids within 30 days before inclusion; suffered from cognitive deficits, severe hand dysfunction, and/or serious cardiovascular disease (heart failure, cardiac arrhythmia, aortic stenosis, instable hypertension); and had already performed regular endurance (≥2/week) and/or resistance training (≥1/week)
Recruitment / selection of participants	All patients admitted to inpatient rehabilitation at the Neurological Rehabilitation Center Quellenhof between August 2015 and May 2016 were considered eligible for the study.
Intervention(s)	Internet-delivered behaviour-oriented exercise and physical activity promotion programme (following usual inpatient rehabilitation) - 3 months: received usual, goal-oriented, specifically tailored multimodal inpatient rehabilitation programme initially. When discharged, they received a behaviour-oriented exercise and physical activity promotion programme for three months. Aimed at increasing motivational and volitional determinants as well as necessary competences for a self-determined, physically active lifestyle. Programme started with a half-day educational seminar at end of inpatient rehabilitation. Involved two components: web- and phone-based behaviour-oriented physical activity coaching with one individual and four group sessions; and an individual exercise prescription in a 1-1 approach using specialised browser software. Participants used the software to document their exercises and to plan their activities and sessions in a physical activity diary. Exercise therapists used patient feedback and exercise parameters (ratio of perceived exertion, heart rate) to supervise and manage exercises and activities. The communication with patients took place via a built-in messenger or by e-mail, telephone, or video conference. Participants determined their exercise regime in consultation with their therapists, according to their individual goals and health situation. Individual exercise prescription was based on general recommendations for strength training (6–8 exercises for the major muscle groups, 1–2 times per week) and endurance training (free choice of activity, 10–60 min, 1–2 times a week). The recommendation for exercise intensity was light to

	moderate. There was no standardized warmup for training sessions. All exercises could easily be performed at home without expensive equipment. Therapists could choose from a catalogue with 220 exercises (strength, endurance, core stability, balance, and flexibility) that accounted for varying fitness levels and functional limitations. Exercises adapted for those participants that were severely affected were available for example in sitting, lying or kneeling positions with instructions to avoid falling or stepping. The training was performed over a period of 3 months and started directly after discharge from inpatient rehabilitation.
Population subgroups	None reported.
Comparator	Control: usual care following discharge for 3 months. eceived usual, goal-oriented, specifically tailored multimodal inpatient rehabilitation programme initially. When discharged, they received care as usual. Did not receive study intervention and told not to change their habits, including physical activity.
Number of participants	N=84 randomised, n=64 analysed
Duration of follow-up	Up to 6 months post-discharge (3 months after the last intervention session).
Indirectness	None.
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Internet-based physical activity promotion in addition to inpatient rehabilitation (N = 42)

Control - inpatient rehabilitation only (N = 42)

Characteristics

Arm-level characteristics

Characteristic	Internet-based physical activity promotion in addition to inpatient rehabilitation (N = 42)	Control - inpatient rehabilitation only (N = 42)
% Female Sample size	n = 22 ; % = 64.7	n = 17 ; % = 56.7
Mean age (SD) Mean (SD)	47.6 (9.2)	46.4 (12.2)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Disease duration (years) Mean (SD)	13.4 (7.9)	9 (7.5)
EDSS score Scale 0-10. Higher indicates increased disability. Median (IQR)	4.3 (3.5 to 5)	4 (3 to 6)

Characteristic	Internet-based physical activity promotion in addition to inpatient rehabilitation (N = 42)	Control - inpatient rehabilitation only (N = 42)
Relapsing-remitting MS type Sample size	n = 19 ; % = 55.9	n = 20 ; % = 66.7

Note that baseline values are given for those analysed (n=34 vs. n=30) rather than those randomised (n=42 per group)

Outcomes

Study timepoints

- Baseline
- 6 month (6 months post-discharge (3 months after last intervention session))

Results - change from baseline

Outcome	Internet-based physical activity promotion in addition to inpatient rehabilitation, 6 month vs Baseline, N = 34	Control - inpatient rehabilitation only, 6 month vs Baseline, N = 30
WEIMuS fatigue scale Scale 0-68. Median (IQR) values at baseline were: 45 (38-52) vs. 39 (36-46). P-value vs. control	less than 0.001	NA
WEIMuS fatigue scale Scale 0-68. Median (IQR) values at baseline were: 45 (38-52) vs. 39 (36-46). Median (IQR)	22.5 (8 to 30)	5.5 (1 to 11)

WEIMuS fatigue scale - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results WEIMus Fatigue Scale 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Fleming, 2019

Bibliographic Reference	**Fleming, K. M.; Coote, S. B.; Herring, M. P.; The feasibility of Pilates to improve symptoms of anxiety, depression, and fatigue among people with Multiple Sclerosis: an eight-week randomized controlled pilot trial; Psychology of sport and exercise; 2019; vol. 45; npag**

Study details

Trial name / registration number	Not reported.
Study location	Ireland
Study setting	Outpatient
Study dates	Recruited from March 2017 to June 2017.
Sources of funding	No financial disclosures or conflicts of interest reported by any authors.
Inclusion criteria	>18 years old; Patient Determine Disease Steps (PDDS) score <3.0; free from any other significant physical or psychiatric condition; no previous Pilates experience; and no medical contraindications to safe participation in physical activity (assessed by Physical Activity Readiness Questionnaire).
Exclusion criteria	No further criteria reported.
Recruitment / selection of participants	Through MS Society of Ireland Midwest region via posters and participation information leaflets on social media, and text alerts to members.
Intervention(s)	Pilates. Two separate groups were randomised but combined for the purpose of this review. Pilates included two weekly sessions for 8 weeks (1 h per session). Mat-based beginner level exercise. Four repetitions of each movement during first 2 weeks and intensity self-regulated by participant based on physical condition. Repetitions gradually progressed at 2-week

	intervals leading to 10 repetitions at weeks 7 and 8 Post-stretched were maintained for at least 30 seconds. Sessions were either supervised or home-based. Supervised group completed sessions at University of Limerick, with an instructor providing instruction on all movements, maintaining visual contact and providing individual participant feedback if required. The home-based group performed the sessions at home supported by a DVD developed by the research group.
Population subgroups	None reported.
Comparator	Waitlist control group. Asked to maintain pre-trial activity levels for 8 weeks and completed assessments online.
Number of participants	N=18 randomised.
Duration of follow-up	Up to 8 weeks follow-up - end of treatment
Indirectness	None.
Method of analysis	Unclear

Study arms

Pilates (N = 11)

Supervised or home-based Pilates. Two separate randomised groups combined as a single group for the purposes of this review.

Control (N = 7)

Waitlist control group.

Characteristics

Arm-level characteristics

Characteristic	Pilates (N = 11)	Control (N = 7)
% Female Sample size	n = 11 ; % = 100	n = 6 ; % = 86
Mean age (SD) Mean (SD)	49.5 (9.6)	51.3 (6.8)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
STAI-Y1 - anxiety State Subscale of State-Trait Anxiety Inventory. Scale not reported but based on information from elsewhere is usually 20-80. Higher indicates worse anxiety. Mean (SD)	32.2 (8.7)	40.3 (12.2)
STAI-Y2 - anxiety Trait Subscale of State-Trait Anxiety Inventory. Scale not reported but based on information from elsewhere is usually 20-80. Higher indicates worse anxiety. Mean (SD)	36.2 (10.4)	46.4 (13.1)

Characteristic	Pilates (N = 11)	Control (N = 7)
MFIS total Modified Fatigue Impact Scale. Scale usually 0-84. Higher indicates worse fatigue. Mean (SD)	36.1 (12.6)	49 (15.7)
MFIS - physical Modified Fatigue Impact Scale. Scale usually 0-36. Higher indicates worse fatigue. Mean (SD)	20.2 (8.2)	23.6 (7.4)
MFIS - cognitive Modified Fatigue Impact Scale. Scale usually 0-40. Higher indicates worse fatigue. Mean (SD)	12.3 (4.6)	20.1 (9.2)
MFIS - psychosocial Modified Fatigue Impact Scale. Scale usually 0-8. Higher indicates worse fatigue. Mean (SD)	3.6 (2.6)	5.3 (1.5)
HADS - anxiety Hospital Anxiety and Depression Scale. Scale usually 0-21. Higher indicates worse anxiety. Mean (SD)	12.5 (1.7)	11.1 (2.4)
HADS - depression Hospital Anxiety and Depression Scale. Scale usually 0-21. Higher indicates worse depression. Mean (SD)	7.5 (1.3)	8.4 (1.4)

Characteristic	Pilates (N = 11)	Control (N = 7)
QIDS - depression Quick Inventory of Depressive Symptomatology. Scale usually 0-27. Higher indicates worse depression. Mean (SD)	6.3 (3.8)	8.7 (4.8)
POMS-B TMD Profile of Mood States-Brief Total Mood Disturbance. Scale unclear. Higher is worse outcome. Mean (SD)	12.4 (14.5)	21.4 (15.6)
POMS - Depression subscale Profile of Mood States-Brief, Depression subscale. Scale unclear. Higher is worse outcome. Mean (SD)	2.1 (3.6)	3 (2.8)
POMS - Fatigue Profile of Mood States-Brief, Fatigue subscale. Scale unclear. Higher is worse outcome. Mean (SD)	6.2 (4.5)	8.7 (4.5)

Outcomes

Study timepoints

- Baseline
- 8 week (End of 8-week treatment period. Indirectness as specified minimum follow-up of 3 months in protocol.)

Results - raw data

Outcome	Pilates, Baseline, N = 11	Pilates, 8 week, N = 9	Control, Baseline, N = 7	Control, 8 week, N = 6
MFIS total Modified Fatigue Impact Scale. Scale usually 0-84. Mean (SD)	36.1 (12.6)	24.4 (10.3)	49 (15.7)	48.3 (13.7)
MFIS - physical Modified Fatigue Impact Scale. Scale usually 0-36. Mean (SD)	20.2 (8.2)	13.1 (4.2)	23.6 (7.4)	22.8 (6.7)
MFIS - cognitive Modified Fatigue Impact Scale. Scale usually 0-40. Mean (SD)	12.3 (4.6)	8.9 (7.3)	20.1 (9.2)	20.8 (9.4)
MFIS - psychosocial Modified Fatigue Impact Scale. Scale usually 0-8. Mean (SD)	3.6 (2.6)	2.3 (1.3)	5.3 (1.5)	4.7 (0.8)
STAI-Y1 - anxiety State Subscale of State-Trait Anxiety Inventory. Scale not reported but based on information from elsewhere is usually 20-80. Mean (SD)	32.2 (8.7)	24.5 (3.8)	40.3 (12.2)	43 (7.3)

Outcome	Pilates, Baseline, N = 11	Pilates, 8 week, N = 9	Control, Baseline, N = 7	Control, 8 week, N = 6
STAI-Y2 - anxiety Trait Subscale of State-Trait Anxiety Inventory. Scale not reported but based on information from elsewhere is usually 20-80. Mean (SD)	36.2 (10.4)	32.6 (8.7)	46.4 (13.1)	48.5 (14.2)
HADS - anxiety Hospital Anxiety and Depression Scale. Scale usually 0-21. Mean (SD)	12.5 (1.7)	13 (2)	11.1 (2.4)	10.7 (2.7)
HADS - depression Hospital Anxiety and Depression Scale. Scale usually 0-21. Mean (SD)	7.5 (1.3)	4 (5.9)	8.4 (1.4)	9.3 (2.7)
QIDS - depression Quick Inventory of Depressive Symptomatology. Scale usually 0-27. Mean (SD)	6.3 (3.8)	4.3 (3.2)	8.7 (4.8)	9.5 (7.1)
POMS-B TMD Profile of Mood States-Brief Total Mood Disturbance. Scale unclear. Mean (SD)	12.4 (14.5)	1.6 (5.6)	21.4 (15.6)	26 (20.6)

Outcome	Pilates, Baseline, N = 11	Pilates, 8 week, N = 9	Control, Baseline, N = 7	Control, 8 week, N = 6
POMS-B Depression subscale Profile of Mood States-Brief, Depression subscale. Scale unclear. Mean (SD)	2.1 (3.6)	0.1 (0.3)	3 (2.8)	4.3 (3.9)
POMS-B Fatigue subscale Profile of Mood States-Brief, Fatigue subscale. Scale unclear. Mean (SD)	6.2 (4.5)	1.7 (2.2)	8.7 (4.5)	9.3 (6.6)
Adverse events Reported to be no adverse events. No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Compliance - completion of all 16 sessions Only reported for the Pilates group, no measure for control. Custom value	NA	8 did not complete all Pilates sessions (n=2 missed two and n=1 missed three) - all in supervised.	NA	All reported to have completed all outcome assessments.
Compliance - completion of all 16 sessions Only reported for the Pilates group, no measure for control. Number analysed	NA	11	NA	9

MFIS total - Polarity - Lower values are better

MFIS - physical - Polarity - Lower values are better

MFIS - cognitive - Polarity - Lower values are better

MFIS - psychosocial - Polarity - Lower values are better

STAI-Y1 - anxiety - Polarity - Lower values are better

STAI-Y2 - anxiety - Polarity - Lower values are better

HADS - anxiety - Polarity - Lower values are better

HADS - depression - Polarity - Lower values are better

QIDS - depression - Polarity - Lower values are better

POMS-B TMD - Polarity - Lower values are better

POMS-B Depression subscale - Polarity - Lower values are better

POMS-B Fatigue subscale - Polarity - Lower values are better

Numbers analysed as shown in participant flow diagram.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results MFIS physical 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results MFIS cognitive 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results MFIS psychosocial 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results STAI-Y1 anxiety 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results STAI-Y2 anxiety 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results HADS anxiety 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results HADS depression 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results QIDS depression 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results POMS-B TMD 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results POMS Depression subscale 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results POMS Fatigue subscale 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results adverse events 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Results compliance 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up less than the 3 months minimum specific in protocol)*

Fleming, 2021

Bibliographic Reference	**Fleming, K. M.; Coote, S. B.; Herring, M. P.; Home-based Pilates for symptoms of anxiety, depression and fatigue among persons with multiple sclerosis: An 8-week randomized controlled trial; Multiple Sclerosis; 2021; 13524585211009216**

Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	NCT04120207
Study location	Ireland
Study setting	Outpatient
Study dates	Recruitment began in January 2018 and data collection ended August 2019
Sources of funding	Received no financial support for the research, authorship and/or publication of the article
Inclusion criteria	Adults (>18 years) with self-reported, physician-diagnosed MS; patient-determined disease steps score < 3; no conditions or medical contraindications that would preclude safely participating in a Pilates programme established with Physical Activity Readiness Questionnaire (PARQ); and no previous Pilates experience.
Exclusion criteria	Pregnancy; MS relapse; or changes to MS medication or steroid treatment in the prior 12 weeks
Recruitment / selection of participants	Recruitment began in January 2018 and data collection ended August 2019. Home-based setting allowed recruitment through MS Ireland via posters and participation information leaflets distributed on social media and via text alerts. Males and females recruited to obtain representative population.
Intervention(s)	Home-based Pilates: twice weekly sessions, 48 h apart, for 8 weeks at home. Supported by a DVD that was developed, implemented and evaluated in a feasibility trial among people with MS. DVD Pilates instructor qualified with experience of 10 years, does not have CBT, psychology or coaching training but regularly teaches group classes to people with various

	abilities. Participants supported by weekly telephone call about frequency, intensity and duration of completed sessions, exercise completion difficulties, adverse events or relapses.
Population subgroups	None
Comparator	Waitlist control: maintained pre-intervention physical activity levels and contacted by email or telephone to ensure completion of biweekly outcome assessments.
Number of participants	80 randomised, 80 analysed at week 8
Duration of follow-up	Up to 8 weeks - end of intervention
Indirectness	Outcome - 8-week follow-up (<3-month minimum specified in the protocol)
Additional comments	Primary analysis stated to be intention to treat in the full sample, despite some missing data at 8-weeks (n=29 and n=34 with data at week 8 in two groups, respectively).

Study arms

Home-based Pilates (N = 39)

Waitlist control (N = 41)

Characteristics

Arm-level characteristics

Characteristic	Home-based Pilates (N = 39)	Waitlist control (N = 41)
% Female Sample size	n = 36 ; % = 92.31	n = 33 ; % = 80.49
Mean age (SD) Mean (SD)	46.7 (10)	47.4 (10.2)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Fatigued (>38 on MFIS total) Modified Fatigue Impact Scale. Sample size	n = 27 ; % = 69.2	n = 28 ; % = 68.3

Outcomes

Study timepoints

Baseline

8 week (8-weeks - end of intervention)

Results - raw data

Outcome	Home-based Pilates, Baseline, N = 39	Home-based Pilates, 8 week, N = 39	Waitlist control, Baseline, N = 41	Waitlist control, 8 week, N = 41
MFIS - total Modified Fatigue Impact Scale. Scale usually 0-84. Mean (SD)	43.6 (9.8)	31 (13.5)	43.6 (14.3)	40.5 (15.8)
MFIS - physical subdomain Modified Fatigue Impact Scale. Scale usually 0-36. Mean (SD)	22.1 (5.5)	16.1 (6.2)	22.3 (7.1)	21.3 (7.9)
MFIS - cognitive subdomain Modified Fatigue Impact Scale. Scale usually 0-40. Mean (SD)	16.8 (7.1)	11.7 (8.3)	17.1 (7.8)	15.3 (9)
MFIS - psychosocial Modified Fatigue Impact Scale. Scale usually 0-8. Mean (SD)	4.6 (1.5)	3.2 (1.8)	4.3 (2.3)	4 (2.2)
Anxiety - STAI-Y2 Trait Subscale of the State-Trait Anxiety Inventory. Scale usually 20-80. Mean (SD)	43 (9.8)	37.1 (9.1)	41.3 (11.8)	38.7 (10.2)
Anxiety - HADS Hospital Anxiety and Depression Scale. Scale usually 0-21. Mean (SD)	8.4 (4.1)	5.1 (3)	7 (4.3)	5.8 (4.3)

Outcome	Home-based Pilates, Baseline, N = 39	Home-based Pilates, 8 week, N = 39	Waitlist control, Baseline, N = 41	Waitlist control, 8 week, N = 41
Depression - QIDS Quick Inventory of Depressive Symptomatology. Scale usually 0-27. Mean (SD)	8.7 (4.1)	5.1 (2.7)	7.8 (4.9)	7.4 (3.7)
Depression - HADS Hospital Anxiety and Depression Scale. Scale usually 0-21. Mean (SD)	6.8 (3.3)	4 (3.1)	5.7 (3.1)	5.3 (3)
Adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Discontinuation possibly related to intervention either unable to commit at that moment in time (n=3) or found exercise difficult (n=2) No of events	n = NA ; % = NA	n = 5 ; % = 12.8	n = NA ; % = NA	n = 6 ; % = 14.6

MFIS - total - Polarity - Lower values are better

MFIS - physical subdomain - Polarity - Lower values are better

MFIS - cognitive subdomain - Polarity - Lower values are better

MFIS - psychosocial - Polarity - Lower values are better

Anxiety - STAI-Y2 - Polarity - Lower values are better

Anxiety - HADS - Polarity - Lower values are better

Depression - QIDS - Polarity - Lower values are better

Depression - HADS - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results MFIS physical 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results MFIS cognitive 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results MFIS psychosocial 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results STAI-Y2 anxiety 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results HADS anxiety 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results QIDS depression 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results HADS depression 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results adverse events 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at time-point <3-month minimum specified in the protocol)*

Results adherence - discontinuation due to intervention 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Grubic Kezele, 2019

Bibliographic Reference	**Grubic Kezele, T.; Babic, M.; Stimac, D.; Exploring the feasibility of a mild and short 4-week combined upper limb and breathing exercise program as a possible home base program to decrease fatigue and improve quality of life in ambulatory and non-ambulatory multiple sclerosis individuals; Neurological Sciences; 2019; vol. 40 (no. 4); 733-743**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	Croatia
Study setting	MS Society Center - outpatient
Study dates	NR
Sources of funding	NR
Inclusion criteria	Diagnosis of MS with mild to severe disability (EDSS score between 0.0 [normal neurological exam] and 8.0 [essentially restricted to wheelchair, retains many self-care functions, generally has effective use of arms]), adults between the age of 18 and 70 years, patients with Standardized Mini-Mental State Examination [19] > 24 and with no contraindications for performing breathing and UL exercises.
Exclusion criteria	An exacerbation of MS or corticosteroid treatment within the past 4 weeks, the presence of concomitant neurological and musculoskeletal disorders affecting arms, acute or chronic lung pathologies, breathing difficulties or any other serious illness that might interfere with the intervention

Recruitment / selection of participants	The patients with diagnosed MS were randomly selected based on previous EDDS score (from 6 months ago) from the MSSC register. To establish the participants' interest in the research, the first contact was by phone. Before being included in the study, all 19 individuals were invited to the MSSC to meet the study inclusion and exclusion criteria checked by a two physicians (researchers). The physician (the principal researcher) assessed the participants' characteristics (sex, age, medications). Another physician (researcher blind to the intervention), who was trained to assess EDSS status, as well the type of MS based on standard diagnostic criteria, confirmed EDSS score
Intervention(s)	The exercise group exercised under physiotherapist guidance performing strengthening, coordination stretches and breathing exercises. They exercised 2 days/week, 60 min/session in the MSSC and performed independent home exercise 3 days/week for 4 weeks, at least 20 min/session. Adherence was monitored every week by registering the number of completed sessions at the MSSC and at home. The amount of physical activity performed with HE was monitored 2/week by asking the number of sessions per week and duration of each exercise during a session. The on-going physical therapy (without UL and breathing exercises 2/week for 45 min) was unchanged during the study for all patients (exercise and control group). At the end of the study (day after the last session), outcome measures were collected by the same independent researcher who assessed the baseline data.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - over 6 · Disease modifying treatment status (currently using and not currently using) - mixed · Group vs individual - group and home based · Delivered remotely vs in person - in person Reports data separately for ambulatory and non-ambulatory groups, threshold used to define this unclear but median EDSS in two groups was <6.0 (3.0-4.75 in the two groups) and ≥6.0 (7.0 in both groups), respectively.
Comparator	The control group performed no exercise during the investigation but they were required to visit the MSSC 2 days/week (≤ 60 min) where they could freely socialize, having thereby approximately the same contact with the investigators as the exercise group. The control group was offered the exercise program at the end of the study, which everyone accepted. The

	on-going physical therapy (without UL and breathing exercises 2/week for 45 min) was unchanged during the study for all patients (exercise and control group). At the end of the study (day after the last session), outcome measures were collected by the same independent researcher who assessed the baseline data.
Number of participants	19 randomised and analysed
Duration of follow-up	4 weeks - end of treatment
Indirectness	indirect FU period - marked down as less than 3 months
Method of analysis	Intention to treat - all randomised
Additional comments	Results reported separately for ambulatory and non-ambulatory groups but combined for the purpose of this review.

Study arms

Combined upper limb and breathing exercise for a home-based program (N = 10)

Control group - no exercise (N = 9)

Characteristics

Arm-level characteristics

Characteristic	Combined upper limb and breathing exercise for a home-based program (N = 10)	Control group - no exercise (N = 9)
% Female Sample size	n = 4 ; % = 40	n = 3 ; % = 33
Age Mean (SD)	53.9 (10.7)	48.2 (9.3)
Relapsing-remitting MS Sample size	n = 4 ; % = 40	n = 6 ; % = 67
Primary progressive MS Sample size	n = 2 ; % = 20	n = 0 ; % = 0
Secondary progressive MS Sample size	n = 4 ; % = 40	n = 3 ; % = 33
EDSS Expanded Disability Status Scale. Scale 0-10. Higher indicates higher disability. Median (range)	6.5 (1.0-8.0)	7.0 (1.0-7.5)
Interferon beta-1a Sample size	n = 1 ; % = 10	n = 0 ; % = 0
Fingolimod	n = 1 ; % = 10	n = 1 ; % = 11

Characteristic	Combined upper limb and breathing exercise for a home-based program (N = 10)	Control group - no exercise (N = 9)
Sample size		
Azathioprine Sample size	n = 0 ; % = 0	n = 1 ; % = 11
Glatiramer acetate Sample size	n = 1 ; % = 10	n = 2 ; % = 22
None Sample size	n = 7 ; % = 70	n = 5 ; % = 56

Outcomes

Study timepoints

Baseline

4 week

outcomes

Outcome	Combined upper limb and breathing exercise for a home-based program, Baseline, N = 10	Combined upper limb and breathing exercise for a home-based program, 4 week, N = 10	Control group - no exercise, Baseline, N = 9	Control group - no exercise, 4 week, N = 9
MFIS physical Modified Fatigue Impact Scale. Scale usually 0-36. Mean (SD)	22 (6.1)	16.6 (6.2)	20.5 (11.2)	19.9 (10.9)
MFIS cognitive Modified Fatigue Impact Scale. Scale usually 0-40 Mean (SD)	14 (7.6)	10.3 (6.7)	12.2 (8.6)	11.6 (7.6)
MFIS psychosocial Modified Fatigue Impact Scale. Scale usually 0-8 Mean (SD)	3.3 (2.1)	2.2 (1.9)	3.3 (2.7)	3.6 (2.3)
MFIS total Modified Fatigue Impact Scale. Scale usually 0-84 - reports as 0-82 in report but likely this is incorrect based on number of items said to be included. Mean (SD)	39.3 (12.6)	29.5 (13.6)	36 (18.2)	35.9 (17.8)
SF-36 general health Scale 0-100.	48 (16.9)	49.5 (11.8)	46.7 (21.6)	41.1 (24.1)

Outcome	Combined upper limb and breathing exercise for a home-based program, Baseline, N = 10	Combined upper limb and breathing exercise for a home-based program, 4 week, N = 10	Control group - no exercise, Baseline, N = 9	Control group - no exercise, 4 week, N = 9
Mean (SD)				
SF-36 Physical Functioning Scale 0-100. Mean (SD)	32.5 (31.9)	38.5 (34.8)	45.6 (43.4)	43.9 (43.9)
SF-36 Physical Limitation Scale 0-100. Mean (SD)	30 (24.4)	50 (30.6)	41.2 (45.7)	44.4 (43)
SF-36 Emotional Limitation Scale 0-100 Mean (SD)	80.1 (37.8)	86.7 (33.9)	51.8 (44.1)	59.1 (42.7)
SF-36 Emotional Wellbeing Scale 0-100 Mean (SD)	71.4 (25.9)	75.6 (18.9)	66.4 (15.8)	64 (15.8)
SF-36 Pain Scale 0-100. Mean (SD)	66.8 (29.3)	76.3 (28.2)	65 (42.7)	64.2 (36.4)
SF-36 Energy/fatigue Scale 0-100.	55.5 (28.8)	60.5 (16)	48.3 (25.2)	49.1 (22.9)

Outcome	Combined upper limb and breathing exercise for a home-based program, Baseline, N = 10	Combined upper limb and breathing exercise for a home-based program, 4 week, N = 10	Control group - no exercise, Baseline, N = 9	Control group - no exercise, 4 week, N = 9
Mean (SD)				
SF-36 social functioning Scale 0-100. Mean (SD)	71.3 (25.6)	73.5 (26.4)	63.9 (30.7)	58.6 (31)
Adverse events (harm) Reported to be none. No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Compliance (% of exercise sessions attended) Not applicable for the control group Mean (SD)	NA (NA)	98 (4.2)	NA (NA)	NR (NR)

MFIS physical - Polarity - Lower values are better

MFIS cognitive - Polarity - Lower values are better

MFIS psychosocial - Polarity - Lower values are better

MFIS total - Polarity - Lower values are better

SF-36 general health - Polarity - Higher values are better

SF-36 Physical Functioning - Polarity - Higher values are better

SF-36 Physical Limitation - Polarity - Higher values are better

SF-36 Emotional Limitation - Polarity - Higher values are better

SF-36 Emotional Wellbeing - Polarity - Higher values are better

SF-36 Pain - Polarity - Higher values are better

SF-36 Energy/fatigue - Polarity - Higher values are better

SF-36 social functioning - Polarity - Higher values are better

Compliance (% of exercise sessions attended) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS physical 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results MFIS cognitive 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results MFIS psychosocial 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results MFIS total 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 general health 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 physical functioning 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 physical limitation 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 emotional limitation 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 emotional wellbeing 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 pain 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 energy/fatigue 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results SF-36 social functioning 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results adverse events (harm) 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Results compliance 4 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up 4 weeks and not the minimum of three months specified in protocol)*

Hasanpour Dehkordi, 2016

Bibliographic Reference	**Hasanpour Dehkordi, A.; Influence of yoga and aerobics exercise on fatigue, pain and psychosocial status in patients with multiple sclerosis: a randomized trial; Journal of Sports Medicine & Physical Fitness; 2016; vol. 56 (no. 11); 1417-1422**

Study details

Trial name / registration number	Not reported.
Study location	Iran
Study setting	Unclear
Study dates	Not reported.

Sources of funding	Not reported.
Inclusion criteria	Not reported.
Exclusion criteria	Not reported.
Recruitment / selection of participants	Not reported.
Intervention(s)	Yoga: three sessions (60-70 min) weekly for 12 weeks. Hatha yoga (breathing techniques, postures and meditation). Stretching followed by standing, supine, prone-lying and sitting postures. Each pose held for 10-30 seconds with rest periods in between of 30 seconds to 1 min. Emphasis on breathing for relaxation and concentration during the classes. Each session ended with a 10 min deep relaxation session. Practice at home was recommended. Given leaflet detailing the poses to allow practice at home. Performed in a sports centre or gym near the hospital and supervised by a nurse and neurologist. All poses planned based on individual need. Aerobic exercise: three sessions (40 min) weekly for 12 weeks. Consisted of 5-10 min warm-up, 25-30 min exercise (walking) and 5 min cooling down. Performed at sports centre or gym near to the hospital. Supervised by nurse or a neurologist. Target was to reach 60% of heart rate reserve when exercising. After 6 sessions, duration of walking increased to 30-35 min and heart rate to 70% heart rate reserve. Each individual exercised based on their ability and resistance. Stopped when participants were physically tired or experienced severe dyspnoea, fatigue, dizziness or other problems that could be a risk to health based on Rhoten Fatigue Scale.
Population subgroups	None reported.
Comparator	Control: no exercise protocol. Educational support. Asked to maintain prescribed medications and usual lifestyle and were supervised by their nurse and physicians.

Number of participants	N=90 randomised, n=61 analysed
Duration of follow-up	12 weeks - end of treatment
Indirectness	None.
Method of analysis	Unclear
Additional comments	

Study arms

Yoga (N = 30)

Hatha yoga three times weekly for 12 weeks.

Aerobic exercise (N = 30)

Walking exercise formed main component. Three sessions weekly for 12 weeks.

Control (N = 30)

Educational support - no exercise intervention.

Characteristics

Study-level characteristics

Characteristic	Study (N = 61)
% Female Sample size	n = 60 ; % = 98
Mean age (SD) (years) Mean	31.9
Ethnicity Custom value	NR
Comorbidities Custom value	NR

Study gives characteristics for those analysed (n=61) not randomised (n=90)

Outcomes

Study timepoints

- Baseline
- 12 week (12-weeks - end of treatment)

Results - raw data

Outcome	Yoga, Baseline, N = 20	Yoga, 12 week, N = 20	Aerobic exercise, Baseline, N = 20	Aerobic exercise, 12 week, N = 20	Control, Baseline, N = 21	Control, 12 week, N = 21
Rhoten Fatigue Scale VAS. Scale 0-10. Mean (SD)	4.75 (1.71)	3.35 (0.81)	4.9 (1.33)	2.55 (0.94)	3.8 (1.64)	3.55 (1.23)
SF-36 physical functioning Scale usually 0-100. Mean (SD)	40.1 (7.16)	50.14 (11.15)	44.14 (7.38)	52.12 (9.87)	42.2 (8.3)	38.12 (7.88)
SF-36 emotional limitations Scale usually 0-100. Mean (SD)	41.9 (9.16)	35.65 (12.3)	39.4 (12.8)	36.23 (12.65)	42.11 (4.7)	47.15 (11.65)
SF-36 physical role limitations Scale usually 0-100. Mean (SD)	49.14 (11.41)	45.45 (10.32)	52.1 (14.44)	46.14 (13.45)	48.12 (13.87)	52.14 (12.4)
SF-36 energy/vitality Scale usually 0-100. Mean (SD)	45.36 (12.18)	52.65 (11.87)	47.24 (13.78)	55.24 (11.54)	44.52 (9.45)	43.32 (8.45)
SF-36 Mental Health Scale usually 0-100.	53.98 (13.67)	60.54 (14.44)	54.87 (8.54)	61.78 (10.87)	52.4 (16.56)	50.44 (14.45)

Outcome	Yoga, Baseline, N = 20	Yoga, 12 week, N = 20	Aerobic exercise, Baseline, N = 20	Aerobic exercise, 12 week, N = 20	Control, Baseline, N = 21	Control, 12 week, N = 21
Mean (SD)						
SF-36 social functioning Scale usually 0-100. Mean (SD)	43.54 (11.48)	51.54 (9.45)	39.2 (11.87)	47.22 (8.78)	41.4 (9.54)	40.7 (8.44)
SF-36 Body Pain Scale usually 0-100. Mean (SD)	43.24 (6.98)	38.54 (9.25)	44.54 (8.4)	39.65 (11.19)	45.12 (10.54)	55.71 (9.47)
SF-36 general health Scale usually 0-100. Mean (SD)	46.24 (11.69)	51.22 (8.65)	47.65 (9.52)	55.23 (10.96)	48.54 (7.45)	42.65 (9.25)

Rhoten Fatigue Scale - Polarity - Lower values are better

SF-36 physical functioning - Polarity - Higher values are better

SF-36 emotional limitations - Polarity - Higher values are better

SF-36 physical role limitations - Polarity - Higher values are better

SF-36 energy/vitality - Polarity - Higher values are better

SF-36 Mental Health - Polarity - Higher values are better

SF-36 social functioning - Polarity - Higher values are better

SF-36 Body Pain - Polarity - Higher values are better

SF-36 general health - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results Rhoten Fatigue Scale 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional limitations 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical role limitations 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 energy/vitality 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 mental health 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 body pain 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 12 weeks yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Rhoten Fatigue Scale 12 weeks yoga vs. exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Rhoten Fatigue Scale 12 weeks exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 12 weeks yoga vs. aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 12 weeks aerobic exercise vs control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical role limitations 12 weeks yoga vs. aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical role limitations 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional limitations 12 weeks yoga vs. aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional limitations 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 energy/vitality 12 weeks yoga vs. aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 energy/vitality 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 mental health 12 weeks yoga vs aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 mental health 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 12 weeks yoga vs aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 body pain 12 weeks yoga vs. aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 body pain 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 12 weeks yoga vs. aerobic exercise

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 12 weeks aerobic exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hebert, 2018

Bibliographic Reference	**Hebert, J. R.; Corboy, J. R.; Vollmer, T.; Forster, J. E.; Schenkman, M.; Efficacy of Balance and Eye-Movement Exercises for Persons With Multiple Sclerosis (BEEMS); Neurology; 2018; vol. 90 (no. 9); e797-e807**

Study details

Trial name / registration number	NCT01698086.
Study location	USA
Study setting	Outpatient
Study dates	Not reported.

Sources of funding	Supported by a grant from the National Multiple Sclerosis Society (award NMSS research grant RG 4710A1/1). Some authors also reported receiving compensation for lectures and/or research support from the NMSS as well as from industry.
Inclusion criteria	Clinically definite MS; ambulation of at least 100 m with no greater than intermittent or unilateral constant use of an assistive device; aged 18-60 years; CDP-SOT composite score (balance test) ≤82 out of 100; and MFIS total score ≥22 out of 84.
Exclusion criteria	Non-ambulation; lower extremity orthoses, lower extremity spasticity >1 on Modified Ashworth Spasticity Scale; another neurological disorder contributing to balance problems; relapse within 3 months of enrolment; contraindication to physical activity; and participation in exercise specifically designed to improve balance or visual stability within 12 weeks of enrolment.
Recruitment / selection of participants	Recruited through Rocky Mountain MS Center, University of Colorado an by community-based advertisement.
Intervention(s)	Balance and eye movement exercises: twice weekly sessions with supervision and daily home exercise for 6 weeks (phase 1) followed by once weekly sessions with supervision and daily home exercise for 8 weeks (phase 2). Three main components were standing balance on different surfaces, mobility-based balance in walking with and without head movements and visual stability (including voluntary saccadic eye, smooth pursuit movements and dynamic gaze fixation). Visual input alterations included absent (eyes closed), conflicting (head and body movements without gaze fixation) and visual field movement and hand eye coordination (ball tossing and catching with eyes open). Somatosensory input alterations included base of support (progressive narrowing) and progressive complexity of surface (e.g. firm, compliant, rocking, reactive). Vestibular input alterations or stimulation of the peripheral end organ included head movements in the yaw and pitch directions and body movements in elevation and translation.
Population subgroups	None reported.
Comparator	Control - no treatment control, waitlist control.

Number of participants	N=88 randomised, n=76 analysed (per protocol analyses)
Duration of follow-up	Up to 14 weeks - end of treatment period
Indirectness	None.
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Balance and eye movement exercises (N = 44)

Received balance and eye movement exercises for 14 weeks.

Control (N = 44)

Waitlist control group.

Characteristics

Arm-level characteristics

Characteristic	Balance and eye movement exercises (N = 44)	Control (N = 44)
% Female Sample size	n = 37 ; % = 84	n = 38 ; % = 86

Characteristic	Balance and eye movement exercises (N = 44)	Control (N = 44)
Mean age (SD) Mean (SD)	46.5 (8.8)	43 (10.8)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Time since diagnosis (years) Mean (SD)	8.34 (5.7)	8.54 (7.6)
EDSS score Scale 0-10. Higher indicates increased disability. Mean (SD)	3.5 (1.1)	3.34 (1.1)

Outcomes

Study timepoints

- Baseline
- 14 week (14-weeks - end of intervention period)

Results - raw data

Outcome	Balance and eye movement exercises, Baseline, N = 44	Balance and eye movement exercises, 14 week, N = 38	Control, Baseline, N = 44	Control, 14 week, N = 38
MFIS total score Modified Fatigue Impact Scale. Scale 0-84. Mean (SE)	49.9 (2.1)	32.5 (2.4)	48.7 (2.1)	43.6 (2.3)
MFIS - physical score Modified Fatigue Impact Scale. Scale 0-36. Mean (SE)	23.9 (1)	16 (1.2)	23 (1)	20.7 (1.1)
MFIS - cognitive Modified Fatigue Impact Scale. Scale 0-40. Mean (SE)	21.6 (1.1)	14.2 (1.2)	21.4 (1.1)	19.3 (1.2)
MFIS - psychosocial Modified Fatigue Impact Scale. Scale 0-8. Mean (SE)	4.42 (0.26)	2.44 (0.31)	4.34 (0.26)	3.61 (0.3)
SF-36 physical component score. Scale usually 0-100. Mean (SE)	35.8 (1.3)	41 (1.4)	35.4 (1.3)	37.3 (1.4)
SF-36 mental component score Scale usually 0-100. Mean (SE)	42.6 (1.6)	48.2 (1.7)	42.9 (1.6)	44.6 (1.8)

Outcome	Balance and eye movement exercises, Baseline, N = 44	Balance and eye movement exercises, 14 week, N = 38	Control, Baseline, N = 44	Control, 14 week, N = 38
Perceived Deficits questionnaire Scale usually 0-80. Measure of cognitive deficit. Mean (SE)	37.8 (2.1)	29 (2.3)	37.6 (2.1)	35.3 (2.2)
Adverse events - MS relapse All lost to follow-up due to the relapse. Other minor adverse events occurred but proportion not reported in each group. Reported to be no serious adverse events. No of events	n = NA ; % = NA	n = 2 ; % = 5	n = NA ; % = NA	n = 3 ; % = 7.3
Adverse events - MS relapse All lost to follow-up due to the relapse. Other minor adverse events occurred but proportion not reported in each group. Reported to be no serious adverse events. Number analysed	NA	40	NA	41
Compliance Only reported for intervention group as no similar measure available for the control group. Custom value	NA	92% and 88% compliance in phase 1/2 supervised training, respectively. 81% returned home-based log.	NA	NR

MFIS total score - Polarity - Lower values are better

MFIS - physical score - Polarity - Lower values are better

MFIS - cognitive - Polarity - Lower values are better

MFIS - psychosocial - Polarity - Lower values are better

SF-36 physical component score. - Polarity - Higher values are better

SF-36 mental component score - Polarity - Higher values are better

Perceived Deficits questionnaire - Polarity - Lower values are better

Per protocol analyses for most outcomes but available case analysis (n=40 vs. n=41) could be calculated for the adverse events (relapse) outcome.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total score 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical score 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive score 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial score 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical component 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 mental component 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results PDQ cognitive 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events – relapse 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results compliance 14 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Heine, 2017

Bibliographic Reference	**Heine, M.; Verschuren, O.; Hoogervorst, E. L.; van Munster, E.; Hacking, H. G.; Visser-Meily, A.; Twisk, J. W.; Beckerman, H.; de Groot, V.; Kwakkel, G.; group, Trefams-Ace study; Does aerobic training alleviate fatigue and improve societal participation in patients with multiple sclerosis? A randomized controlled trial; Multiple Sclerosis; 2017; vol. 23 (no. 11); 1517-1526**

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	TREFAMS-AT (part of a multi-trial programme, TREFAMS-ACE). ISRCTN69520623.
Study type	Randomised controlled trial (RCT)

Study location	The Netherlands
Study setting	Outpatient follow up.
Study dates	October 2011 to October 2014
Sources of funding	The TREFAMS-ACE study was funded by the Fonds NutsOhra (ZonMw 89000005). The funding organisation had no role in the design and conduct of the study; collection, management, analysis and interpretation of data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.
Inclusion criteria	People with definite MS; age between 18 and 70 years, ambulant (EDSS 6 or less), severe fatigue (Checklist Individual Strength fatigue subscale of at least 35) and no signs of an MS exacerbation or corticosteroid treatment <3 months.
Exclusion criteria	Severe mood disorders (HADS depression subscale >11), severe co-morbidity (Cumulative Illness Rating Scale item scores of at least 3), current pregnancy or given birth <3 months, newly initiated pharmacological (e.g. amantadine) or non-pharmacological treatment for fatigue (e.g. structured aerobic training) <3 months.
Recruitment / selection of participants	People were recruited through physician or neurologist lists of patients at St Antonius Hospital, Nieuwegein, The Netherlands and Jeroen Bosch Hospital, Den Bosch, The Netherlands.
Intervention(s)	Aerobic training programme consisting of aerobic interval training, three times a week, for the duration of 16 weeks. In total 12 sessions were given in an outpatient clinic and supervised by an experienced physiotherapist whereas the remaining 36 sessions were home-based using identical equipment as provided by the study team for the duration of the intervention. The frequency of supervised sessions declined gradually during the intervention phase. Each training session consisted of 30 minutes of aerobic interval training on an electro-magnetic cycle ergometer. Each training session entailed six interval cycles consisting of 3 minutes at 40%, 1 minute at 60% and 1 minute at 80% of peak power. Peak power was determined at the start of training and re-evaluated after 8 weeks by means of a cardiopulmonary exercise test (CPET) until voluntary exhaustion. People logged the date and time of training, the number of minutes completed, the perceived exertion at the end of their training session and any comments or reasons for not completing the training session.

	Concomitant treatment: No additional information. Intervention subgroups: Individual vs. group - Mostly individual (some sessions in an outpatient clinic where it is unclear) Remote vs. in person - Mixed. Remote for the most part, with some elements in person.
Population subgroups	According to type: Mixed (see participants characteristics table). Majority relapsing remitting. According to disability: EDSS less than or equal to 6 in the inclusion criteria. Disease modifying treatment: Mixed. 50% are taking disease modifying treatment while 50% are not.
Comparator	Usual care: Three 45-minute consultations with an MS nurse over the 16 week period. The content of the consultations covered two important aspects in relation to the experimental intervention: 1) reliable information on MS-related fatigue, 2) guidance from the experienced MS nurse that aimed to reassure the patient that his or her concerns or questions were being taken seriously. The MS nurse was not allowed to refer the patient to any other outpatient or inpatient facilities for the treatment of fatigue.
Number of participants	89
Duration of follow-up	52 weeks in total (outcomes reported at 8, 16, 26 and 52 weeks. Outcomes extracted will be at 26 weeks (3-6 months) and 52 weeks (>6 months - 1 year).
Indirectness	No indirectness
Additional comments	Analysed by intention-to-treat basis.

Study arms

Exercise including aerobic exercise training (N = 43)

Aerobic training programme consisting of aerobic interval training, three times a week, for the duration of 16 weeks. In total 12 sessions were given in an outpatient clinic and supervised by an experienced physiotherapist whereas the remaining 36 sessions were home-based using identical equipment as provided by the study team for the duration of the intervention. The frequency of supervised sessions declined gradually during the intervention phase. Each training session consisted of 30 minutes of aerobic interval training on an electro-magnetic cycle ergometer. Each training session entailed six interval cycles consisting of 3 minutes at 40%, 1 minute at 60% and 1 minute at 80% of peak power. Peak power was determined at the start of training and re-evaluated after 8 weeks by means of a cardiopulmonary exercise test (CPET) until voluntary exhaustion. People logged the date and time of training, the number of minutes completed, the perceived exertion at the end of their training session and any comments or reasons for not completing the training session.

Usual care (N = 46)

Three 45-minute consultations with an MS nurse over the 16 week period. The content of the consultations covered two important aspects in relation to the experimental intervention: 1) reliable information on MS-related fatigue, 2) guidance from the experienced MS nurse that aimed to reassure the patient that his or her concerns or questions were being taken seriously. The MS nurse was not allowed to refer the patient to any other outpatient or inpatient facilities for the treatment of fatigue.

Characteristics

Arm-level characteristics

Characteristic	Exercise including aerobic exercise training (N = 43)	Usual care (N = 46)
% Female Sample size	n = NR ; % = 74.4	n = NR ; % = 71.7
Mean age (SD)	43.1 (9.8)	48.2 (9.2)

Characteristic	Exercise including aerobic exercise training (N = 43)	Usual care (N = 46)
Mean (SD)		
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
EDSS Range	2 to 3.5	2 to 4
EDSS Mean (SD)	2.5 (NR)	3 (NR)
Relapsing-remitting MS Nominal	31	34
Secondary progressive MS Nominal	3	5
Primary progressive MS Nominal	9	7
Disease duration (years) Range	2 to 10	2 to 19

Characteristic	Exercise including aerobic exercise training (N = 43)	Usual care (N = 46)
Disease duration (years) Mean (SD)	7 (NR)	12 (NR)

Outcomes

Study timepoints

- Baseline
- 26 week
- 52 week

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months-1 year - Continuous outcomes (final values)

Outcome	Exercise including aerobic exercise training, Baseline, N = 43	Exercise including aerobic exercise training, 26 week, N = 37	Exercise including aerobic exercise training, 52 week, N = 33	Usual care, Baseline, N = 46	Usual care, 26 week, N = 34	Usual care, 52 week, N = 30
Patient-reported outcome measures to assess MS fatigue (modified fatigue impact scale - total score) Scale range: 0-84 Mean (SD)	40.8 (12.1)	38.3 (13.7)	39 (13.4)	41.5 (12.3)	34.7 (11.8)	39.9 (11.9)

Outcome	Exercise including aerobic exercise training, Baseline, N = 43	Exercise including aerobic exercise training, 26 week, N = 37	Exercise including aerobic exercise training, 52 week, N = 33	Usual care, Baseline, N = 46	Usual care, 26 week, N = 34	Usual care, 52 week, N = 30
Cognitive Functions (checklist individual strength concentration) Scale range: 5-35. Mean (SD)	20.9 (6.6)	19.7 (7.3)	20.7 (6.8)	18.7 (8.2)	18.8 (7)	19.5 (7.7)
Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) Scale range: 1-7 Mean (SD)	5.2 (1)	5.2 (0.9)	5.2 (1.1)	5.3 (0.9)	5.1 (1.1)	5.1 (1.1)
Patient-reported outcome measures to assess MS fatigue (checklist individual strength-20 fatigue subscale) Scale range: 8-56 Mean (SD)	42.6 (7.4)	40.2 (9.5)	41.7 (8.3)	42.4 (8.5)	40.6 (9.5)	41.2 (11.6)
Acceptability of intervention (adherence) (%) % completed sessions. Can't be compared as mean (SD) given for the intervention group but in the control group a proportion completing all three sessions is given rather than the mean (SD) completed for the group overall. Mean (SD)	NA (NA)	74 (25)	NA (NA)	NA (NA)	87 (NR)	NA (NA)

Patient-reported outcome measures to assess MS fatigue (modified fatigue impact scale - total score) - Polarity - Lower values are better

Cognitive Functions (checklist individual strength concentration) - Polarity - Lower values are better

Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) - Polarity - Lower values are better

Patient-reported outcome measures to assess MS fatigue (checklist individual strength-20 fatigue subscale) - Polarity - Lower values are better

Acceptability of intervention (adherence) - Polarity - Higher values are better

Exercise relative to control

Outcome	Exercise including aerobic exercise training vs Usual care, Baseline, N2 = 46, N1 = 43	Exercise including aerobic exercise training vs Usual care, 26 week, N2 = 34, N1 = 37	Exercise including aerobic exercise training vs Usual care, 52 week, N2 = 30, N1 = 33
Adverse events - MS relapse unclear if any other adverse events occurred. Only gives for population with relapsing-remitting MS. Adjusted for disease severity. Time-point unclear, assuming applies to the longest follow-up. Number analysed	NA	NA	65 (31 in exercise and 34 in control)
Adverse events - MS relapse unclear if any other adverse events occurred. Only gives for population with relapsing-remitting MS. Adjusted for disease severity. Time-point unclear, assuming applies to the longest follow-up. P-value	NA	NA	0.016
Adverse events - MS relapse unclear if any other adverse events occurred. Only gives for population with relapsing-remitting MS.	NA (NA to NA)	NR (NR to NR)	0.28 (0.097 to 0.79)

Outcome	Exercise including aerobic exercise training vs Usual care, Baseline, N2 = 46, N1 = 43	Exercise including aerobic exercise training vs Usual care, 26 week, N2 = 34, N1 = 37	Exercise including aerobic exercise training vs Usual care, 52 week, N2 = 30, N1 = 33
Adjusted for disease severity. Time-point unclear, assuming applies to the longest follow-up. Odds ratio/95% CI			

Adverse events - MS relapse - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year – Continuous outcomes (final values) – Patient-reported outcome measures to assess MS fatigue (modified fatigue impact scale – total score) – Mean SD - Exercise including aerobic exercise training-Usual care-t26

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year-Continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (modified fatigue impact scale – total score) – Mean SD-Exercise including aerobic exercise training-Usual care-t52

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months -1 year-Continuous outcomes (final values) – Cognitive Functions (checklist individual strength concentration) – Mean SD - Exercise including aerobic exercise training-Usual care-t26

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year-Continuous outcomes (final values) – Cognitive Functions (checklist individual strength concentration) – Mean SD-Exercise including aerobic exercise training-Usual care-t52

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year-Continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) – Mean SD - Exercise including aerobic exercise training-Usual care-t26

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months - 1 year -Continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) – Mean SD - Exercise including aerobic exercise training-Usual care-t52

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year -Continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (checklist individual strength – 20 fatigue subscale) – Mean SD-Exercise including aerobic exercise training-Usual care-t26

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year -Continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (checklist individual strength – 20 fatigue subscale) – Mean SD- Exercise including aerobic exercise training-Usual care-t52

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year-Continuous outcomes (final values) – Acceptability of intervention (adherence) – Mean SD - Exercise including aerobic exercise training-Usual care-t26

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise including aerobic exercise training compared to usual care at 3-6 months and >6 months – 1 year -Continuous outcomes (final values) – Acceptability of intervention (adherence) – Mean SD - Exercise including aerobic exercise training-Usual care-t52

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Exercise relative to control – Adverse events – MS relapse – Odds Ratio Nine Five Percent CI-Exercise including aerobic exercise training-Usual care-t52

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hersche, 2019

Bibliographic Reference	**Hersche, R.; Weise, A.; Michel, G.; Kesselring, J.; Bella, S. D.; Barbero, M.; Kool, J.; Three-week inpatient energy management education (IEME) for persons with multiple sclerosis-related fatigue: Feasibility of a randomized clinical trial; Multiple Sclerosis and Related Disorders; 2019; vol. 35; 26-33**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	Switzerland
Study setting	multidisciplinary inpatient rehabilitation centre
Study dates	August - November 2017

Sources of funding	This research was supported by grants from the Swiss MS Society Trust, the 5 Foundation for Occupational Therapy Zürich and the Swiss Association of Occupational 6 Therapists (ErgotherapeuteInnen Verband Schweiz EVS), as well as the University of 7 Applied Sciences and Arts of Southern Switzerland and the Kliniken Valens.
Inclusion criteria	Inclusion criteria: >18 years of age; confirmed diagnosis of MS according to the McDonald criteria; Fatigue Severity Scale score >4; and Expanded Disability Status Scale (EDSS) score ≤6.5
Exclusion criteria	exclusion criteria comprised the following: telephone-based Mini Mental state Examination score <21) and Beck Depression Inventory-fast 2 screening score >4.
Recruitment / selection of participants	The pwMS who were on the waiting list for a 3-week rehabilitation period at the RCV from 26 August to November 2017, and who fulfilled the inclusion criteria were informed by post about the study. A few days before admission, they were contacted by phone by a researcher (AW) who verified their literacy in German and agreement to attend the IEME or control (progressive muscle relaxation [PMR] intervention, in addition to a 3-week rehabilitation as usual (RAU) program.
Intervention(s)	All participants took part in the RAU program. This individualized program included physiotherapy (endurance and reinforcement training), occupational therapy (ability and adaptation training), speech therapy, neuropsychological training, and counselling (involving a physician and/or social worker), if relevant. The difficulties due to fatigue were discussed in individual OT sessions but no systematic fatigue management education was provided as part of RAU. In addition to RAU, the participants received the experimental intervention. That means that IEME participants received fatigue management group-based education during the experimental intervention and that they attended individual OT sessions only for other issues. Participants acquired knowledge and understanding about factors that influence energy and the consequences of fatigue on their habits and lifestyle. Subsequently, they identified and implemented tailored behavior modification. The IEME involved face-to-face education sessions of 6.5 h in duration over a 3-week period, which was conducted by a trained OT. The IEME started with a 1-h individual session, followed by five 1-h self-contained IEME group sessions (min. 2, max. 7 pwMS) delivered twice a week, and it concluded with a 0.5-h individual session. Between the IEME sessions, the participants received training regarding the use of energy conservation strategies and planned the implementation of behavioral changes in their daily routine using self-training tasks. Six weeks after returning home, the participants received reinforcement in the form of a letter. The treatment manual describes every session in detail, integrating the behavioral change techniques that can be used. The participant workbook contains detailed information on all topics, worksheets, and self-training tasks.

Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - NR · Group vs individual - individual and group sessions · Delivered remotely vs in person - in person
Comparator	All participants took part in the RAU program. This individualized program included physiotherapy (endurance and reinforcement training), occupational therapy (ability and adaptation training), speech therapy, neuropsychological training, and counselling (involving a physician and/or social worker), if relevant. The difficulties due to fatigue were discussed in individual OT sessions but no systematic fatigue management education was provided as part of RAU. In addition to RAU, the participants received the control intervention. The control group worked on fatigue management and other OT relevant issues during individual OT sessions as part of RAU. PMR was developed in 1938 by Edmond Jacobson (Conrad and Roth 10 2007). The aim of PMR is to achieve enhanced mental relaxation by reducing muscle tension. (Dayapoğlu and Tan, 2012). PMR involves a standardized series of relaxation exercises (involving 11 large muscle groups) combined with deep breathing. During the PMR sessions, the participants lay on the floor in a quiet room and were instructed by a trained physical therapist for 1 h. The control participants attended six 1-h face-to-face group sessions of PMR (max. 12 participants), which were held twice a week over a 3-week period. They were also encouraged to continue to perform the PMR exercises after discharge from the clinic. Research has shown that PMR has a moderate to large effect on QoL in pwMS (Ghafari et al., 2009). At 3 weeks after discharge, a reinforcement letter was sent to all control participants, to foster continuation of the PMR exercises.
Number of participants	47
Duration of follow-up	4 months
Indirectness	

Additional comments	NR

Study arms

inpatient energy management education (N = 24)

progressive muscle relaxation control group (N = 23)

Characteristics

Study-level characteristics

Characteristic	Study (N = 47)
% Female Nominal	31

Arm-level characteristics

Characteristic	inpatient energy management education (N = 24)	progressive muscle relaxation control group (N = 23)
Age Mean (SD)	51.2 (1.7)	51.8 (2.2)

Outcomes

Study timepoints

4 month

outcomes

Outcome	inpatient energy management education, 4 month, N = 14	progressive muscle relaxation control group, 4 month, N = 15
MFIS global score 0-84 Mean (SD)	34.5 (16.6)	34.5 (10.9)
SF-36 physical functioning 0-100 Mean (SD)	44.8 (24.7)	30 (16.5)
SF-36 fatigue/vitality 0-100 Mean (SD)	46.5 (16.6)	43.5 (18.3)

MFIS global score - Polarity - Lower values are better

SF-36 physical functioning - Polarity - Higher values are better

SF-36 fatigue/vitality - Polarity - Higher values are better

SF-36-PF (physical functioning) had n= 17 in intervention group and n= 16 in control; SF-36-FV (fatigue/vitality) had n=18 in intervention group and n=17 in control group

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

outcomes-MFISglobalscore-MeanSD- inpatient energy management education-progressive muscle relaxation control group-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

outcomes-SF-36physicalfunctioning-MeanSD- inpatient energy management education-progressive muscle relaxation control group-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes-SF-36fatigue/vitality-MeanSD- inpatient energy management education-progressive muscle relaxation control group-t4

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Hugos, 2019

Bibliographic Reference	**Hugos, C. L.; Cameron, M. H.; Chen, Z.; Chen, Y.; Bourdette, D.; A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Long-term (12-month) follow-up at one site; Multiple Sclerosis; 2019; vol. 25 (no. 6); 871-875**

Study details

Secondary publication of another included study- see primary study for details	Hugos, C. L., Chen, Z., Chen, Y. et al. (2019) A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Short- and medium-term benefits. Multiple Sclerosis 25(2): 275-285

Hugos, 2019

Bibliographic Reference	**Hugos, C. L.; Chen, Z.; Chen, Y.; Turner, A. P.; Haselkorn, J.; Chiara, T.; McCoy, S.; Bever, C. T., Jr.; Cameron, M. H.; Bourdette, D.; Group, Va Ms Fatigue Study; A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Short- and medium-term benefits; Multiple Sclerosis; 2019; vol. 25 (no. 2); 275-285**

Study details

Other publications associated with this study included in review	Hugos, C. L., Cameron, M. H., Chen, Z. et al. (2019) A multicenter randomized controlled trial of two group education programs for fatigue in multiple sclerosis: Long-term (12-month) follow-up at one site. Multiple Sclerosis 25(6): 871-875
Trial name / registration number	NCT01918800
Study location	USA
Study setting	Outpatient
Study dates	Randomised between April 2013 and June 2015
Sources of funding	Funding was provided by VA Office of Research and Development (F7777-R) and Oregon Clinical and Translational Research Institute (OCTRI; NCATS-funded CTSA grant UL1TR000128).
Inclusion criteria	Definite MS of any subtype; age 18 years or older; moderate-to-severe fatigue (scores $\geqslant$25 on the MFIS); Expanded Disability Status Scale (EDSS) $\leqslant$6.5; Beck Depression Inventory II (BDI) $\leqslant$28; stable on disease modifying medications for at least 3 months; free of relapses for the prior 30 days; not pregnant; able to comply with study procedures, and complete measures independently.
Exclusion criteria	No further criteria reported.

Recruitment / selection of participants	Participants were recruited from the Portland, Seattle, Baltimore, and North Florida/South Georgia VA Medical Centers, affiliated academic medical center MS clinics, and surrounding communities.
Intervention(s)	Fatigue: Take Control programme: in-person group programme with facilitator manual providing programme format, class agendas, learning objectives, questions for discussion and tips for small group management, as well as participant manuals with all class content and space for self-reflection and notes. Delivered in six weekly 2 h group sessions and facilitated by someone with at least 1 year experience working with people with MS. Intervention included DVD viewing, topic-focused group discussion, individual goal setting and homework assignments. The sessions address important aspects of MS fatigue identified in the fatigue and MS guideline including managing depression, sleep disturbance, heat sensitivity, and deconditioning; setting priorities and goals; making environmental modifications; managing mobility problems; using energy conservation strategies; and exercising appropriately. The DVD segments, featuring MS professionals discussing fatigue management approaches and people with MS sharing their stories, helped facilitate discussion among the group participants.
Population subgroups	None reported.
Comparator	MS: Take Control programme: in-person group programme with facilitator manual providing programme format, class agendas, learning objectives, questions for discussion and tips for small group management, as well as participant manuals with all class content and space for self-reflection and notes. Delivered in six weekly 2 h group sessions and facilitated by someone with at least 1 year experience working with people with MS. Used the following educational pamphlets from the National MS Society: MS and Your Emotions; Solving Cognitive Problems; Taming Stress in MS; Food for Thought: MS and Nutrition; Urinary Dysfunction and MS; and Vitamins, Minerals and Herbs in MS. The pamphlets were formalised into a program with facilitator and participant manuals. Homework was to read the pamphlet to be discussed at the next session. There were no DVDs or goal setting activities and no overlap between information in the pamphlets and the intervention in the Fatigue: Take Control intervention group. If the topic of fatigue arose, discussion was allowed to proceed naturally until conversation redirected back to the day's topic.
Number of participants	N=218 randomised, n=203 at 6-month follow-up

Duration of follow-up	Up to 6 months following programme completion
Indirectness	None.
Method of analysis	Available case analysis reported

Study arms

Fatigue management programme (N = 109)

Fatigue: Take Control programme. Fatigue management intervention.

Self-management programme (N = 109)

MS: Take Control programme. General MS education/self-management programme not specific to fatigue.

Characteristics

Arm-level characteristics

Characteristic	Fatigue management programme (N = 109)	Self-management programme (N = 109)
% Female Sample size	n = 80 ; % = 73.4	n = 77 ; % = 70.6
Mean age (SD) Mean (SD)	53.9 (9.8)	53.6 (10.5)

Characteristic	Fatigue management programme (N = 109)	Self-management programme (N = 109)
Caucasian/Hispanic/Latino Sample size	n = 80 ; % = 73.4	n = 85 ; % = 78
Comorbidities Custom value	NR	NR
Time since diagnosis (years) Mean (SD)	12.3 (7.6)	12.7 (9.3)
EDSS score Scale 0-10. Higher indicates increased disability. Mean (SD)	5.1 (1.1)	5.3 (1.1)
Taking disease-modifying medication Sample size	n = 66 ; % = 66	n = 73 ; % = 70
Relapsing-remitting MS Sample size	n = 67 ; % = 62.6	n = 60 ; % = 55.6
Secondary progressive MS Sample size	n = 15 ; % = 14	n = 21 ; % = 19.4
Primary progressive MS Sample size	n = 26 ; % = 24.3	n = 26 ; % = 24.1

Outcomes

Study timepoints

- Baseline
- 6 week (6 weeks - end of treatment)
- 6 month (6 months after completion of intervention)
- 12 month (12 months after completion of intervention)

Results - raw data (final values)

Outcome	Fatigue management programme, Baseline, N = 109	Fatigue management programme, 6 week, N = 100	Fatigue management programme, 6 month, N = 99	Fatigue management programme, 12 month, N = 38	Self-management programme, Baseline, N = 109	Self-management programme, 6 week, N = 104	Self-management programme, 6 month, N = 104	Self-management programme, 12 month, N = 40
MFIS total score Scale usually 0-84. Mean (SD)	46.1 (12.2)	NA (NA)	40.9 (17.2)	38.6 (18.4)	46.7 (11.9)	NA (NA)	41.9 (14)	43.7 (12.8)
Beck Depression Inventory Scale usually 0-63. Mean (SD)	11.5 (6.9)	9.5 (7.7)	NR (NR)	NR (NR)	11.8 (6.2)	10.7 (7.7)	NR (NR)	NR (NR)

Outcome	Fatigue management programme, Baseline, N = 109	Fatigue management programme, 6 week, N = 100	Fatigue management programme, 6 month, N = 99	Fatigue management programme, 12 month, N = 38	Self-management programme, Baseline, N = 109	Self-management programme, 6 week, N = 104	Self-management programme, 6 month, N = 104	Self-management programme, 12 month, N = 40
Adverse events n=4 relapses reported in both groups. No study-related serious adverse events. No of events	n = NA ; % = NA	n = 4 ; % = 4	n = NR ; % = NR	n = NR ; % = NR	n = NA ; % = NA	n = 4 ; % = 3.8	n = NR ; % = NR	n = NR ; % = NR
Adherence - completed intervention as specified (at least 4 sessions attended) Also reported adherence to programme materials and agenda using facilitator checklists and	n = NA ; % = NA	n = 94 ; % = 86.2	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = 94 ; % = 86.2	n = NA ; % = NA	n = NA ; % = NA

Outcome	Fatigue management programme, Baseline, N = 109	Fatigue management programme, 6 week, N = 100	Fatigue management programme, 6 month, N = 99	Fatigue management programme, 12 month, N = 38	Self-management programme, Baseline, N = 109	Self-management programme, 6 week, N = 104	Self-management programme, 6 month, N = 104	Self-management programme, 12 month, N = 40
was reported to be >90%. No of events								
Adherence - completed intervention as specified (at least 4 sessions attended) Also reported adherence to programme materials and agenda using facilitator checklists and was reported to be >90%. Number analysed	NA	109	NA	NA	NA	109	NA	NA

MFIS total score - Polarity - Lower values are better

Beck Depression Inventory - Polarity - Lower values are better

Only 6-week data (end of treatment) available for the BDI outcome. For the 12-month time-point only data from one of the trial sites was available.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS total score 12 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results BDI score 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at 6 weeks post intervention rather than a minimum of 3 months specified in protocol)*

Results adverse events end of treatment (6 weeks)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at 6 weeks post intervention rather than a minimum of 3 months specified in protocol)*

Results adherence (4 sessions) end of treatment

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(reported at 6 weeks post intervention rather than a minimum of 3 months specified in protocol)*

Irish, 2017

Bibliographic Reference	**Irish, A. K.; Erickson, C. M.; Wahls, T. L.; Snetselaar, L. G.; Darling, W. G.; Randomized control trial evaluation of a modified Paleolithic dietary intervention in the treatment of relapsing-remitting multiple sclerosis: a pilot study; Degenerative Neurological & Neuromuscular Disease; 2017; vol. 7; 1-18**

Study details

Trial name / registration number	NCT02687919
Study location	USA
Study setting	Outpatient

Study dates	Not reported
Sources of funding	This study was supported by a grant from TZ Press, which is owned by Dr TLW, one of the authors of the paper.
Inclusion criteria	aged 18-45 years; had stable relapsing-remitting MS (defined as no medication changes within 3 months); were able to walk 25 feet with or without an assistive device; were on no other “diets” recommended to treat MS (such as Best Bet, Swank, McDougall, MS Recovery, Paleo or modified Paleo, gluten-free, vegetarian, and/or vegan); willing to be randomised to diet or “usual care” control groups and to follow a modified Paleo diet (described as nine cups of vegetables and some fruits, meat protein including organ meat, and complete abstinence from products containing gluten [wheat, barley, rye, etc], dairy, potatoes, and legumes [beans, lentils, peanuts, soy, etc]); computer literate, able to keep Food Logs recording their daily food intake, and stated they were able to accommodate a possible 30% increase in grocery expenses
Exclusion criteria	If they had cancer, liver disease, kidney disease, diabetes, active heart disease, heart block or arrhythmias, bleeding disorders, concurrent diuretic use, anticoagulant or antiplatelet use, psychosis or other psychiatric disorders likely to impact ability to comply with study procedures; any change in prescription medication for mental health problems such as depression or anxiety during the 3 months preceding enrolment; did not obtain neurologist verification of their relapsing-remitting MS diagnosis; and did not complete a baseline Automated Self-Administered 24-hour dietary recall application (ASA-24) or a 2-week Food Diary before randomization.
Recruitment / selection of participants	All subjects were recruited from The University of Iowa (UI) mass-email system, local databases of the National Multiple Sclerosis Society, from posters and flyers distributed to neurology clinics in the Iowa City/Cedar Rapids, Iowa corridor area (to include the Iowa City Veterans Affairs Medical Center), and by word-of-mouth.
Intervention(s)	Modified Paleolithic diet: 3-month diet protocol. Described as nine cups of vegetables and some fruits, meat protein including organ meat, and complete abstinence from products containing gluten [wheat, barley, rye, etc], dairy, potatoes, and legumes [beans, lentils, peanuts, soy, etc]). Training consisted of subject orientation to the diet and maintenance of the Food Log. All subjects received one short follow-up phone call per week for the first 3 weeks, then every other week thereafter. Both groups were asked to continue their current MS therapy and/or medications.
Population subgroups	None reported.

Comparator	Control - maintain usual diet and usual care for 3 months. Usual care is defined as the typical physician recommendations for MS. Training for the control group consisted of reviewing study expectations (maintenance of a normal diet) and maintenance of the Food Diary. All subjects received one short follow-up phone call per week for the first 3 weeks, then every other week thereafter. Both groups were asked to continue their current MS therapy and/or medications.
Number of participants	N=34 randomised, n=17 analysed
Duration of follow-up	3 months - end of diet intervention
Indirectness	None.
Method of analysis	Per protocol - those completing and that were adherent

Study arms

Modified Paleolithic dietary intervention (N = 17)

Control - maintain usual diet (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Modified Paleolithic dietary intervention (N = 17)	Control - maintain usual diet (N = 17)
% Female	n = 7 ; % = 87.5	n = 8 ; % = 88.9

Characteristic	Modified Paleolithic dietary intervention (N = 17)	Control - maintain usual diet (N = 17)
Sample size		
Mean age (SD) Mean (SD)	35.4 (5.7)	37.1 (3.7)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Number analysed Nominal	8	9

Baseline characteristics given for those analysed (n=17) rather than those randomised (n=34), with n=8 in intervention group and n=9 in the control group.

Outcomes

Study timepoints

- Baseline
- 3 month (3 months - end of treatment)

Results - change from baseline

Outcome	Modified Paleolithic dietary intervention, Baseline, N = 17	Modified Paleolithic dietary intervention, 3 month, N = 8	Control - maintain usual diet, Baseline, N = 17	Control - maintain usual diet, 3 month, N = 9
Fatigue Severity Scale Scale likely 1-9 based on information provided in paper.. Mean scores at baseline were 4.2±1.6 and 4.0±1.2, respectively. SD not reported but calculated using mean values and P-value for difference between groups. Custom value	NA	P-value for difference between the two groups	NA	P-value for difference between the two groups
Fatigue Severity Scale Scale likely 1-9 based on information provided in paper.. Mean scores at baseline were 4.2±1.6 and 4.0±1.2, respectively. SD not reported but calculated using mean values and P-value for difference between groups. Mean (p value)	NA (NA)	-1.4 (0.05)	NA (NA)	0.2 (0.05)

Fatigue Severity Scale - Polarity - Lower values are better

Results and baseline values only given for the n=17 that were analysed as per protocol analysis.

Results - raw data

Outcome	Modified Paleolithic dietary intervention, Baseline, N = 17	Modified Paleolithic dietary intervention, 3 month, N = 8	Control - maintain usual diet, Baseline, N = 17	Control - maintain usual diet, 3 month, N = 9
>1 point reduction in Fatigue Severity Scale Mean scores at baseline were 4.2±1.6 and 4.0±1.2, respectively. No of events	n = NA ; % = NA	n = 4 ; % = 50	n = NA ; % = NA	n = 0 ; % = 0
At least 5-point improvement on MSQOL-54 - mental health composite score Scale usually 0-100. Baseline values were 74.5±10.8 and 65.5±11.5, respectively. No of events	n = NA ; % = NA	n = 8 ; % = 100	n = NA ; % = NA	n = 3 ; % = 33.3
Improvement in MSQOL-54 physical composite score No definition/threshold for improvement, just any improvement. Scale usually 0-100. Baseline values were 67.3±15.2 and 68.1±11.8, respectively. No of events	n = NA ; % = NA	n = 7 ; % = 87.5	n = NA ; % = NA	n = 3 ; % = 33.3
Adverse events Reported to be no adverse events but some flare-ups reported which could be considered an adverse event. All three were withdrawn from the study. No of events	n = NA ; % = NA	n = 1 ; % = 11.1	n = NA ; % = NA	n = 2 ; % = 18.2

Outcome	Modified Paleolithic dietary intervention, Baseline, N = 17	Modified Paleolithic dietary intervention, 3 month, N = 8	Control - maintain usual diet, Baseline, N = 17	Control - maintain usual diet, 3 month, N = 9
Adverse events Reported to be no adverse events but some flare-ups reported which could be considered an adverse event. All three were withdrawn from the study. Number analysed	NA	9	NA	11
Adverse events leading to withdrawal all above events also led to withdrawal, so included under adverse events leading to withdrawal as well as general adverse events No of events	n = NA ; % = NA	n = 1 ; % = 11.1	n = NA ; % = NA	n = 2 ; % = 18.2
Adverse events leading to withdrawal all above events also led to withdrawal, so included under adverse events leading to withdrawal as well as general adverse events No of events	NA	9	NA	11
Adherence to intervention/control Calculated using numbers that were withdrawn due to non-adherence. No of events	n = NA ; % = NA	n = 8 ; % = 80	n = NA ; % = NA	n = 9 ; % = 100

Outcome	Modified Paleolithic dietary intervention, Baseline, N = 17	Modified Paleolithic dietary intervention, 3 month, N = 8	Control - maintain usual diet, Baseline, N = 17	Control - maintain usual diet, 3 month, N = 9
Adherence to intervention/control Calculated using numbers that were withdrawn due to non-adherence. Number analysed	NA	10	NA	9

>1 point reduction in Fatigue Severity Scale - Polarity - Lower values are better

At least 5-point improvement on MSQOL-54 - mental health composite score - Polarity - Higher values are better

Improvement in MSQOL-54 physical composite score - Polarity - Higher values are better

Results and baseline values only given for the n=17 that were analysed as per protocol analysis.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS change from baseline 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results FSS 1 point reduction 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 mental health 5-point improvement

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 physical health improvement 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	High
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events leading to withdrawal 3-months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Karami, 2018

Bibliographic Reference	**Karami, F.; Afrasiabifar, A.; Doulatabad, S. N.; Comparing the effectiveness of vestibular rehabilitation and frenkel exercise on fatigue reduction in patients with multiple sclerosis: A randomized controlled trial; Iranian Red Crescent Medical Journal; 2018; vol. 20 (no. 12)**

Study details

Trial name / registration number	IRCT2016031527063N1
Study location	Iran
Study setting	Outpatient
Study dates	Not reported
Sources of funding	Supported by a Master thesis grant from the Deputy of Research and Technology of the Yasuj University of Medical Sciences, Iran.
Inclusion criteria	Confirmed diagnosis of disease by a neurologist; passing at least six months from the onset; being in the remission period; being between the ages of 15 and 55 years; ability to stand for 30 seconds; able t walk a distance of six meters without any

	assistance; Fatigue Impact Scale (FIS) score from 54 to 107; no history of participation in a rehabilitation program within the last six months; no diseases other than MS; and Berg Balance Score from 21 to 40 or a moderate imbalance.
Exclusion criteria	Refusing to continue participation or inability to participate in exercises; and the relapse of diseases during the period of study.
Recruitment / selection of participants	The population of the study included MS patients, who had medical records at the Society of Special Diseases of Yasuj University of Medical Sciences, Iran, during the year 2016. Selected using the convenience sampling method.
Intervention(s)	Vestibular rehabilitation or Frenkel exercises: exercise sessions held in the outpatient clinic of Shahid Beheshti Hospital during three exercise sessions, on alternate days, for a total span of 12 weeks. Each session ~ 60 min (two 30 min sessions with 15 min rest intervals). The vestibular rehabilitation exercise was performed based on the protocols established by Cawthorne and Cooksey, in sitting and upright position (once with eyes open and subsequently with eyes closed). Patients in the Frenkel group performed exercises based on established protocols. Performed in lying down, sitting up and standing positions.
Population subgroups	None reported.
Comparator	Control group: received only routine care.
Number of participants	N=75 randomised, N=72 analysed
Duration of follow-up	Up to 12 weeks - end of intervention
Indirectness	None.
Method of analysis	Available case analysis reported

Additional comments	

Study arms

Vestibular rehabilitation or Frenkel exercises (N = 50)

Two groups that received either vestibular rehabilitation or Frenkel exercises, combined for the purpose of this review as they both focus on balance/coordination.

Control (N = 25)

Routine care only.

Characteristics

Study-level characteristics

Characteristic	Study (N = 72)
% Female Sample size	n = 56 ; % = 77.8
Mean age (SD) Mean (SD)	32.7 (7.4)
Ethnicity Custom value	NR

Characteristic	Study (N = 72)
Comorbidities Custom value	Diseases in addition to MS was an exclusion criterion
Relapsing-remitting MS Sample size	n = 68 ; % = 94.4
Primary or secondary progressive MS Sample size	n = 4 ; % = 5.6
Using interferon Beta-1a Sample size	n = 42 ; % = 58.4
Using interferon Beta-1b Sample size	n = 16 ; % = 22.2
Other drugs Statement suggests all of the others used at least type of drug for MS but is unclear. Sample size	n = 14 ; % = 19.4
Duration of MS (Months) Mean (SD)	60.5 (37.4)

Gives baseline characteristics for those analysed (n=72) rather than those randomised (n=75)

Outcomes

Study timepoints

- Baseline
- 12 week (12 weeks - end of treatment)

Results - raw data

Outcome	Vestibular rehabilitation or Frenkel exercises, Baseline, N = 50	Vestibular rehabilitation or Frenkel exercises, 12 week, N = 47	Control, Baseline, N = 25	Control, 12 week, N = 25
Fatigue Impact Scale - total score Scale 0-160. Mean (SD)	91.2 (14.8)	70.8 (17.2)	89.2 (15.5)	96.5 (18)
Fatigue Impact Scale - cognitive subscale Scale 0-40. Mean (SD)	21.4 (3.9)	17.1 (3.6)	19.7 (4)	22 (3.6)
Fatigue Impact Scale - physical subscale Scale 0-40. Mean (SD)	28.1 (5.2)	19 (6.5)	26.6 (6.9)	28.8 (6.4)
Fatigue Impact Scale - psychosocial subscale Mean (SD)	41.7 (10.9)	32.3 (10.2)	42.8 (10.1)	45.8 (11.5)

Outcome	Vestibular rehabilitation or Frenkel exercises, Baseline, N = 50	Vestibular rehabilitation or Frenkel exercises, 12 week, N = 47	Control, Baseline, N = 25	Control, 12 week, N = 25
Adverse events - relapse leading to withdrawal Taken from CONSORT diagram and does not report whether any not requiring withdrawal occurred. No of events	n = NA ; % = NA	n = 1 ; % = 2.1	n = NA ; % = NA	n = 0 ; % = 0
Adverse events - relapse leading to withdrawal Taken from CONSORT diagram and does not report whether any not requiring withdrawal occurred. Number analysed	NA	48	NA	50

Fatigue Impact Scale - total score - Polarity - Lower values are better

Fatigue Impact Scale - cognitive subscale - Polarity - Lower values are better

Fatigue Impact Scale - physical subscale - Polarity - Lower values are better

Fatigue Impact Scale - psychosocial subscale - Polarity - Lower values are better

Reported as final values. Reports results at baseline only for the 72 analysed at 12 weeks, despite there being 75 randomised initially. Available case analysis calculated based on information given for adverse event outcome.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results Fatigue Impact Scale total score 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Fatigue Impact Scale cognitive subscale 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Fatigue Impact Scale physical subscale 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results Fatigue Impact Scale psychosocial subscale 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events (relapse leading to withdrawal) 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Kargarfard, 2018

Bibliographic Reference	**Kargarfard, M.; Shariat, A.; Ingle, L.; Cleland, J. A.; Kargarfard, M.; Randomized Controlled Trial to Examine the Impact of Aquatic Exercise Training on Functional Capacity, Balance, and Perceptions of Fatigue in Female Patients With Multiple Sclerosis; Archives of Physical Medicine & Rehabilitation; 2018; vol. 99 (no. 2); 234-241**

Study details

Trial name / registration number	NCT02882724
Study location	Iran
Study setting	Community
Study dates	Not stated
Sources of funding	None stated
Inclusion criteria	Diagnosed with relapsing-remitting MS by the Isfahan Multiple Sclerosis Society. Presented with MS of a minimum of 2 yrs, had no relapses in the past month and were able to exercise regularly assessed by a pre-study checklist.
Exclusion criteria	Relapse during the intervention, developed any comorbidities during the intervention or both
Intervention(s)	Aquatic exercise - Education session consisted on meeting 2 to 3 times a week with a neurologic physical therapist for approximately 30 to 40 minutes. Education sessions explained the following: nature of MS and risk factors; diagnosis and treatment; stress reduction techniques and advice on a healthy lifestyle. Aquatic exercise training consistent of 3 sessions per week for 8 weeks. Each session consisted of 60 minutes of training at an intensity between 50% and 75% of estimated maximum heart rate. The session included a warm-up for 10 minutes, followed by 40 minutes of conditioning exercise, and the final 10 minutes acted as a cool-down. The aquatic exercises included activities focused on join mobility, functional exercises, balance and walking at different intensities.

Population subgroups	None
Comparator	Aquatic exercise - Education session consisted on meeting 2 to 3 times a week with a neurologic physical therapist for approximately 30 to 40 minutes. Education sessions explained the following: nature of MS and risk factors; diagnosis and treatment; stress reduction techniques and advice on a healthy lifestyle.
Number of participants	Aquatic exercise N=17 Control N=15
Duration of follow-up	8 weeks
Indirectness	No indirectness

Study arms

Aquatic training program (N = 17)

Education session consisted on meeting 2 to 3 times a week with a neurologic physical therapist for approximately 30 to 40 minutes. Education sessions explained the following: nature of MS and risk factors; diagnosis and treatment; stress reduction techniques and advice on a healthy lifestyle. Aquatic exercise training consistent of 3 sessions per week for 8 weeks. Each session consisted of 60 minutes of training at an intensity between 50% and 75% of estimated maximum heart rate. The session included a warm-up for 10 minutes, followed by 40 minutes of conditioning exercise, and the final 10 minutes acted as a cool-down. The aquatic exercises included activities focused on join mobility, functional exercises, balance and walking at different intensities.

Control (N = 15)

Education session consisted on meeting 2 to 3 times a week with a neurologic physical therapist for approximately 30 to 40 minutes. Education sessions explained the following: nature of MS and risk factors; diagnosis and treatment; stress reduction techniques and advice on a healthy lifestyle. Instructed to continue with their normal routine and not to participate in any exercise programs during the 8-week study

Characteristics

Arm-level characteristics

Characteristic	Aquatic training program (N = 17)	Control (N = 15)
% Female Sample size	n = 17 ; % = 100	n = 15 ; % = 100
Mean age (SD) Mean (SD)	36.5 (9)	36.2 (7.4)
Disease duration (years) Mean (SD)	6.4 (2.3)	6.1 (2)
EDSS score Mean (SD)	3.4 (1.1)	3.7 (1)

Outcomes

Study timepoints

- Baseline
- 8 week

Results - raw data

Outcome	Aquatic training program, Baseline, N = 17	Aquatic training program, 8 week, N = 17	Control, Baseline, N = 15	Control, 8 week, N = 15
Modified fatigue impact scale (total) Scale usually 0-84 Mean (SD)	43.1 (14.6)	32.8 (5.9)	44.5 (9.3)	61 (8.2)
Modified Fatigue Impact Scale - physical Scale usually 0-36. Mean (SD)	19.5 (6.9)	14.1 (3.1)	20.4 (7.8)	29.4 (5.5)
MFIS cognitive Scale used in this study unclear - usually 0-40 but values seem low and may have mixed up cognitive and psychosocial as that scale is usually 0-8 but values reported for that outcome are higher than 8? Mean (SD)	6 (1.8)	4.2 (1.6)	6.3 (1.3)	6.7 (1.4)
MFIS psychosocial Scale usually 0-8 but values are higher than that in this study - possibly mixed up cognitive and psychosocial domains? Mean (SD)	17.6 (7.9)	14.5 (2.7)	17.8 (7.1)	24.9 (4.9)

Modified fatigue impact scale (total) - Polarity - Lower values are better

Modified Fatigue Impact Scale - physical - Polarity - Lower values are better

MFIS cognitive - Polarity - Lower values are better

MFIS psychosocial - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

MFIS total score 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up duration less than the minimum of three months specified in protocol)*

MFIS physical score 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up duration less than the minimum of three months specified in protocol)*

MFIS cognitive score 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up duration less than the minimum of three months specified in protocol)*

MFIS psychosocial score 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(follow-up duration less than the minimum of three months specified in protocol)*

Katz Sand, 2019

Bibliographic Reference	**Katz Sand, I.; Benn, E. K. T.; Fabian, M.; Fitzgerald, K. C.; Digga, E.; Deshpande, R.; Miller, A.; Gallo, S.; Arab, L.; Randomized-controlled trial of a modified Mediterranean dietary program for multiple sclerosis: A pilot study; Multiple Sclerosis and Related Disorders; 2019; vol. 36; 101403**

Study details

Trial name / registration number	NCT02986893
Study location	USA
Study setting	Outpatient
Study dates	Screened between December 2016 and September 2017.
Sources of funding	Funded by research grant from National Multiple Sclerosis Society (RG-1601-07277).
Inclusion criteria	Aged 18-65 years; female; diagnosis of MS; and currently following a Western-style diet that included at least one of the major exclusions for the study (meat and dairy).
Exclusion criteria	Dietary supplements other than vitamin D that had been recommended by a health care provider were not permitted (washout of 2 weeks was required for these supplements).
Recruitment / selection of participants	Recruited at Corinne Goldsmith Dickinson Center for MS at Mount Sinai in New York City.
Intervention(s)	Dietary intervention: duration of 6 months. Encouraged intake of fresh vegetables and fruit, fish, nuts, legumes, whole grains, avocados and the use of olive oil in cooking. Advised against intake of meat (including red meat and poultry), dairy, white grains and processed foods. Also advised to limit intake of salt to 2g/day and abstain from eating for at least 12 h per night (recommended 7 pm to 7 am). No specific advice given about overall calorie intake or weight loss. Met with dietician for an education session in groups of five at the start of the intervention. Provided with handouts with tips for shopping, a sample menu plan and guidance regarding reading food labels, eating in restaurants and travel. Attended or dialled into monthly meetings to discuss issues with following the diet and complete questionnaires. Dietician and investigators available in between meetings to help and troubleshoot issues.

Population subgroups	None reported.
Comparator	No dietary intervention for 6 months - offered education sessions on MS and the option of meeting with dietician and access to handouts once study was complete.
Number of participants	N=36 randomised, unclear number analysed
Duration of follow-up	up to 6 months - end of dietary intervention
Indirectness	None.
Method of analysis	Unclear
Additional comments	

Study arms

Modified Mediterranean dietary intervention (N = 18)

Control - no dietary intervention (N = 18)

Characteristics

Arm-level characteristics

Characteristic	Modified Mediterranean dietary intervention (N = 18)	Control - no dietary intervention (N = 18)
% Female Sample size	n = 18 ; % = 100	n = 18 ; % = 100
Mean age (SD) Median (IQR)	44 (37 to 51)	41 (30 to 49)
Non-white Sample size	n = 2 ; % = 11.1	n = 5 ; % = 27.8
White Sample size	n = 16 ; % = 88.9	n = 13 ; % = 72.2
Hispanic/other Sample size	n = 1 ; % = 5.6	n = 5 ; % = 27.8
Non-Hispanic Sample size	n = 17 ; % = 94.4	n = 13 ; % = 72.2
Comorbidities Custom value	NR	NR
Disease duration (years) Median (IQR)	5.4 (2 to 10.7)	4.1 (2.1 to 11.7)

Characteristic	Modified Mediterranean dietary intervention (N = 18)	Control - no dietary intervention (N = 18)
Relapsing-remitting MS Sample size	n = 14 ; % = 77.8	n = 14 ; % = 77.8
Secondary progressive MS Sample size	n = 1 ; % = 5.6	n = 2 ; % = 11.8
Primary progressive MS Sample size	n = 1 ; % = 5.6	n = 0 ; % = 0
Clinically isolated syndrome Sample size	n = 2 ; % = 11.1	n = 1 ; % = 5.9
EDSS score Scale 0-10. Higher indicates increased disability. Median (IQR)	2 (0 to 3)	2 (0 to 5)

Outcomes

Study timepoints

Baseline

6 month (6 months - end of dietary intervention period)

Change vs. baseline in the diet group relative to the control group

Outcome	Modified Mediterranean dietary intervention vs Control - no dietary intervention, 6 month vs Baseline, N2 = 18, N1 = 18
Neurological Fatigue Index - Multiple Sclerosis Scale used unclear, possibly 0-30 based on reference cited? Mean (SE) score at baseline for control group was 11.77 (1.51) and diet group was mean (SE) 2.95 (2.13) higher (P=0.17). P-value	0.01
Neurological Fatigue Index - Multiple Sclerosis Scale used unclear, possibly 0-30 based on reference cited? Mean (SE) score at baseline for control group was 11.77 (1.51) and diet group was mean (SE) 2.95 (2.13) higher (P=0.17). Mean (SE)	-4.55 (1.58)
MSIS-29 Multiple Sclerosis Impact Scale-29. Scale usually 0-100. Mean (SE) score at baseline for control group was 49.41 (4.37) and diet group was mean (SE) 0.41 (6.10) lower (P=0.95). P-value	0.12
MSIS-29 Multiple Sclerosis Impact Scale-29. Scale usually 0-100. Mean (SE) score at baseline for control group was 49.41 (4.37) and diet group was mean (SE) 0.41 (6.10) lower (P=0.95). Mean (SE)	-7.36 (4.57)

Outcome	Modified Mediterranean dietary intervention vs Control - no dietary intervention, 6 month vs Baseline, N2 = 18, N1 = 18
EDSS score Expanded Disability Status Scale. Scale 0-10. Mean (SE) score at baseline for control group was 2.56 (0.62) and diet group was mean (SE) 0.33 (0.88) lower (P=0.71). P-value	0.01
EDSS score Expanded Disability Status Scale. Scale 0-10. Mean (SE) score at baseline for control group was 2.56 (0.62) and diet group was mean (SE) 0.33 (0.88) lower (P=0.71). Mean (SE)	-0.98 (0.36)

Neurological Fatigue Index - Multiple Sclerosis - Polarity - Lower values are better

MSIS-29 - Polarity - Lower values are better

EDSS score - Polarity - Lower values are better

Assumed all of those randomised included in analysis though this is unclear.

Results - raw data

Outcome	Modified Mediterranean dietary intervention, Baseline, N = 18	Modified Mediterranean dietary intervention, 6 month, N = 18	Control - no dietary intervention, Baseline, N = 18	Control - no dietary intervention, 6 month, N = 18
Engagement and adherence Not reported in a way that could also apply to	NA	Attendance at monthly sessions or by phone was	NA	NR

Outcome	Modified Mediterranean dietary intervention, Baseline, N = 18	Modified Mediterranean dietary intervention, 6 month, N = 18	Control - no dietary intervention, Baseline, N = 18	Control - no dietary intervention, 6 month, N = 18
the control group. Completion rate for both groups reported but not useful to inform about intervention acceptability as non-completion includes events unrelated to intervention. Custom value		90.6% overall. Mean self-reported adherence was 90.3%		

Assumed all of those randomised included in analysis but is unclear.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results neurological fatigue index 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results EDSS score 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results engagement and adherence 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Khayeri, 2016

Bibliographic Reference	**Khayeri, F.; Rabiei, L.; Shamsalinia, A.; Masoudi, R.; Effect of Fordyce Happiness Model on depression, stress, anxiety, and fatigue in patients with multiple sclerosis; Complementary Therapies in Clinical Practice; 2016; vol. 25; 130-135**

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with	No additional information.

this study included in review	
Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Iran.
Study setting	Community.
Study dates	Conducted in 2015-2016.
Sources of funding	No additional information.
Inclusion criteria	Being definitely diagnosed with multiple sclerosis and having records in the Society
Exclusion criteria	Having history of other psychiatric disorders including major depressive disorder (according to the medical records and the physicians examinations) or bipolar disorder (except for cognitive disorders by which MS is categorized), substance dependency, any neurological disorders, history of taking corticosteroids or the disease recurrence within the previous 6 months.
Recruitment / selection of participants	People referred to the Multiple Sclerosis Society of Isfahan.
Intervention(s)	Cognitive behavioural therapy (Fordyce Happiness Model) Training program conducted within eight 1- 1.5-hour sessions, two sessions a week through lecturing, group discussions and question and answering, such that scientific materials were offered within the first half-time of each session and, after a rest, the group discussions and questioning and answering were run about the drills of the subject of interest in the second

	half-time. At the end of each session, the participants were asked to run through certain drills empirically outside the research environment. The intervention consisted of: defining depression, stress, anxiety and their symptoms, defining happiness, and explaining its necessity, reviewing the results of previous studies on happiness (the first session); the technique of increasing physical activity, the technique of being productive and doing useful and meaningful things (the second session); the principles of planning and better organization-the technique of removing concerns, the technique of reducing expectations and wishes (the third session); the technique of enhancing creativity, the technique of living at present (the fourth session); the technique of increasing social relationships, the technique of being the real self (the fifth session). The technique of increasing intimacy as the most important source of happiness-the technique of giving priority to happiness and making it invaluable (the sixth session); the technique of expressing emotions, the technique of enhancing optimism (the seventh session); reviewing all the techniques taught, administering post-test (the eighth session). After completion, all techniques were briefly reviewed with the participants, the participants were asked some questions about their current happiness and optimism levels, and their questions, if any, were answered. Concomitant therapy: No additional information. Intervention subgroups: Group vs. individual - Not stated/unclear. Remote vs. in person - In person
Population subgroups	According to type: Not stated/unclear. According to disability: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.
Comparator	Control Not well defined. Had to attend the society for the same number of days a week, but different days to the intervention arm. Otherwise no additional information.

Number of participants	140
Duration of follow-up	4 months (intervention for 1 month, 3 months additional follow up).
Indirectness	No indirectness
Additional comments	Unclear.

Study arms

Cognitive behavioural therapy (Fordyce Happiness Model) (N = 70)

Training program conducted within eight 1- 1.5-hour sessions, two sessions a week through lecturing, group discussions and question and answering, such that scientific materials were offered within the first half-time of each session and, after a rest, the group discussions and questioning and answering were run about the drills of the subject of interest in the second half-time. At the end of each session, the participants were asked to run through certain drills empirically outside the research environment. The intervention consisted of: defining depression, stress, anxiety and their symptoms, defining happiness, and explaining its necessity, reviewing the results of previous studies on happiness (the first session); the technique of increasing physical activity, the technique of being productive and doing useful and meaningful things (the second session); the principles of planning and better organization-the technique of removing concerns, the technique of reducing expectations and wishes (the third session); the technique of enhancing creativity, the technique of living at present (the fourth session); the technique of increasing social relationships, the technique of being the real self (the fifth session). The technique of increasing intimacy as the most important source of happiness-the technique of giving priority to happiness and making it invaluable (the sixth session); the technique of expressing emotions, the technique of enhancing optimism (the seventh session); reviewing all the techniques taught, administering post-test (the eighth session). After completion, all techniques were briefly reviewed with the participants, the participants were asked some questions about their current happiness and optimism levels, and their questions, if any, were answered.

Control (N = 70)

Not well defined. Had to attend the society for the same number of days a week, but different days to the intervention arm. Otherwise no additional information.

Characteristics

Study-level characteristics

Characteristic	Study (N = 140)
Mean age (SD) Mean (SD)	49.32 (6.86)

Arm-level characteristics

Characteristic	Cognitive behavioural therapy (Fordyce Happiness Model) (N = 70)	Control (N = 70)
% Female Sample size	n = NR ; % = 55.88	n = NR ; % = 61.76
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

Baseline

4 month

Cognitive behavioural therapy compared to usual care at 3-6 months - continuous outcomes

Outcome	Cognitive behavioural therapy (Fordyce Happiness Model), Baseline, N = 70	Cognitive behavioural therapy (Fordyce Happiness Model), 4 month, N = 70	Control, Baseline, N = 70	Control, 4 month, N = 70
Anxiety subscale Mean (SD)	16.94 (2.41)	14.93 (2.81)	16.11 (1.95)	16.08 (2.53)
Depression subscale Mean (SD)	14.57 (2.54)	12.66 (2.59)	14.25 (2.45)	14.06 (1.98)
Stress subscale Mean (SD)	14.88 (2.5)	13.57 (3.81)	15.05 (2.08)	14.97 (2.89)
Patient-reported outcome measures to assess MS fatigue (Piper Fatigue scale) Scale range: Unclear. Likely 0-10? The p-value are between groups (only reported in intervention arm category for this table). Mean (p value)	6.25 (>0.05)	4.33 (0.007)	6.6 (NA)	6.81 (NA)

Psychological symptoms (DASS-21) - Polarity - Lower values are better

Patient-reported outcome measures to assess MS fatigue (Piper Fatigue scale) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Cognitive behavioural therapy compared to usual care at 3-6 months – continuous outcomes – Psychological symptoms (DASS-21) - Anxiety subscale – Mean SD - Cognitive behavioural therapy (Fordyce Happiness Model)-Control-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Cognitive behavioural therapy compared to usual care at 3-6 months – continuous outcomes – Psychological symptoms (DASS-21) - Depression subscale – Mean SD - Cognitive behavioural therapy (Fordyce Happiness Model) - Control-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Cognitive behavioural therapy compared to usual care at 3-6 months – continuous outcomes – Psychological symptoms (DASS-21) - Stress subscale – Mean SD - Cognitive behavioural therapy (Fordyce Happiness Model)-Control-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Cognitive behavioural therapy compared to usual care at 3-6 months – continuous outcomes – Patient -reported outcome measures to assess MS fatigue (Piper Fatigue scale) – Mean P Value - Cognitive behavioural therapy (Fordyce Happiness Model)-Control-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Kooshiar, 2015

Bibliographic Reference	**Kooshiar, H.; Moshtagh, M.; Sardar, M. A.; Foroughipour, M.; Shakeri, M. T.; Vahdatinia, B.; Fatigue and quality of life of women with multiple sclerosis: a randomized controlled clinical trial; Journal of Sports Medicine & Physical Fitness; 2015; vol. 55 (no. 6); 668-74**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	no additional information
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)

Study location	Iran
Study setting	MS clinic
Study dates	NR
Sources of funding	Mashad university of medical sciences
Inclusion criteria	Female patients affected by MS, cognitive competency to give consent, citizen of Iran and residing in Mashad, age from 10-45 years and an EDSS score of 1-5.5.
Exclusion criteria	older than 45 years, EDSS score >5.5, pregnancy, primary progressive MS, experience of acute and severe stress in the previous 4 weeks such as job loss, death, divorce; relapse in the past 4 weeks before sampling or during the 8 weeks of exercise intervention, using immune modulator drugs apart from interferon beta-1a, haemoglobin level <10, history of doing routine exercises. participating at less than 12 exercise sessions, any other acute or chronic physical or psychological disorders, co-morbid conditions such as cardiovascular disease, metabolic or MSK, chronic respiratory or urinary infections, cancer or other diseases of the immune system .
Recruitment / selection of participants	patients gave their informed consent for voluntary participation. eligible participants were randomly assigned into exercise and control groups. These subjects were randomised by writing the names on pieces of paper and randomly drawing them from a hat. the first 20 were assigned to exercise and the second 20 to control.
Intervention(s)	Aquatic exercise was performed in 45 mins sessions, 3 x per week for 8 weeks, in the shallow section of an indoor swimming pool, with a water temperature of 28-29.5C. the programme included 36 movements such as warm-up, stretching, endurance, balance/coordination, strengthening and cool down. all exercises were supervised by 2 physiotherapists.
Population subgroups	Type - relapsing remitting MS and secondary progressive MS. did not include primary progressive Disability (EDSS <6 and EDSS ≥6) = EDSS <5. Disease modifying treatment status (currently using and not currently using) = unclear

	Group vs individual = group Delivered remotely vs in person = in person
Comparator	The control group did not receive any interventions (aquatic exercise) and were asked to maintain their normal treatments.
Number of participants	40
Duration of follow-up	8 weeks
Indirectness	?very strict inclusion/exclusion criteria
Additional comments	no additional information

Study arms

Aquatic exercise (N = 18)

Aquatic exercise was performed for 45 minutes, 3 times per week for 8 weeks

Control group (N = 19)

Did not receive any interventions (aquatic exercise) and were asked to maintain their normal treatments

Characteristics

Study-level characteristics

Characteristic	Study (N = 40)
% Female Sample size	n = 40 ; % = 100
Mean age (SD) Mean (SD)	29.24 (7.98)

Outcomes

Study timepoints

- 8 week

Study outcomes

Outcome	Aquatic exercise, 8 week, N = 18	Control group, 8 week, N = 19
FSS score Mean (SD)	35.06 (12.2)	39.14 (8.1)
MFIS global score Mean (SD)	32.56 (16.07)	42 (12.15)
QoL MQLIM Mean (SD)	80.06 (11.53)	66.52 (6.22)

FSS score - Polarity - Lower values are better

MFIS global score - Polarity - Lower values are better

QoL - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Study outcomes – FSS score – Mean SD - Aquatic exercise Control group-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Study outcomes – MFIS global score – Mean SD - Aquatic exercise-Control group-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Study Outcomes – QoL – Mean SD - Aquatic exercise - Control group-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Kos, 2016

Bibliographic Reference	**Kos, D.; Duportail, M.; Meirte, J.; Meeus, M.; D'Hooghe M, B.; Nagels, G.; Willekens, B.; Meurrens, T.; Ilsbroukx, S.; Nijs, J.; The effectiveness of a self-management occupational therapy intervention on activity performance in individuals with multiple sclerosis-related fatigue: a randomized-controlled trial; International Journal of Rehabilitation Research; 2016; vol. 39 (no. 3); 255-62**

Study details

Trial name / registration number	NCT01512329
Study location	Belgium
Study setting	Outpatient
Study dates	Not reported.
Sources of funding	Supported by a grant from Research Council of Artesis Plantijn University College of Antwerp, Belgium and Koning Boudewijn Stichting Belgium.

Inclusion criteria	Definite diagnosis of MS confirmed by neurologist; aged between 18 and 65 years; Dutch speaking; ambulatory (EDSS ≤5.0); and high impact of fatigue (VAS score of at least 60).
Exclusion criteria	Involved in rehabilitation programme during study period; pregnancy; relapse 3 months prior to study; and severe cognitive disorders (as judged by neurologist).
Recruitment / selection of participants	Recruited from National MS Center Melsbroek and University Hospital Antwerp, Belgium.
Intervention(s)	Self-management occupational therapy, with fatigue management component: SMOoTh programme based on recommendations of MS Council 'Energy Conservation/Envelope Theory' as described by Packer et al. Includes strategies to support taking control of performance of activities within limits of available energy and raise self-efficacy in managing fatigue. Includes several techniques to support behavioural change (e.g. goal setting, self-monitoring and feedback). Consists of three individual sessions (60-90 min duration) for three consecutive weeks provided by occupational therapist. Booklets provided with evidence-based information on fatigue, strategies to cope with fatigue and pace activities. Fatigue diaries used in treatment sessions to support self-awareness and self-efficacy in balancing activities.
Population subgroups	None reported.
Comparator	Control - relaxation: education about role of stress in MS and practicing relaxation techniques such as Jacobson, Schultz, visualisation etc. depending on preferences. All information provided in evidence-based information booklet and completed stress-reaction diary to register activities or events that caused stress. Diary used to coach clients in improving coping with similar future events. Mode, duration and frequency of this therapy were identical to the SMOoTh intervention.
Number of participants	N=31 randomised, n=25 analysed (those that were compliant)
Duration of follow-up	up to 3 months follow-up - ~9 weeks after end of intervention

Indirectness	None.
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

- Self-management occupational therapy intervention (N = 17)
- Control - relaxation (N = 14)

Characteristics

Arm-level characteristics

Characteristic	Self-management occupational therapy intervention (N = 17)	Control - relaxation (N = 14)
% Female Custom value	NR	NR
Mean age (SD) Mean (SD)	37 (8.2)	44 (8.9)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Characteristic	Self-management occupational therapy intervention (N = 17)	Control - relaxation (N = 14)
EDSS score Scale 0-10. Higher indicates increased disability. Median (IQR)	3 (0.75)	3.5 (1.5)

Outcomes

Study timepoints

- Baseline
- 3 month (3-month time-point. ~9 weeks following end of intervention.)

Results - raw data

Outcome	Self-management occupational therapy intervention , Baseline, N = 17	Self-management occupational therapy intervention , 3 month, N = 14	Control - relaxation , Baseline, N = 14	Control - relaxation , 3 month, N = 11
MFIS total score Modified Fatigue Impact Scale. Scale 0-84. Mean (SD)	43.8 (8.5)	32.3 (11.1)	44.9 (14.2)	41.9 (15.4)
MFIS physical Modified Fatigue Impact Scale. Scale usually 0-36. Mean (SD)	21.2 (3.8)	16.6 (5.4)	22.2 (6.7)	20.4 (7.5)

Outcome	Self-management occupational therapy intervention , Baseline, N = 17	Self-management occupational therapy intervention , 3 month, N = 14	Control - relaxation , Baseline, N = 14	Control - relaxation , 3 month, N = 11
MFIS cognitive Modified Fatigue Impact Scale. Scale usually 0-40. Mean (SD)	17.8 (6.3)	12.8 (6.7)	18.7 (7.2)	17.7 (8.3)
MFIS psychosocial score Modified Fatigue Impact Scale. Scale usually 0-8. Mean (SD)	4.4 (3.9)	2.9 (1)	1.5 (2)	3.8 (2.4)
Checklist individual strength (CIS) total Scale possibly 20-140? Mean (SD)	91.6 (12.9)	77 (14.6)	83.6 (25.2)	74.8 (32.7)
CIS concentration Scale possibly 5-35. Mean (SD)	20.9 (6.4)	18.6 (8.5)	18.1 (9.1)	17.1 (8.8)
CIS physical activity Scale possibly 3-21. Mean (SD)	12.1 (4.1)	10.6 (5.5)	9.6 (5.8)	9.4 (5.5)
CIS motivation Scale possibly 4-28.	15.2 (5.8)	10.6 (5.5)	14 (7)	9.4 (5.5)

Outcome	Self-management occupational therapy intervention , Baseline, N = 17	Self-management occupational therapy intervention , 3 month, N = 14	Control - relaxation , Baseline, N = 14	Control - relaxation , 3 month, N = 11
Mean (SD)				
CIS subjective fatigue Scale possibly 8-56. Mean (SD)	43.3 (5.9)	37.9 (8)	42 (11.4)	36.6 (16)
SF-36 physical functioning Scale usually 0-100. Mean (SD)	63.2 (20.2)	66.9 (16.9)	51.4 (23.2)	58.3 (24.1)
SF-36 role physical function Scale usually 0-100. Mean (SD)	35.3 (36.5)	59.4 (40)	39.3 (32.1)	66.7 (35.4)
SF-36 physical pain Scale usually 0-100. Mean (SD)	62.9 (25.7)	83.3 (11.4)	56.3 (22.8)	59.2 (17.2)
SF-36 general health Scale usually 0-100. Mean (SD)	47.9 (15.5)	48.8 (16.9)	45 (20)	47.6 (14.2)

Outcome	Self-management occupational therapy intervention , Baseline, N = 17	Self-management occupational therapy intervention , 3 month, N = 14	Control - relaxation , Baseline, N = 14	Control - relaxation , 3 month, N = 11
SF-36 vitality Scale usually 0-100. Mean (SD)	48.5 (15)	54.4 (16.8)	46.1 (16.9)	48.9 (16.4)
SF-36 social functioning Scale usually 0-100. Mean (SD)	47.8 (16.1)	71.9 (17.4)	58.9 (22.2)	68.1 (16.7)
SF-36 role emotional function Scale usually 0-100. Mean (SD)	60.8 (35.8)	79.2 (35.4)	76.2 (33.2)	85.2 (33.8)
SF-36 Mental Health Scale usually 0-100. Mean (SD)	65.2 (14)	64 (11.7)	65.4 (16.3)	70.7 (17.8)
SF-36 health change Scale usually 0-100. Mean (SD)	49.1 (28.7)	43.8 (25.9)	56.1 (27)	58.3 (17.7)

MFIS total score - Polarity - Lower values are better

MFIS physical - Polarity - Lower values are better

MFIS cognitive - Polarity - Lower values are better

MFIS psychosocial score - Polarity - Lower values are better

Checklist individual strength (CIS) total - Polarity - Lower values are better

CIS concentration - Polarity - Lower values are better

CIS physical activity - Polarity - Lower values are better

CIS motivation - Polarity - Lower values are better

CIS subjective fatigue - Polarity - Lower values are better

SF-36 physical functioning - Polarity - Higher values are better

SF-36 role physical function - Polarity - Higher values are better

SF-36 physical pain - Polarity - Higher values are better

SF-36 general health - Polarity - Higher values are better

SF-36 vitality - Polarity - Higher values are better

SF-36 social functioning - Polarity - Higher values are better

SF-36 role emotional function - Polarity - Higher values are better

SF-36 Mental Health - Polarity - Higher values are better

SF-36 health change - Polarity - Higher values are better

Final values. Baseline values for MFIS total given for total randomised but only for those that completed the protocol (n=14 vs. n=11) for the other outcomes.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total score 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS total score 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS concentration 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS physical activity 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS motivation 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CIS subjective fatigue 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 role physical function 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical pain 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 vitality 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional function 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 mental health 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 health change 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Kucuk, 2016

Bibliographic Reference	**Kucuk, F.; Kara, B.; Poyraz, E. C.; Idiman, E.; Improvements in cognition, quality of life, and physical performance with clinical Pilates in multiple sclerosis: a randomized controlled trial; Journal of Physical Therapy Science; 2016; vol. 28 (no. 3); 761-8**

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.

Trial name / registration number	No additional information.
Study type	Randomised controlled trial (RCT)
Study location	Turkey
Study setting	Community
Study dates	Not stated/unclear.
Sources of funding	Not stated/unclear.
Inclusion criteria	Over 18 years of age, diagnosed with MS, an Expanded Disability Status Scale score of 6 or lower, and able to act, or move independently, able to walk alone or with support.
Exclusion criteria	An MS-related acute attack, cardiovascular diseases, thyroid disorders, gout or orthopedic limitation or irregular attendance.
Recruitment / selection of participants	No additional information.
Intervention(s)	Pilates Pilates. The Pilates key elements were taught to patients before the clinical Pilates exercise lessons. The key elements were breathing, focus, and placement of the rib cage, shoulder, head and neck. All Pilates movements were checked, and necessary corrections were made by a physical therapist during Pilates exercise sessions. The exercises were repeated 8-10 times. When the Pilates exercises could be done by the patients with maintaining the key elements, the level of exercise was increased. Exercises were started with closed chain exercises, and advanced to open chain exercises. On the other hand, exercises started at level 1 and advanced to level 3. The exercises were studies as group exercises. Each exercise session was planned to be 45-60 minutes long. Each session was comprised of a 10 min warm-up, 25-45 min of mat exercises, and 10 min cool-down. Pilates warm-up exercises consisted of Cleopatra, the Chest stretch, the Toy soldier,

	Upper extremity proprioceptive neuromuscular facilitation patterns, and Roll down. Pilates mat exercises performed in 5 different positions. 1. The one leg stretch, Hundreds, the Double leg stretch, Scissors, the Shoulder bridge, Oblique preparation, and the Hip twist were performed in the supine position. 2. The Clare, the Side kick, Arm openings, the Lower lif, Leg lifts, and the Side bend were performed in the side-lying position. 3. The Swan dive, the One leg kick, Swimming, the Breast stroke preparations, the Breast stroke and the Cobra were performed in the prone position. 3. The Half roll back, Oblique roll up were performed in the sitting position. 5. Swimming was perofmred in the kneeling position. The Pilates cooldown exercises were the Spine stretch, Saw, Mermaid, Cleopatra, Chest stretch, Toy soldier. Concomitant therapy: Not stated/unclear Intervention subgroups: Group vs. individual - Group Remote vs. in person - In person
Population subgroups	According to type: Not stated/unclear. According to disability: EDSS <6 (see participants characteristics table) Disease modifying treatment status: Not stated/unclear.
Comparator	Resistance training Traditional exercises including strength, balance and coordination exercises were applied to the control group. People were not allowed to start any new exercises.
Number of participants	20

Duration of follow-up	8 weeks (this is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)
Indirectness	Outcome indirectness - follow up duration less than 3 months (8 weeks)
Additional comments	Not stated.

Study arms

Pilates (N = 11)

Pilates. The Pilates key elements were taught to patients before the clinical Pilates exercise lessons. The key elements were breathing, focus, and placement of the rib cage, shoulder, head and neck. All Pilates movements were checked, and necessary corrections were made by a physical therapist during Pilates exercise sessions. The exercises were repeated 8-10 times. When the Pilates exercises could be done by the patients with maintaining the key elements, the level of exercise was increased. Exercises were started with closed chain exercises, and advanced to open chain exercises. On the other hand, exercises started at level 1 and advanced to level 3. The exercises were studies as group exercises. Each exercise session was planned to be 45-60 minutes long. Each session was comprised of a 10 min warm-up, 25-45 min of mat exercises, and 10 min cool-down. Pilates warm-up exercises consisted of Cleopatra, the Chest stretch, the Toy soldier, Upper extremity proprioceptive neuromuscular facilitation patterns, and Roll down. Pilates mat exercises performed in 5 different positions. 1. The one leg stretch, Hundreds, the Double leg stretch, Scissors, the Shoulder bridge, Oblique preparation, and the Hip twist were performed in the supine position. 2. The Clare, the Side kick, Arm openings, the Lower left, Leg lifts, and the Side bend were performed in the side-lying position. 3. The Swan dive, the One leg kick, Swimming, the Breast stroke preparations, the Breast stroke and the Cobra were performed in the prone position. 3. The Half roll back, Oblique roll up were performed in the sitting position. 5. Swimming was performed in the kneeling position. The Pilates cooldown exercises were the Spine stretch, Saw, Mermaid, Cleopatra, Chest stretch, Toy soldier.

Resistance training (N = 9)

Traditional exercises including strength, balance and coordination exercises were applied to the control group. People were not allowed to start any new exercises.

Characteristics

Arm-level characteristics

Characteristic	Pilates (N = 11)	Resistance training (N = 9)
% Female Sample size	n = 7 ; % = 63.6	n = 6 ; % = 66.7
Mean age (SD) (years) Mean (SD)	47.2 (9.5)	49.7 (8.9)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR
EDSS Mean (SD)	3.2 (2.2)	2.8 (1.4)
Illness duration (years) Mean (SD)	14.8 (7.4)	14.2 (9.5)

Outcomes

Study timepoints

- Baseline
- 8 week (Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)

Pilates compared to resistance training at 3-6 months - continuous outcomes (final values)

Outcome	Pilates, Baseline, N = 11	Pilates, 8 week, N = 11	Resistance training, Baseline, N = 9	Resistance training, 8 week, N = 9
Physical subscale Mean (SD)	9.73 (4.43)	7.18 (3.63)	11.56 (9.33)	7.44 (5.27)
Cognitive subscale Mean (SD)	8.82 (5.49)	5.82 (5.04)	8.11 (10.73)	7.33 (6.6)
Psychosocial subscale Mean (SD)	15.45 (12.88)	7.64 (9.6)	17.33 (13.09)	13.11 (10.24)
Health-related Quality of Life (Multiple Sclerosis International Quality of Life questionnaire) Scale range: 0-100 Mean (SD)	28.22 (9.06)	23.82 (7.53)	44.44 (16.06)	40.05 (17.96)
Cognitive Function (MSFC - Paced Auditory Serial Addition Test) (Number of correct answers) Mean (SD)	44.91 (11.63)	47.82 (11.21)	27 (16.91)	27.89 (13.17)
Psychological symptoms (Beck depression inventory) Scale range: 0-63	10.18 (5.23)	7.91 (6.86)	11.44 (6.52)	9.78 (5.26)

Outcome	Pilates, Baseline, N = 11	Pilates, 8 week, N = 11	Resistance training, Baseline, N = 9	Resistance training, 8 week, N = 9
Mean (SD)				

Patient-reported outcome measures to assess MS fatigue (MFIS) - Polarity - Lower values are better

Health-related Quality of Life (Multiple Sclerosis International Quality of Life questionnaire) - Polarity - Higher values are better

Cognitive Function (MSFC - Paced Auditory Serial Addition Test) - Polarity - Higher values are better

Psychological symptoms (Beck depression inventory) - Polarity - Lower values are better

Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Pilates compared to resistance training at 3-6 months – continuous outcomes (final values) – Patient -reported outcome measures to assess MS fatigue (MFIS) – Physical subscale – Mean SD - Pilates-Resistance training-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)*

Pilates compared to resistance training at 3-6 months – continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (MFIS) – Cognitive subscale – Mean SD - Pilates-Resistance training-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)*

Pilates compared to resistance training at 3-6 months – continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (MFIS)-Psycho social subscale – Mean SD - Pilates-Resistance training-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)*

Pilates compared to resistance training at 3-6 months – continuous outcomes (final values) - Health-related Quality of Life (Multiple Sclerosis International Quality of Life questionnaire) – Mean SD – Pilates - Resistance training-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)*

Pilates compared to resistance training at 3-6 months – continuous outcomes (final values) – Cognitive Function (MSFC-Paced Auditory Serial Addition Test) – Mean SD – Pilates - Resistance training-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)*

Pilates compared to resistance training at 3-6 months – continuous outcomes (final values) -Psychological symptoms (Beck depression inventory) – Mean SD – Pilates - Resistance training-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up at 8 weeks. This is less than 3 months and therefore the outcomes will be downgraded due to outcome indirectness)*

Lutz, 2017

Bibliographic Reference	**Lutz, C.; Kersten, S.; Haas, C. T.; Short-Term and Long-Term Effects of an Exercise-Based Patient Education Programme in People with Multiple Sclerosis: A Pilot Study; Multiple Sclerosis International; 2017; vol. 2017; 2826532**

Study details

Trial name / registration number	Not reported.
Study location	Germany
Study setting	Outpatient

Study dates	Recruitment between May and July 2013.
Sources of funding	Financial support from Aenne Speck Foundation and IKK Sudwest.
Inclusion criteria	Definite diagnosis of MS; age ≥ 18 years; documentation of the current state of disease (EDSS score, medication, and clinical course); disease-related problems in daily life (self-reported); ability to stand and walk with or without assistive devices (self-reported); physician approval for beginning a physical activity programme; and signed letter of written informed consent.
Exclusion criteria	MS relapse, changing medication, or cortisone therapy one month prior to recruitment and during the study; concurrent neurological, internal, or orthopaedic disorders interfering with standing and walking ability; and participation in other active therapies during the study.
Recruitment / selection of participants	Participants were recruited between May and July 2013 by the German Society of Multiple Sclerosis and the health insurance company IKK Sudwest.
Intervention(s)	Exercise-based patient education programme: six-week programme providing participants with knowledge to work out independently. Taught neurophysiological essentials in MS disease, physiological effects of sports and physical exercises in general and specific for MS, MS-specific recommendations of exercise training, training principles and the importance of resting periods. Various types of exercise training were offered (cardiorespiratory, strength, coordination/reflex-based and flexibility) were offered based on individual performance abilities. Psychological determinants for adoption and maintenance of health-related behaviour such as self-efficacy, problem-solving and patient-generated goal setting taught in order to enhance exercise motivation and self-management skills. Explained benefits of exercise and offered opportunities to experience four main sources of self-efficacy such as mastery experience, vicarious experience, symbolic experience and emotional arousal (feedback). Group discussions, assignments and documentation of training and symptoms were contained in the programme. Taught how to set goals using SMART concept. Delivered over 6 weeks, twice weekly sessions for 60-90 min. Supervised by at least one sports scientist and one assistant. Patient booklets with theoretical background and practical information were provided. After the programme, participants performed exercise training with self-generated training schedule autonomously at home for 12 weeks and a further 36 weeks until 1 year after baseline.

Population subgroups	None reported.
Comparator	Control - waitlist control group. For the first 6 weeks did not receive the training programme. After that they received the training programme as described above for the intervention group.
Number of participants	N=18 randomised, n=18 analysed
Duration of follow-up	Up to 6 weeks - study reports a longer follow-up but after 6 weeks the control group received the same intervention as the intervention group.
Indirectness	Outcome indirectness - follow-up for intervention and control groups <3 months minimum specified in protocol
Method of analysis	Intention to treat - all randomised

Study arms

Exercise-based patient education programme (N = 9)

Self-management + exercise intervention.

Control (N = 9)

Waitlist control group.

Characteristics

Arm-level characteristics

Characteristic	Exercise-based patient education programme (N = 9)	Control (N = 9)
% Female Sample size	n = 7 ; % = 87.5	n = 6 ; % = 100
Mean age (SD) Mean (SD)	52.4 (10.4)	56 (7.4)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score Scale 0-10. Higher indicates increased disability. Median (IQR)	3.5 (2.25 to 3.5)	3.5 (2 to 3.5)
Time since diagnosis (years) Mean (SD)	12.5 (10)	17.2 (7.4)
Relapsing-remitting MS Sample size	n = 3 ; % = 37.5	n = 4 ; % = 66.7
Primary progressive MS Sample size	n = 3 ; % = 37.5	n = 1 ; % = 16.7

Characteristic	Exercise-based patient education programme (N = 9)	Control (N = 9)
Secondary progressive MS Sample size	n = 1 ; % = 12.5	n = 1 ; % = 16.7
Benign Sample size	n = 1 ; % = 12.5	n = 0 ; % = 0
Immunotherapy Sample size	n = 5 ; % = 62.5	n = 3 ; % = 50
Symptomatic therapy Sample size	n = 2 ; % = 25	n = 1 ; % = 16.7
None Sample size	n = 1 ; % = 12.5	n = 2 ; % = 33.3

Characteristics given for those analysed (n=8 vs. n=6) rather than the total number randomised (n=18)

Outcomes

Study timepoints

- Baseline
- 6 week (6-weeks - end of treatment sessions)

Results - raw data

Outcome	Exercise-based patient education programme, Baseline, N = 9	Exercise-based patient education programme, 6 week, N = 8	Control, Baseline, N = 9	Control, 6 week, N = 6
WEIMuS fatigue scale Scale usually 0-68. Mean (SD)	26 (17.7)	22.1 (15.5)	21.3 (6.1)	18.8 (9.2)
WEIMuS fatigue - mental Scale usually 0-36. Mean (SD)	10.5 (10.2)	9.5 (8.4)	8.8 (3.9)	7.5 (2.3)
WEIMuS fatigue - physical Scale 0-32 usually. Mean (SD)	15.5 (10)	12.6 (8.3)	12.5 (5.8)	11.3 (8.4)
MusiQol Score Scale usually 0-100. Mean (SD)	68.1 (10.6)	77.2 (11.4)	70 (7.8)	74.6 (11.5)
Adverse events Reported to be no adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Compliance This measure could not be applied to the control group as did not attend any sessions	NA	more than 80% for all - not missing more than 2 lessons	NA	NR

Outcome	Exercise-based patient education programme, Baseline, N = 9	Exercise-based patient education programme, 6 week, N = 8	Control, Baseline, N = 9	Control, 6 week, N = 6
Custom value				

WEIMuS fatigue scale - Polarity - Lower values are better

WEIMuS fatigue - mental - Polarity - Lower values are better

WEIMuS fatigue - physical - Polarity - Lower values are better

MusiQol Score - Polarity - Higher values are better

Note that baseline values are only given for the n=8 and n=6 that were analysed at the end of the 6-week period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results WEIMuS fatigue total 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(follow-up <3 months minimum specified in protocol)*

Results WEIMuS fatigue mental 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(follow-up <3 months minimum specified in protocol)*

Results WEIMus fatigue physical 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(follow-up <3 months minimum specified in protocol)*

Results MusiQol score 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(follow-up <3 months*

Section	Question	Answer
		minimum specified in protocol)

Results adverse events 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(follow-up <3 months minimum specified in protocol)*

Results compliance 6 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(follow-up <3 months minimum specified in protocol)*

Maurer, 2018

Bibliographic Reference	**Maurer, M.; Schuh, K.; Seibert, S.; Baier, M.; Hentschke, C.; Streber, R.; Tallner, A.; Pfeifer, K.; A randomized study to evaluate the effect of exercise on fatigue in people with relapsing-remitting multiple sclerosis treated with fingolimod; Multiple Sclerosis Journal Experimental Translational & Clinical; 2018; vol. 4 (no. 1); 2055217318756688**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	PACE study/ NCT01490840
Study location	Germany
Study setting	MS outpatient centres in Germany
Study dates	2011-2014
Sources of funding	This study and medical writing support was funded by Novartis Pharma GmbH.
Inclusion criteria	18 to 65 years with an established diagnosis of RRMS. To avoid confounding effects of background disease-modifying therapy on the outcomes, only patients who received stable fingolimod therapy for at least one month prior to screening were included. A maximum Expanded Disability Status Scale (EDSS) score of 3.5 was allowed, and the MFIS score had to be above 14 at screening. Patients had to be neurologically stable with no evidence of relapse within 30 days prior to recruitment. Patients were required to have access to the internet in order to enter the e-training platform.
Exclusion criteria	Prior treatment with immunosuppressive or immunomodulating medications within one to three months before randomisation, depending on the medication (except for cladribine, which was not allowed at any time before

	randomization) to avoid medication-induced bias. Further, patients with a cardiovascular risk profile, severe respiratory or pulmonary disease, or any clinically relevant internal disease or orthopaedic diseases that could interfere with exercise were excluded to ensure that patients were able to safely and effectively follow a training program.
Recruitment / selection of participants	A total of 198 PwMS were screened for study eligibility at 32 German study centers. In total, 20 patients were screening failures, thus 178 patients were randomized
Intervention(s)	The e-training intervention employed a web-based application to administer an adaptive and individualised exercise protocol for 6 months. The exercise intervention was home based and supervised via the internet by a physiotherapist or exercise therapist with experience in the prevention and rehabilitation setting with different indications including MS. Target exercise intensity was moderate and progression was regulated by each participant's subjective, perceived exertion, which was rated between 6 and 20 on the Borg Scale. The individual exercise schedules comprised strengthening exercises twice a week and endurance training once a week. Balance or core stability exercise could be added. The personal exercise schedule and the comprised exercises were explained in a two-day on-site introductory group session at the beginning of the intervention period. Participants documented each exercise session via a web-based application (duration, type of exercises, number of repetitions, and sets, perceived exertion) and used an electronic exercise diary that could be supervised by the exercise therapist.
Population subgroups	
Comparator	wait list control for 6 months
Number of participants	178
Duration of follow-up	6 months
Indirectness	only included relapsing–remitting MS patients receiving fingolimod

Additional comments	NR

Study arms

structured internet based exercise program (N = 94)

wait list control (N = 84)

Characteristics

Arm-level characteristics

Characteristic	structured internet based exercise program (N = 94)	wait list control (N = 84)
% Female Sample size	n = 64 ; % = 68.8	n = 57 ; % = 67.9
Mean age (SD) Mean (SD)	40.9 (10.4)	39.4 (8.7)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR

Characteristic	structured internet based exercise program (N = 94)	wait list control (N = 84)
Time since diagnosis (years) Mean (SD)	8 (7.1)	9.2 (7.2)
Time since first MS symptoms (years) Mean (SD)	10.4 (8.9)	11.4 (7.4)
Relapse in the past 6 months Sample size	n = 0 ; % = 0	n = 4 ; % = 4.8
EDSS score Scale 0-10. Higher indicates increased disability. Mean (SD)	2.2 (1)	2.2 (1.1)

Note that baseline values are given for those analysed (n=93 vs. n=84) rather than those randomised (n=94 vs. n=84)

Outcomes

Study timepoints

- Baseline
- 6 month (6 months - end of intervention period)

Results - change from baseline

Outcome	structured internet-based exercise program, 6 month vs Baseline, N = 93	wait list control, 6-month vs Baseline, N = 84
MFIS Modified Fatigue Impact Scale. Scale 0-84. Baseline values were 30.6 (14.9) vs. 34.4 (13.8). Mean (95% CI)	-4.2 (-6.58 to -1.83)	-1.81 (-4.29 to 0.67)
WEIMuS fatigue score Scale 0-68. Baseline values were 28.1 (14.9) vs. 30.0 (13.9). Mean (95% CI)	-2.94 (-5.19 to -0.68)	-0.89 (-3.24 to 1.46)
Beck Depression Inventory II Scale usually 0-63. Mean (95% CI)	-2.62 (-4.42 to -0.81)	-1.97 (-3.43 to -0.52)

MFIS - Polarity - Lower values are better

WEIMuS fatigue score - Polarity - Lower values are better

Beck Depression Inventory II - Polarity - Lower values are better

Results - raw data

Outcome	structured internet based exercise program, Baseline, N = 94	structured internet based exercise program, 6 month, N = 94	wait list control, Baseline, N = 84	wait list control, 6 month, N = 84
Any adverse event Full list of types of events included not provided	n = NA ; % = NA	n = 55 ; % = 58.5	n = NA ; % = NA	n = 51 ; % = 60.7

Outcome	structured internet based exercise program, Baseline, N = 94	structured internet based exercise program, 6 month, N = 94	wait list control, Baseline, N = 84	wait list control, 6 month, N = 84
No of events				
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = 2 ; % = 2.33	n = NA ; % = NA	n = 1 ; % = 1.27
Withdrawal due to adverse events Number analysed	NA	86	NA	79
Compliance Did not apply to control group. Definition of compliant/non-compliant individual was completing or not completing at least 70% of scheduled exercise sessions during months 1-6. Custom value	NA	% sessions completed was variable (0-442.0%). Mean compliance was 82.4 (64.1)%. 39.8% non-compliant	NA	NR
Usability in general Scale 1-5 (very good to very bad) Number analysed	NA	129	NA	NA
Usability in general Scale 1-5 (very good to very bad) Mean (SD)	NA (NA)	2.34 (0.94)	NA (NA)	NA (NA)

Outcome	structured internet based exercise program, Baseline, N = 94	structured internet based exercise program, 6 month, N = 94	wait list control, Baseline, N = 84	wait list control, 6 month, N = 84
Usability - graphical appeal Scale 1-5 (not at all to yes, very much) Number analysed	NA	126	NA	NA
Usability - graphical appeal Scale 1-5 (not at all to yes, very much) Mean (SD)	NA (NA)	4.12 (0.98)	NA (NA)	NA (NA)
Usability - problems with software Scale 1-5 (never to always) Number analysed	NA	127	NA	NA
Usability - problems with software Scale 1-5 (never to always) Mean (SD)	NA (NA)	2.31 (0.93)	NA (NA)	NA (*empty data*)
Therapeutic support - satisfaction with the therapist and their support at the introductory group session Scale 1-5 (very good to very bad) Number analysed	NA	128	NA	NA
Therapeutic support - satisfaction with the therapist and their support at the introductory	NA (NA)	1.4 (0.64)	NA (NA)	NA (NA)

Outcome	structured internet based exercise program, Baseline, N = 94	structured internet based exercise program, 6 month, N = 94	wait list control, Baseline, N = 84	wait list control, 6 month, N = 84
group session Scale 1-5 (very good to very bad) Mean (SD)				
Therapeutic support - satisfaction with the training support Scale 1-5 (very good to very bad) Number analysed	NA	128	NA	NA
Therapeutic support - satisfaction with the training support Scale 1-5 (very good to very bad) Mean (SD)	NA (NA)	1.4 (0.66)	NA (NA)	NA (NA)
Therapeutic support - satisfaction with the support at the central assessment center Scale 1-5 (very good to very bad) Number analysed	NA	128	NA	NA
Therapeutic support - satisfaction with the support at the central assessment center Scale 1-5 (very good to very bad) Mean (SD)	NA (NA)	1.4 (0.56)	NA (NA)	NA (NA)

Outcome	structured internet based exercise program, Baseline, N = 94	structured internet based exercise program, 6 month, N = 94	wait list control, Baseline, N = 84	wait list control, 6 month, N = 84
Satisfaction about the quality of the information about the internet-based training and to independently conduct the training at home at the introductory group session Scale 1-5 (not at all to yes, very much) Number analysed	NA	128	*empty data*	NA
Satisfaction about the quality of the information about the internet-based training and to independently conduct the training at home at the introductory group session Scale 1-5 (not at all to yes, very much) Mean (SD)	NA (NA)	4.4 (0.72)	NA (NA)	NA (NA)
Usefulness and meaningfulness of an internet-supported training Scale 1-5 (not at all to yes, very much) Number analysed	NA	126	NA	NA
Usefulness and meaningfulness of an internet-supported training Scale 1-5 (not at all to yes, very much) Mean (SD)	NA (NA)	4.4 (0.89)	NA (NA)	NA (NA)

Outcome	structured internet based exercise program, Baseline, N = 94	structured internet based exercise program, 6 month, N = 94	wait list control, Baseline, N = 84	wait list control, 6 month, N = 84
Interest in the continuation of the training Scale 1-5 (not at all to yes, very much) Number analysed	NA	127	NA	NA
Interest in the continuation of the training Scale 1-5 (not at all to yes, very much) Mean (SD)	NA (NA)	3.9 (1.1)	NA (NA)	NA (NA)

Analysed population for any adverse event outcome includes all of those randomised, while an available case analysis was extracted for those leading to withdrawal.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS change from baseline 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results WEIMuS fatigue change from baseline 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results Beck Depression II change from baseline 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results any adverse event 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results withdrawal due to adverse events 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results compliance 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results usability in general 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results graphical appeal 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results problems with software 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results satisfaction with therapist and group session support 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results satisfaction with training support 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results satisfaction with support at central assessment centre 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results satisfaction with quality of information and conducting training at home 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results usefulness and meaningfulness of internet-supported intervention 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results interest in continuation of the training 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Mousavi-Shirazi-Fard, 2020

Bibliographic Reference	**Mousavi-Shirazi-Fard, Z.; Mazloom, Z.; Izadi, S.; Fararouei, M.; The effects of modified anti-inflammatory diet on fatigue, quality of life, and inflammatory biomarkers in relapsing-remitting multiple sclerosis patients: a randomized clinical trial; International Journal of Neuroscience; 2020; 1-9**

Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	IRCT20171217037916N2
Study location	Iran
Study setting	Outpatient
Study dates	Not reported.
Sources of funding	Financially supported by Shiraz University of Medical Sciences, Shiraz, Iran.
Inclusion criteria	BMI between 18.5 and 30 kg/m2; relapsing-remitting MS diagnosis; deficiency in at least 2 antioxidant micronutrients based on Food Frequency Questioner; aged 20-50 years (prior to menopause); EDSS score <5.5; and no change in medications for at least 2 months.
Exclusion criteria	Relapse occurring during study; lack of cooperation; and participants that had used a particular diet during the previous 3 months, consumed antidepressants or fatigue drugs; and suffered from heart diseases, renal disorders, cancer, or endocrine and metabolic disease, as well as those that were pregnant or lactating.

Recruitment / selection of participants	Randomly selected from previous cross-sectional study from June 2018 to February 2019. Patients informed by SMS, telephone and announcements in specialised clinics affiliated to Shiraz University of Medical Sciences.
Intervention(s)	Diet intervention - 12 weeks: diet designed for each patient based on an anti-inflammatory diet. Target was 55% energy from carbohydrates, 15% from proteins and 30% from fat. Diet prescribed for weight maintenance not weight loss. High amounts of vegetables and fruit included in the diet. Advised to substitute white rice with brown rice, white bread with whole what bread and high fat dairy products with probiotic low-fat products. Legumes and soy products were also recommended. Healthy fats such as olive oil and canola included in diet for cooking or salad dressing. Nuts were advised to replace butter and cream. Spices also recommended. White or green tea and moderate amounts of dark chocolate permitted. Protein sources such as lean poultry and fish were included but consumption of lean red meat and eggs limited to 1-2 times per week. Refined carbohydrates such as pastries, cookies and cakes, as well as processed and fast food were not recommended. Each patient followed up every 2 weeks and visited once per month. Dietician's phone number provided to contact if they had any problems.
Population subgroups	None reported.
Comparator	Control - healthy diet recommendations based on WHO healthy diet. No personalised diet plan. Each patient followed up every 2 weeks and visited once per month. Dietician's phone number provided to contact if they had any problems.
Number of participants	N=104 randomised, n=100 analysed
Duration of follow-up	up to 12 weeks - end of intervention
Indirectness	None.
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Anti-inflammatory diet (N = 52)

Control - WHO healthy diet recommendations (N = 52)

Characteristics

Arm-level characteristics

Characteristic	Anti-inflammatory diet (N = 52)	Control - WHO healthy diet recommendations (N = 52)
% Female Sample size	n = 43 ; % = 86	n = 44 ; % = 88
Mean age (SD) Mean (SD)	35.2 (6.61)	36.26 (7.23)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS Score 0-4 Sample size	n = 44 ; % = 88	n = 43 ; % = 86

Characteristic	Anti-inflammatory diet (N = 52)	Control - WHO healthy diet recommendations (N = 52)
EDSS Score 4.5-5.5 Sample size	n = 6 ; % = 12	n = 7 ; % = 14
Disease duration (years) Mean (SD)	6.61 (2.88)	5.74 (2.7)
Fingolimode Sample size	n = 10 ; % = 20	n = 11 ; % = 22
Interferon beta-1a Sample size	n = 19 ; % = 38	n = 19 ; % = 38
Interferon beta-1b Sample size	n = 6 ; % = 12	n = 4 ; % = 8
Natalizumab Sample size	n = 4 ; % = 8	n = 4 ; % = 8
Glatiramer acetate Sample size	n = 7 ; % = 14	n = 8 ; % = 16
Rituximab Sample size	n = 2 ; % = 4	n = 2 ; % = 4
Dimethyl fumarate	n = 2 ; % = 4	n = 2 ; % = 4

Characteristic	Anti-inflammatory diet (N = 52)	Control - WHO healthy diet recommendations (N = 52)
Sample size		

Baseline values are given for the group analysed and (n=50 in each group) rather than randomised (n=52 in each group).

Outcomes

Study timepoints

- Baseline
- 12 week (12 weeks - end of dietary intervention)

Results - raw data

Outcome	Anti-inflammatory diet, Baseline, N = 52	Anti-inflammatory diet, 12 week, N = 50	Control - WHO healthy diet recommendations, Baseline, N = 52	Control - WHO healthy diet recommendations, 12 week, N = 50
MFIS total score Modified Fatigue Impact Scale. Scale 0-84. Mean (SD)	47.96 (12.63)	47.22 (12.54)	47.84 (11.18)	47.92 (11.11)
MFIS - physical score Modified Fatigue Impact Scale. Scale 0-36. Mean (SD)	22.42 (6.39)	22.18 (6.37)	22.9 (4.19)	22.98 (4.21)

Outcome	Anti-inflammatory diet, Baseline, N = 52	Anti-inflammatory diet, 12 week, N = 50	Control - WHO healthy diet recommendations, Baseline, N = 52	Control - WHO healthy diet recommendations, 12 week, N = 50
MFIS - cognitive Modified Fatigue Impact Scale. Scale 0-40. Mean (SD)	22.58 (7.88)	22.24 (7.8)	22.68 (8.18)	22.72 (8.2)
MFIS - psychosocial Modified Fatigue Impact Scale. Scale 0-8. Note there is a larger baseline difference between groups for this outcome. Mean (SD)	2.96 (1.89)	2.66 (1.81)	2.24 (1.39)	2.28 (1.4)
MSQOL-54 - physical composite Scale 0-100. Note there is a larger baseline difference between groups for this outcome. Mean (SD)	49.15 (23.56)	49.5 (23.25)	46.63 (21.98)	46.57 (23.92)
MSQOL-54 - mental health composite Scale 0-100. Note there is a larger baseline difference between groups for this outcome. Mean (SD)	58.27 (24.96)	58.52 (24.14)	64.16 (27.37)	64.43 (28.25)

Outcome	Anti-inflammatory diet, Baseline, N = 52	Anti-inflammatory diet, 12 week, N = 50	Control - WHO healthy diet recommendations, Baseline, N = 52	Control - WHO healthy diet recommendations, 12 week, N = 50
Adverse events - relapse and withdrawal No mention of any other adverse events occurring. No of events	n = NA ; % = NA	n = 2 ; % = 3.8	n = NA ; % = NA	n = 1 ; % = 2
Adverse events - relapse and withdrawal No mention of any other adverse events occurring. Number analysed	NA	52	NA	51

MFIS total score - Polarity - Lower values are better

MFIS - physical score - Polarity - Lower values are better

MFIS - cognitive - Polarity - Lower values are better

MFIS - psychosocial - Polarity - Lower values are better

MSQOL-54 - physical composite - Polarity - Higher values are better

MSQOL-54 - mental health composite - Polarity - Higher values are better

Note that baseline values are given for the n=50 analysed in each group and not the n=52 per group that were randomised. Available case analysis could be extracted for the adverse event outcome.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS total score 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical score 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive score 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial score 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 physical composite 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQOL-54 mental health composite 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events relapse withdrawal 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Nazari, 2015

Bibliographic Reference	**Nazari, F.; Shahreza, M. S.; Shaygannejad, V.; Valiani, M.; Comparing the effects of reflexology and relaxation on fatigue in women with multiple sclerosis; Iranian Journal of Nursing and Midwifery Research; 2015; vol. 20 (no. 2); 200-4**

Study details

Trial name / registration number	3920940
Study location	Iran
Study setting	Community
Study dates	2013
Sources of funding	Isfahan University of Medical Sciences, Isfahan, Iran
Inclusion criteria	Women aged 18–50 years; had types of MS (relapsing-remitting, primary progressive, and secondary progressive), diagnosed by neurologists based on Mc Donald's criteria with the elapse of at least 6 months from relevant diagnosis; had willingness to participate in the research; and had healthy feet without deformity, callus or corn, cleft, active thrombosis or phlebitis, varicose veins, recent ankle trauma, sprain, fracture, inflammation, or infection. Other inclusion criteria for the study participants were: No previous participation in treatment sessions such as reflexology, relaxation, or massage in the

	last 6 months; having fatigue severity score of equal to and over 4 based on fatigue severity scale (FSS) and having scores 0–5.5 based on the Expanded Disability Status Scale (EDSS); not being in the menstruation period; not afflicted with diseases other than MS, such as febrile acute or chronic mental or psychic disorders such as severe depression, speech or hearing disorder; not addicted to narcotics and psychotropic drugs; not being a member of the treatment crew (physician or nurse); and not being pregnant.
Exclusion criteria	Not willing to continue in the research; use of other types of complementary and alternative medicine methods; disability to participate in the sessions (over two consecutive absences in the reflexology and relaxation meetings); and disease recurrence within 1 month before the start of the interventions and/or during the intervention, which caused hospitalization.
Recruitment / selection of participants	Patients with MS referring to Ayatollah Kashani Hospital MS Clinic affiliated to Isfahan University of Medical Sciences
Intervention(s)	For the experimental groups, the interventions of reflexology and relaxation were performed for 4 weeks, twice a week for 40 min in each session. The intervention technique for the relaxation group was the combination of Jacobson and Benson applied upon full description on the intervention using the relaxation method with a CD which had been previously recorded and prepared, in which the research subjects were encouraged to perform the instructions. They should contract the muscles of each part of their body in an orderly manner for 5 s and then maintain them for 15 s in full relaxation state. Afterward, through mental conceptualization and application of all their senses, creative visualization, and concentration and respiration, relaxation was completed. In the reflexology group, upon full description of the intervention, first of all, a general reflex therapy was performed by massaging all plantar reflexology points and then, a special reflex therapy was done. The major reflexive points in the feet were put under pressure using the thumb and index finger. Finally, the intervention was completed by the researcher with massage of the solar plexus.

Population subgroups	None reported.
Comparator	The control group received only routine treatment and care recommended by the attending physician
Number of participants	75
Duration of follow-up	2 months
Indirectness	Outcome indirectness due to short duration of follow-up

Study arms

Foot reflexology (N = 25)

A general reflex therapy was performed by massaging all plantar reflexology points and then, a special reflex therapy was done.

Relaxation (N = 25)

Control (N = 25)

Characteristics

Study-level characteristics

Characteristic	Study (N = 75)
% Female Sample size	n = 75 ; % = 100
Ethnicity Custom value	Iranian

Arm-level characteristics

Characteristic	Foot reflexology (N = 25)	Relaxation (N = 25)	Control (N = 25)
Mean age (SD) Mean (SD)	34.4 (6.6)	33.9 (5.6)	34.4 (7.7)
Duration of MS (years) Mean (SD)	6.66 (5.47)	5.18 (4.69)	4.78 (3.36)

Outcomes

Study timepoints

- Baseline
- 2 month (2-month follow-up - 1 month following end of treatment. Indirect as <3 months in protocol.)

Fatigue Severity Scale

Outcome	Foot reflexology, Baseline, N = 25	Foot reflexology, 2 month, N = 25	Relaxation, Baseline, N = 25	Relaxation, 2 month, N = 25	Control, Baseline, N = 25	Control, 2 month, N = 25
Fatigue Severity Scale Mean (SD)	4.98 (0.98)	2.89 (0.94)	4.93 (0.87)	4.37 (0.78)	4.89 (0.95)	4.74 (0.86)

Fatigue Severity Scale - Polarity - Lower values are better

Final value

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Fatigue Severity Scale 2 months reflexology vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(length of follow-up <3 months specified)*

Fatigue Severity Scale 2 months relaxation vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(length of follow-up <3 months specified)*

Fatigue Severity Scale 2 months reflexology vs. relaxation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(length of follow-up <3 months specified)*

Nedeljkovic, 2016

Bibliographic Reference	**Nedeljkovic, U.; Raspopovic, E. D.; Ilic, N.; Vujadinovic, S. T.; Soldatovic, I.; Drulovic, J.; Effectiveness of rehabilitation in multiple sclerosis relapse on fatigue, self-efficacy and physical activity; Acta Neurologica Belgica; 2016; vol. 116 (no. 3); 309-15**

Study details

Trial name / registration number	None reported
Study location	Serbia
Study setting	In hospital and community
Study dates	July 2011 - October 2013
Sources of funding	None reported
Inclusion criteria	(a) confirmed relapse requiring application of HDMP in patients with established diagnosis of relapsing remitting (RR) MS, according to the Revised McDonald criteria [15]; (b) admission to the Clinic of Neurology as either day case or inpatient; (c) age 18 years and above. Patients were excluded if they suffered from dementia, alcoholism, had any serious medical co-morbidities or were pregnant
Exclusion criteria	Participants were excluded if they had a relapse of disease.
Recruitment / selection of participants	Participants were admitted to the Clinic of Neurology as either a day case or inpatient
Intervention(s)	All eligible patients received 5 days' therapy of one gram per day intravenous methylprednisolon (IVMP). Treatment group was included in multidisciplinary rehabilitation (MDR) programme which consisted of two parts. The first part took place at Neurology Clinic, during the IVMP treatment and included provision of mobility aids, bladder management and instruction on some basic exercises based on actual neurological status of patients, which were afterwards performed at home for 5 days. The second part included an outpatient rehabilitation programme that started 1–3 days after the IVMP treatment. At the beginning of rehabilitation programme, each participant had an initial half-hour counselling with the rehabilitation physician. Counselling included analysis of patient's perception of fatigue and prescription of rehabilitation programme after thorough neurological exam. Patients were encouraged to create their own fatigue management strategy regarding

	activities of daily living, based on evaluation of their perception of fatigue and behaviour related to it. Principles of exercise programme were also explained, with emphasis on continuous monitoring of fatigue. Tree appointments were arranged with the physician during exercise sessions to monitor the progress of exercise programme and provide additional consultation. At the beginning of rehabilitation programme, each participant had an initial half-hour counselling with the rehabilitation physician. Counselling included analysis of patient's perception of fatigue and prescription of rehabilitation programme after thorough neurological exam. Patients were encouraged to create their own fatigue management strategy regarding activities of daily living, based on evaluation of their perception of fatigue and behaviour related to it. Principles of exercise programme were also explained, with emphasis on continuous monitoring of fatigue. Tree appointments were arranged with the physician during exercise sessions to monitor the progress of exercise programme and provide additional consultation 310 Acta Neurol Belg (2016) 116:309–315 123 if needed. At the end of rehabilitation programme (after 3 weeks) another half-hour consultation was scheduled to discuss patients' progression during treatment, impressions on self-implemented fatigue management plan and to emphasise the importance of physical activity and continuous exercising. Patients were advised to continue exercising in community settings and patient's organization. Further consultation on fatigue management and exercise were possible upon the termination of study protocol. Exercise programme was individually tailored, based on participants' impairments and functional limitations (gait deviations, balance and coordination impairment, motor control) and were organized as individual sessions but in the same place with patients admitted for rehabilitation of various medical conditions. Progression was achieved through overload and increased difficulty of tasks, taking into account patient's level of fatigue. Exercises were performed five times a week for 1 h and patients were referred to occupational therapy three times a week 30 min in addition. Aerobic training on treadmill was included in each patient's rehabilitation programme to enhance endurance. Progression of intensity was first achieved through prolonged walking time and later through enhancement of velocity, with the aim of achieving 20 min for a given velocity. Rate of perceived exertion and targeted heart rate were used as indicators of the intensity of training.
Population subgroups	None
Comparator	All eligible patients received 5 days' therapy of one gram per day intravenous methylprednisolon (IVMP). The control group was treated in accordance with a standard procedure, which does not recommend regular inclusion into rehabilitation programme after IVMP treatment.
Number of participants	39

Duration of follow-up	3 months

Study arms

Steroid plus Multidisciplinary Rehabilitation (N = 19)

All eligible patients received 5 days' therapy of one gram per day intravenous methylprednisolon (IVMP). Treatment group was included in multidisciplinary rehabilitation (MDR) programme

Steroid plus control (N = 20)

All eligible patients received 5 days' therapy of one gram per day intravenous methylprednisolon (IVMP). Control group was treated in accordance with a standard procedure, which does not recommend regular inclusion into rehabilitation

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Ethnicity Custom value	Serbian

Arm-level characteristics

Characteristic	Steroid plus Multidisciplinary Rehabilitation (N = 19)	Steroid plus control (N = 20)
% Female Sample size	n = 12 ; % = 63.2	n = 14 ; % = 70
Mean age (SD) Mean (SD)	41.7 (9.5)	39.7 (10.5)
Disease duration (Months) Range	36 to 156	24 to 130
EDSS score Mean (SD)	4.4 (1.3)	4.2 (0.7)

Outcomes

Study timepoints

- Baseline
- 3 month (Follow-up)

Fatigue Severity Scale

Outcome	Steroid plus Multidisciplinary Rehabilitation, Baseline, N = 19	Steroid plus Multidisciplinary Rehabilitation, 3 month, N = 19	Steroid plus control, Baseline, N = 20	Steroid plus control, 3 month, N = 20
Fatigue Severiy Scale	43.1 (15.3)	36.6 (21.1)	41.1 (12.9)	40.6 (15.9)

Outcome	Steroid plus Multidisciplinary Rehabilitation, Baseline, N = 19	Steroid plus Multidisciplinary Rehabilitation, 3 month, N = 19	Steroid plus control, Baseline, N = 20	Steroid plus control, 3 month, N = 20
Mean (SD)				

Fatigue Severiy Scale - Polarity - Lower values are better

FSS is comprised of nine statements that are scored from one to seven (one = completely disagree, seven = completely agree). The final score is the mean of item scores, with lower scores indicating less fatigue. Suggested cut-off value, representing fatigued patients is >36

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Fatigue Severity Scale 3 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Oken, 2004

Bibliographic Reference	**Oken, B. S.; Kishiyama, S.; Zajdel, D.; Bourdette, D.; Carlsen, J.; Haas, M.; Hugos, C.; Kraemer, D. F.; Lawrence, J.; Mass, M.; Randomized controlled trial of yoga and exercise in multiple sclerosis; Neurology; 2004; vol. 62 (no. 11); 2058-64**

Study details

Trial name / registration number	Not reported.
Study location	USA
Study setting	Outpatient
Study dates	Recruitment began in January 1999 and last cohort of subjects had outcome assessments in June 2002.
Sources of funding	Not reported.
Inclusion criteria	Diagnosis of MS; and EDSS ≤6.0; and English as primary language.
Exclusion criteria	Subjects with an underlying medical illness that might impair cognition: insulin-dependent diabetes; uncontrolled hypertension; liver or kidney failure; symptomatic lung disease; alcoholism/drug abuse; symptoms or signs of congestive heart failure, ischemic heart disease, or symptomatic valvular disease; or corrected visual acuity worse than 20/50

	binocularly. Also excluded if had performed yoga or tai-chi in last 6 months or were regularly performing aerobic exercise >30 min per day. Participants taking CNS medications were eligible for inclusion but encouraged to minimise any changes to them during the study.
Recruitment / selection of participants	Subjects were recruited through the local newspaper, the OHSU newsletter Web site, the newsletter of the local MS Society, and through the OHSU MS Center.
Intervention(s)	Yoga - 6 months: 90 min classes once per week. Modifications to usual Iyengar yoga class to take into account fatigue, spasticity and cerebellar dysfunction. All poses were supported with a chair or by the subject resting against the wall or on the floor. Included 19 poses but not all were performed every week. Sequence designed to minimise exertion in getting up or down. Each pose held for 10-30 seconds with rest periods between poses lasting 30 seconds to 1 min. Encouraged to honour their individual limits and hold pose for less time if necessary. Adapted to suit individual needs and modifications for lower ability were available. Emphasis on breathing for concentration and relaxation during the session. Each class ended with 10 min deep relaxation with subject lying supine. Progressive relaxation, visualisation and meditation techniques were introduced. Daily home practice was strongly encouraged and a booklet demonstrating the poses was given to assist this. Aerobic exercise - 6 months: directed by physical therapist with experience in MS population. One class per week along with home exercise. Consisted of cycling on recumbent or dual action stationary bicycle. Each class began and ended with 5 min of stretching cycling muscles. Instructed to cycle at very light to moderate intensity on Borg Rate of Perceived Exertion scale. Periodically also given opportunity to exercise with Swiss ball. Variety introduced by batting a balloon among participants while cycling and adding some arm, trunk and balance work. Cycling continued until they were ready to stop due to fatigue, onset of other MS symptoms or reached their personal goal. Exercise bicycle given for home use if did not already have one. Encouraged to exercise regularly at home (using the bicycle and any other modes of exercise).
Population subgroups	None reported.
Comparator	Control - waitlist control group. Not well defined but assume did not receive any intervention and continued usual lifestyle.

Number of participants	N=69 randomised, n=57 analysed
Duration of follow-up	Up to 6 months - end of interventions
Indirectness	None.
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Yoga (N = 26)

Exercise (stationary bicycle) (N = 21)

Waitlist control (N = 22)

Characteristics

Arm-level characteristics

Characteristic	Yoga (N = 26)	Exercise (stationary bicycle) (N = 21)	Waitlist control (N = 22)
% Female	n = 20 ; % = 90.9	n = 13 ; % = 86.7	n = 20 ; % = 100

Characteristic	Yoga (N = 26)	Exercise (stationary bicycle) (N = 21)	Waitlist control (N = 22)
Sample size			
Mean age (SD) Mean (SD)	49.8 (7.4)	48.8 (10.4)	48.4 (9.8)
Ethnicity Custom value	NR	NR	NR
Comorbidities Custom value	NR	NR	NR
EDSS score Scale 0-10. Higher indicates increased disability. Mean (SD)	3.2 (1.7)	2.9 (1.7)	3.1 (2.1)
MSFC score Multiple Sclerosis Functional Composite. Higher indicates better outcome. No scale. Mean (SD)	0.13 (0.8)	0.18 (0.6)	0.04 (0.7)

Baseline values given for those analysed (n=22, n=15 and n=20, respectively) rather than those randomised (n=26, n=21 and n=22, respectively)

Outcomes

Study timepoints

Baseline

6 month (6 months - end of intervention period)

Results - raw data

Outcome	Yoga, Baseline, N = 26	Yoga, 6 month, N = 22	Exercise (stationary bicycle), Baseline, N = 21	Exercise (stationary bicycle), 6 month, N = 15	Waitlist control, Baseline, N = 22	Waitlist control, 6 month, N = 20
Multidimensional Fatigue Inventory - general fatigue Scale usually 4-20. Mean (SD)	14.7 (3.3)	13 (2.9)	13.2 (4)	12.1 (2.8)	15.1 (3.4)	14.9 (3)
Multidimensional Fatigue Inventory - physical fatigue Scale usually 4-20. Mean (SD)	13.9 (3.5)	12.1 (4.4)	13.2 (4.6)	10.8 (4)	14.4 (4)	13.9 (4.5)
Multidimensional Fatigue Inventory - reduced activity Scale usually 4-20. Mean (SD)	12.2 (4.7)	11.2 (4.1)	10.5 (3.8)	9.9 (3.9)	12.9 (4.2)	11.5 (4.5)
Multidimensional Fatigue Inventory - reduced motivation Scale usually 4-20.	10.1 (3.4)	9.2 (3)	7.9 (2.7)	7.7 (3.4)	10.4 (3.2)	9.8 (3)

Outcome	Yoga, Baseline, N = 26	Yoga, 6 month, N = 22	Exercise (stationary bicycle), Baseline, N = 21	Exercise (stationary bicycle), 6 month, N = 15	Waitlist control, Baseline, N = 22	Waitlist control, 6 month, N = 20
Mean (SD)						
Multidimensional Fatigue Inventory - mental fatigue Scale usually 4-20. Mean (SD)	11.4 (4.7)	10.7 (4)	8.3 (4.8)	7.8 (4.4)	11.7 (3.5)	11.2 (3.9)
SF-36 physical functioning Scale usually 0-100. Mean (SD)	58.6 (31.6)	61 (31.6)	62 (25.9)	60 (27.9)	58.1 (19)	58.1 (23.3)
SF-36 physical health impact Scale usually 0-100. Mean (SD)	50 (44)	48.8 (39.1)	76.7 (25.8)	61.7 (41)	40.3 (37.5)	52.8 (43.6)
SF-36 bodily pain Scale usually 0-100. Mean (SD)	71 (19.8)	69.6 (17.3)	55.1 (13.3)	70.8 (17.4)	65.1 (26)	68.9 (25.3)
SF-36 general health Scale usually 0-100. Mean (SD)	60.7 (24.8)	60.3 (18.4)	62.7 (15.6)	61 (16)	49.9 (19.1)	55.4 (16.5)

Outcome	Yoga, Baseline, N = 26	Yoga, 6 month, N = 22	Exercise (stationary bicycle), Baseline, N = 21	Exercise (stationary bicycle), 6 month, N = 15	Waitlist control, Baseline, N = 22	Waitlist control, 6 month, N = 20
SF-36 energy and fatigue (vitality?) Scale usually 0-100. Mean (SD)	43.1 (17.7)	51.2 (16.7)	45.7 (22.7)	52.8 (18.8)	39.7 (18.1)	36.7 (18.1)
SF-36 social functioning Scale usually 0-100. Mean (SD)	72 (24)	64.9 (17.9)	83.3 (16.8)	81.7 (24)	66 (27.1)	70.8 (23.5)
SF-36 emotional health impact Scale usually 0-100. Mean (SD)	72.4 (32.4)	87.3 (24.7)	82.2 (27.8)	88.9 (30)	72.2 (43.2)	72.2 (36.6)
SF-36 health transition Scale usually 0-100. Mean (SD)	42.9 (25.2)	35.7 (20.8)	43.3 (22.1)	36.7 (28.1)	58.3 (22.7)	48.6 (20.1)
Stroop Colour - Word Interference (attention/concentration) Scale unclear. Mean (SD)	10.8 (6)	8.5 (4.5)	10.1 (3.7)	9.9 (6.2)	11 (7.1)	8.1 (4.4)
Adverse events_6 months None reported to be related to the intervention.	n = NA ; % = NA	n = 1 ; % = 4.35	n = NA ; % = NA	n = 1 ; % = 6.25	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Yoga, Baseline, N = 26	Yoga, 6 month, N = 22	Exercise (stationary bicycle), Baseline, N = 21	Exercise (stationary bicycle), 6 month, N = 15	Waitlist control, Baseline, N = 22	Waitlist control, 6 month, N = 20
Have extracted MS exacerbations only as other events were clearly not related to intervention (car accident, adverse events associated with unrelated surgeries). Unclear whether dropped out as a result of MS exacerbation but it is likely that they were based on similar studies. No of events						
Adverse events_6 months None reported to be related to the intervention. Have extracted MS exacerbations only as other events were clearly not related to intervention (car accident, adverse events associated with unrelated surgeries). Unclear whether dropped out as a result of MS exacerbation but it is likely that they were based on similar studies. Number analysed	NA	23	NA	16	NA	20
Adherence Only relevant for the two active interventions groups. Custom value	NA	Attendance at sessions was 68%; home practice on 51% of non-class days for average of 39 min (14-80)	NA	Attendance was 65%; home exercise average of 45% of non-class days for average of 32 min (15-57 min)	NA	NR

Multidimensional Fatigue Inventory - general fatigue - Polarity - Lower values are better

Multidimensional Fatigue Inventory - physical fatigue - Polarity - Lower values are better

Multidimensional Fatigue Inventory - reduced activity - Polarity - Lower values are better

Multidimensional Fatigue Inventory - reduced motivation - Polarity - Lower values are better

Multidimensional Fatigue Inventory - mental fatigue - Polarity - Lower values are better

SF-36 physical functioning - Polarity - Higher values are better

SF-36 physical health impact - Polarity - Higher values are better

SF-36 bodily pain - Polarity - Higher values are better

SF-36 general health - Polarity - Higher values are better

SF-36 energy and fatigue (vitality?) - Polarity - Higher values are better

SF-36 social functioning - Polarity - Higher values are better

SF-36 emotional health impact - Polarity - Higher values are better

SF-36 health transition - Polarity - Higher values are better

Stroop Colour - Word Interference (attention/concentration) - Polarity - Higher values are better

Baseline values given for those analysed (n=22, n=15 and n=20, respectively) rather than those randomised (n=26, n=21 and n=22, respectively.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFI general fatigue 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI physical fatigue 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI reduced activity 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI reduced motivation 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI mental fatigue 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical health impact 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 bodily pain 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 energy/vitality 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional health impact 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 health transition 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Stroop colour word interference (attention) 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events (MS exacerbation) 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence 6 months

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI general fatigue 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI general fatigue 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI physical fatigue 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI physical fatigue 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI reduced activity 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI reduced activity 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI reduced motivation6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI reduced motivation 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI mental fatigue 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFI mental fatigue 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical functioning 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical health impact 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 physical health impact 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 bodily pain 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 bodily pain 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 general health 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 energy/vitality 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 energy/vitality 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 social functioning 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional health impact 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 emotional health impact 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 health transition 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SF-36 health transition 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Stroop colour word interference (attention) 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Stroop colour word interference (attention) 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events (MS exacerbation) 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adverse events (MS exacerbation) 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence 6 months yoga vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence 6 months exercise vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Ozkul, 2020

Bibliographic Reference	**Ozkul, C.; Guclu-Gunduz, A.; Yazici, G.; Atalay Guzel, N.; Irkec, C.; Effect of immersive virtual reality on balance, mobility, and fatigue in patients with multiple sclerosis: A single-blinded randomized controlled trial; European Journal of Integrative Medicine; 2020; vol. 35 (no. no pagination)**

Study details

Trial name / registration number	NCT03501342
Study location	Turkey
Study setting	Outpatient
Study dates	Not reported.
Sources of funding	Reported to be no specific grant from funding agencies in the public, commercial or not-for-profit sectors.
Inclusion criteria	Diagnosis of definite relapsing-remitting MS according to revised McDonald criteria 2010; aged 18-65 years; and EDSS score <6.0.
Exclusion criteria	Relapse within last 3 months; disease in which exercise is contraindicated; and having orthopaedic, vision, hearing or perception problems.
Recruitment / selection of participants	Not reported
Intervention(s)	Pilates + balance training - 8 weeks: two different randomised groups were combined into a single group to compare with control for the purpose of this review, as both involved a combinations of Pilates and balance exercises. Training started

	with Pilates-based core stability training, which lasted ~30 min. Pilates began with centering and segmental extremity movements for warm-up. Each were performed for 10 repetitions during first 4 weeks and 20 during the last 4 weeks. Subsequently, 10 min of rest and 20 min of immersive virtual reality (games involving balance) or balance training were performed. Stretching, posture exercise and progressive muscle relaxation exercises were performed to cool down. Immersive reality group used RAGU system - exercises performed in virtual world and included two games for improving balance. In the balance training group, exercises were similar to the movements required for the virtual reality games.
Population subgroups	None reported.
Comparator	Control - relaxation: physiotherapist taught patients the Jacobson's progressive relaxation exercise once and they were asked to practice it for 15-20 min at home twice weekly for 8 weeks. No Concurrent rehabilitation received.
Number of participants	N=51 randomised, n=39 analysed
Duration of follow-up	Up to 8 weeks - end of treatment period
Indirectness	Outcome follow-up - 2 months rather than the minimum of 3 months in protocol
Method of analysis	Per protocol - those randomised and that completed the study

Study arms

Balance training + Pilates (N = 34)

Two groups within the study combined for the purpose of this review as they both consisted of balance exercises: immersive virtual reality and balance training groups, with both having Pilates as a key component as well.

Control - relaxation (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Balance training + Pilates (N = 34)	Control - relaxation (N = 17)
% Female Sample size	n = 20 ; % = 76.9	n = 10 ; % = 76.9
Mean age (SD) (years) Median (IQR)	29 (25-41) for virtual reality group and 34 (25.5-45.5) for balance training group	34 (32-42.5)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score Scale 0-10. Higher indicates increased disability. Median (IQR)	1 (1-3) in virtual reality group and 1 (0.75-3.0) for balance training group	2 (1-2.5)
Disease duration (years) Median (IQR)	4 (4-6.5) in virtual reality group and 4 (3-6.5) in balance training group	4 (2.5-14.5)

Characteristic	Balance training + Pilates (N = 34)	Control - relaxation (N = 17)
Number of relapses Median (IQR)	3 (1.5-4.5) for virtual reality group and 2 (1-4) for balance training group	2 (1-4.5)

Baseline values are given for the n=39 analysed (n=26 in intervention and n=13 in control) rather than the n=51 randomised.

Outcomes

Study timepoints

- Baseline
- 8 week (8 weeks - end of treatment period)

Results - raw data

Outcome	Balance training + Pilates, Baseline, N = 34	Balance training + Pilates, 8 week, N = 26	Control - relaxation, Baseline, N = 17	Control - relaxation, 8 week, N = 13
Fatigue Severity Scale. Scale usually 9-63. Median (IQR)	48 (41.5-52.5) for virtual reality group and 49 (34.5-54.5) for balance training group	37 (30.5-44.0) for virtual reality group and 29 (26.0-46.5) for balance training group	46.0 (32.5-53.5)	52.0 (35.5-58.0)
Adverse or harmful events Reported to be none. No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Outcome	Balance training + Pilates, Baseline, N = 34	Balance training + Pilates, 8 week, N = 26	Control - relaxation, Baseline, N = 17	Control - relaxation, 8 week, N = 13
Adherence - discontinuation due to work intensity Higher number discontinuing indicates worse outcome for that intervention. No of events	n = NA ; % = NA	n = 8 ; % = 23.5	n = NA ; % = NA	n = 0 ; % = 0
Adherence - discontinuation due to work intensity Higher number discontinuing indicates worse outcome for that intervention. Number analysed	NA	34	NA	13
Adherence - participation rate Not reported for control group Custom value	NA	Participation was 80.8% (68.8-100.0) for virtual reality and 82.7% (68.8-100) for balance training	NA	Not reported

Fatigue Severity Scale. - Polarity - Lower values are better

Note that results at baseline are given for the analysed population (n=26 vs. n=13) rather than the total number randomised. Only median values available for the continuous outcome of fatigue.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results Fatigue Severity Scale 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8-week follow-up does not reach minimum of 3 months in protocol)*

Results adverse/harmful events 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8-week follow-up does not reach minimum of 3 months in protocol)*

Results discontinuation due to work intensity 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8-week follow-up does not reach minimum of 3 months in protocol)*

Results participation rate 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(8-week follow-up does not reach minimum of 3 months in protocol)*

Pazokian, 2013

Bibliographic Reference	**Pazokian, M.; Shaban, M.; Zakermoghdam, M.; Mehran, A.; Sangelagi, B.; A Comparison between the Effect of Stretching with Aerobic and Aerobic Exercises on Fatigue Level in Multiple Sclerosis Patients; Qom university of medical sciences journal; 2013; vol. 7 (no. 1); 50-56**

Study details

Trial name / registration number	IRCT201203069219N1
Study location	Iran
Study setting	Outpatient
Study dates	Performed between November 2009 and April 2011.
Sources of funding	Not reported.

Inclusion criteria	Confirmed diagnosis of clinically definite MS (relapsing- remitting type); EDSS score of 1-5.5; no history of any medical condition that would preclude participation in the prescribed training programs such as cardiac conditions or in a relapse-stage of their disease process; independently mobile, with or without walking aids; and aged between 20 and 45 years.
Exclusion criteria	Irregular exercise (not maintaining regime?); and relapse phase of disease when patient not capable of doing exercise regularly.
Recruitment / selection of participants	Recruited from Iranian MS Society of Tehran
Intervention(s)	Aerobic exercise with or without stretching - 12 weeks: aerobic exercises three times weekly, with or without stretching prior to the aerobic exercise (upper and lower limbs and trunk muscles for 15 min prior to aerobic exercises). Aerobic exercise consisted of 10 min walking, 10 min cycling and 10 min treadmill at speed of 1m/s.
Population subgroups	None reported.
Comparator	Control - no intervention: no intervention performed.
Number of participants	N=120 randomised, N=120 analysed
Duration of follow-up	Up to 12 weeks - end of treatment
Indirectness	None.
Method of analysis	Intention to treat - all randomised

Study arms

Aerobic exercise with or without stretching (N = 80)

Two separate groups of aerobic exercise only and aerobic exercise + stretching were combined for the purpose of this review and compared to the control group.

Control - no intervention (N = 40)

Characteristics

Study-level characteristics

Characteristic	Study (N = 120)
% Female Sample size	n = 87 ; % = 72.5
Mean age (SD) (years) Mean (SD)	35.21 (7.27)
Ethnicity Custom value	NR
Comorbidities Custom value	NR
5+ years Sample size	n = 12 ; % = 10

Characteristic	Study (N = 120)
5-10 years Sample size	n = 65 ; % = 54.2
10 years or more Sample size	n = 43 ; % = 35.8
Avonex Sample size	n = 78 ; % = 65
Ribif Sample size	n = 102 ; % = 85
Amantadin Sample size	n = 75 ; % = 62.5
Baclofen Sample size	n = 104 ; % = 86.7
Other drugs Sample size	n = 83 ; % = 69.2
Appetite (loss of?) Sample size	n = 94 ; % = 78.3
Confusion	n = 99 ; % = 82.5

Characteristic	Study (N = 120)
Sample size	
Mental rupture Sample size	n = 67 ; % = 55.8
Numbness Sample size	n = 96 ; % = 80
Mental disturbance Sample size	n = 56 ; % = 46.7
Impatience Sample size	n = 66 ; % = 82.5
Infirmity Sample size	n = 104 ; % = 86.7
Headache Sample size	n = 52 ; % = 43.3

Outcomes

Study timepoints

- Baseline
- 12 week (12 weeks - end of treatment period)

Results - raw data

Outcome	Aerobic exercise with or without stretching, Baseline, N = 80	Aerobic exercise with or without stretching, 12 week, N = 80	Control - no intervention, Baseline, N = 40	Control - no intervention, 12 week, N = 40
Fatigue Severity Scale Scale usually 9-63. Mean (SD)	47.15 (14.59)	31.64 (14.13)	48.17 (14.83)	47.65 (14.4)

Fatigue Severity Scale - Polarity - Lower values are better

Note that n=20 in aerobic group were excluded and 'replaced', though n=120 still appear to have been analysed.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Plow, 2019

Bibliographic Reference	**Plow, M.; Finlayson, M.; Liu, J.; Motl, R. W.; Bethoux, F.; Sattar, A.; Randomized Controlled Trial of a Telephone-Delivered Physical Activity and Fatigue Self-management Interventions in Adults With Multiple Sclerosis; Archives of Physical Medicine & Rehabilitation; 2019; vol. 100 (no. 11); 2006-2014**

Study details

Secondary publication of another included study- see primary study for details	
Trial name / registration number	NCT01572714

Study location	USA
Study setting	Outpatient
Study dates	Not reported.
Sources of funding	Supported through National Multiple Sclerosis Society grant.
Inclusion criteria	Physician-confirmed diagnosis of MS and physician consent to initiate physical activity programme; aged between 18 and 65 years; ability to walk ≥25 feet with or without a cane; ability to have telephone conversations in English; PDDS score between 1 and 5; current sedentary lifestyle (purposeful exercise ≤2 days per week for 30 min); and moderate-severe fatigue at baseline (score ≥4.0 on FSS).
Exclusion criteria	Pregnancy; cardiopulmonary diseases that would hinder engagement in physical activity; uncontrolled diabetes (hospitalised within last 6 months); >3 falls in past 6 months; severe cognitive deficits (weighted score <12 on short version of Blessed Orientation Memory Concentration test); and unable to contact physician/treating clinician to confirm MS diagnosis and reasonable risk for the walking programme.
Recruitment / selection of participants	Recruited at Midwest and Northeast regions of USA. Flyers mailed to outpatient clinics and distributed at events sponsored by organisations such as the National Multiple Sclerosis Society.
Intervention(s)	Telephone physical activity + fatigue self-management programme - 12 weeks: delivered entirely over the phone via group conferences and individually tailored phone calls. 12 weeks intervention followed by 12 weeks non-contact to assess sustainability. Consisted of 6 group teleconferences followed by 4 individual phone calls. Group calls typically included 6-10 participants. Taught how to engage in a pedometer-based walking programme, set goals, overcome barriers and self-monitor progress. Also received components of an intervention called 'Managing Fatigue: A 6-week Course for Energy Conservation'. Content of individual phone calls was tailored on participant preferences for learning about topics consistent with those presented din the group teleconferences. These calls began after third teleconference session and occurred every other week. Occupational therapist delivered telephone conferences and research assistant delivered tailored phone calls.

	Telephone physical activity only: 12 weeks: delivered entirely over the phone via group conferences and individually tailored phone calls. 12 weeks intervention followed by 12 weeks non-contact to assess sustainability. Consisted of 3 group teleconferences followed by 4 individual phone calls. Group calls typically included 6-10 participants. Taught how to engage in a pedometer-based walking programme, set goals, overcome barriers and self-monitor progress. Content of individual phone calls was tailored on participant preferences for learning about topics consistent with those presented din the group teleconferences. These calls began after third teleconference session and occurred every other week. Occupational therapist delivered telephone conferences and research assistant delivered tailored phone calls.
Population subgroups	None reported.
Comparator	Control - information only: received information on health topics relevant to MS. Purpose was to control for factors such as differential attention, intervention contacts, social support and non-specific occupational therapy effects. 12 weeks - delivered entirely over the phone via group conferences and individually tailored phone calls. 12 weeks intervention followed by 12 weeks non-contact to assess sustainability. Consisted of 6 group teleconferences followed by 4 individual phone calls. Group calls typically included 6-10 participants. Content of individual phone calls was tailored on participant preferences for learning about topics consistent with those presented din the group teleconferences. These calls began after third teleconference session and occurred every other week. Occupational therapist delivered telephone conferences and research assistant delivered tailored phone calls.
Number of participants	N=208 randomised, n=208 analysed
Duration of follow-up	Up to 26 weeks post-randomisation (24 weeks after starting intervention and 12 weeks since the completion of the intervention)
Indirectness	None
Method of analysis	Intention to treat - all randomised

Study arms

Telephone-delivered physical activity + fatigue self-management (N = 70)

Telephone-delivered physical activity only (N = 69)

Control - information only (N = 69)

Characteristics

Arm-level characteristics

Characteristic	Telephone-delivered physical activity + fatigue self-management (N = 70)	Telephone-delivered physical activity only (N = 69)	Control - information only (N = 69)
% Female Sample size	n = 63 ; % = 90	n = 55 ; % = 79.7	n = 58 ; % = 84.1
Mean age (SD) Mean (SD)	53.2 (6.5)	51.2 (9.2)	51.8 (9.3)
White Sample size	n = 62 ; % = 88.6	n = 65 ; % = 94.2	n = 60 ; % = 87
Non-white Sample size	n = 8 ; % = 11.4	n = 4 ; % = 5.8	n = 9 ; % = 13
Comorbidities	NR	NR	NR

Characteristic	Telephone-delivered physical activity + fatigue self-management (N = 70)	Telephone-delivered physical activity only (N = 69)	Control - information only (N = 69)
Custom value			
Time since diagnosis (years) Mean (SD)	12.7 (7.9)	14.1 (9.6)	11.4 (8.1)
Mild disability Sample size	n = 9 ; % = 12.9	n = 13 ; % = 18.8	n = 12 ; % = 17.4
Moderate disability Sample size	n = 13 ; % = 18.6	n = 18 ; % = 26.1	n = 10 ; % = 14.5
Gait disability Sample size	n = 21 ; % = 30	n = 17 ; % = 24.6	n = 24 ; % = 34.8
Early cane Sample size	n = 17 ; % = 24.3	n = 14 ; % = 20.3	n = 14 ; % = 20.3
Late cane Sample size	n = 10 ; % = 14.3	n = 7 ; % = 10.1	n = 9 ; % = 13
Relapsing remitting MS Sample size	n = 60 ; % = 85.7	n = 60 ; % = 87	n = 56 ; % = 81.2

Characteristic	Telephone-delivered physical activity + fatigue self-management (N = 70)	Telephone-delivered physical activity only (N = 69)	Control - information only (N = 69)
Secondary progressive MS Sample size	n = 5 ; % = 7.1	n = 3 ; % = 4.3	n = 3 ; % = 4.3
Primary progressive MS Sample size	n = 1 ; % = 1.4	n = 2 ; % = 2.9	n = 3 ; % = 4.3
Progressive-relapsing MS Sample size	n = 0 ; % = 0	n = 0 ; % = 0	n = 1 ; % = 1.4
Unknown Sample size	n = 4 ; % = 5.7	n = 4 ; % = 5.8	n = 6 ; % = 8.7

Outcomes

Study timepoints

- Baseline
- 24 week (24-weeks after starting the intervention (12 weeks since the completion of the intervention))

Results - raw data

Outcome	Telephone-delivered physical activity + fatigue self-management, Baseline, N = 70	Telephone-delivered physical activity + fatigue self-management, 24 week, N = 70	Telephone-delivered physical activity only, Baseline, N = 69	Telephone-delivered physical activity only, 24 week, N = 69	Control - information only, Baseline, N = 69	Control - information only, 24 week, N = 69
Fatigue Impact Scale Scale 0-160. Mean (SD)	71.24 (28.34)	53.95 (28.72)	68.03 (31.31)	54.42 (32.24)	71.06 (29.29)	62.63 (35)
MSIS-29 - physical function MS Impact Scale -29. Scale 0-100. Mean (SD)	38.88 (18.47)	31.11 (18.04)	38.47 (19.47)	32.19 (20.47)	39.25 (18.33)	37.81 (22.18)
MSIS-29 - mental function MS Impact Scale -29. Scale 0-100 Mean (SD)	35.28 (17.9)	29.56 (19.07)	33.04 (20.91)	31.08 (20.39)	40.55 (22.07)	35.77 (21.3)
Adherence - completed all teleconference calls with or without at least one make-up session 6 possible in combination group and control group, 3 possible in exercise only group.	n = NA ; % = NA	n = 63 ; % = 90	n = NA ; % = NA	n = 59 ; % = 85.51	n = NA ; % = NA	n = 58 ; % = 84.06

Outcome	Telephone-delivered physical activity + fatigue self-management, Baseline, N = 70	Telephone-delivered physical activity + fatigue self-management, 24 week, N = 70	Telephone-delivered physical activity only, Baseline, N = 69	Telephone-delivered physical activity only, 24 week, N = 69	Control - information only, Baseline, N = 69	Control - information only, 24 week, N = 69
No of events						
Adherence - completed all 1-1 phone calls No of events	n = NA ; % = NA	n = 56 ; % = 80	n = NA ; % = NA	n = 47 ; % = 68.1	n = NA ; % = NA	n = 53 ; % = 76.8
Adverse events - exacerbations No of events	n = NA ; % = NA	n = 14 ; % = 20	n = NA ; % = NA	n = 12 ; % = 17.4	n = NA ; % = NA	n = 17 ; % = 24.6
Adverse events - orthopaedic problems No of events	n = NA ; % = NA	n = 28 ; % = 40	n = NA ; % = NA	n = 16 ; % = 23.2	n = NA ; % = NA	n = 24 ; % = 34.8
Adverse events - reported at least 1 fall No of events	n = NA ; % = NA	n = 22 ; % = 31.4	n = NA ; % = NA	n = 12 ; % = 17.4	n = NA ; % = NA	n = 21 ; % = 30.4

Fatigue Impact Scale - Polarity - Lower values are better

MSIS-29 - physical function - Polarity - Lower values are better

MSIS-29 - mental function - Polarity - Lower values are better

Adherence - completed all teleconference calls with or without at least one make-up session - Polarity - Higher values are better

Adherence - completed all 1-1 phone calls - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results Fatigue Impact Scale 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 physical 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 mental function 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Fatigue Impact Scale 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results Fatigue Impact Scale 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 physical function 24 weeks physical activity + fatigue management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 physical function 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 mental function 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results MSIS-29 mental function 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence individual calls 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence individual calls 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence individual calls 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence group calls 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence group calls 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence group calls 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results exacerbations 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results exacerbations 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results exacerbations 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results orthopaedic problems 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results orthopaedic problems 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Results orthopaedic problems 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results at least 1 fall 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results at least 1 fall 24 weeks physical activity + fatigue self-management vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Results at least 1 fall 24 weeks physical activity only vs. control

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Pottgen, 2018

Bibliographic Reference	**Pottgen, J.; Moss-Morris, R.; Wendebourg, J. M.; Feddersen, L.; Lau, S.; Kopke, S.; Meyer, B.; Friede, T.; Penner, I. K.; Heesen, C.; Gold, S. M.; Randomised controlled trial of a self-guided online fatigue intervention in multiple sclerosis; Journal of Neurology, Neurosurgery & Psychiatry; 2018; vol. 89 (no. 9); 970-976**

Study details

Trial name / registration number	ISRCTN25692173
Study location	Germany
Study setting	Community
Study dates	July 11, 2014 to November 28, 2014
Sources of funding	Gemeinnützige Hertiestiftung (grant 370 no. P1130079 - Multiple Sklerose)
Inclusion criteria	Patients were eligible if they had a diagnosis of MSa 112 , were at least 18 years of age, reported 113 fatigue at screening (as indicated by a score of 43 or higher on the Fatigue Scale of Motor and Cognition; FSMC; 19 114), reported no major neurological or psychiatric comorbidities (dementia, 115 stroke, autism, or psychosis, although comorbid depression was allowed), and no MS relapse 116 in the last 4 weeks.

Exclusion criteria	None reported
Recruitment / selection of participants	Patients were recruited by advertisements published on the website of the German MS patient organisation (Deutsche Multiple Sklerose Gesellschaft DMSG), both by the local DMSG 1chapter as well as nationally. In addition, information about the study was sent out via the e newsletter of the INIMS and leaflets were distributed at the MS outpatient center, University Medical Center Hamburg-Eppendorf.
Intervention(s)	The ELEVIDA program was jointly developed by a multidisciplinary 128 team of physicians, psychologists, psychotherapists and IT experts. In ELEVIDA, content is based on cognitive behavioral therapy (CBT) strategies and is conveyed chiefly via the technique of a “simulated dialogue”. Program modules are comprised of an introduction and a summary and include homework tasks. Patients are advised to access the program once to twice per week. Participants are invited to respond continuously to narrative text passages provided by the program using a multiple-choice format. Depending on patients’ responses, the program 136 tailors subsequently offered information to match the individual needs (e.g., preference for elaborated explanations, additional exercises, shorter texts, etc.).
Population subgroups	None
Comparator	Standard care
Number of participants	275
Duration of follow-up	24 follow up
Indirectness	No indirectness

Study arms

Fatigue Management Program (N = 139)

In ELEVIDA, content is based on cognitive behavioral therapy (CBT) strategies and is conveyed chiefly via the technique of a “simulated dialogue”.

Control (N = 136)

Standard care

Characteristics

Study-level characteristics

Characteristic	Study (N =)
Ethnicity Custom value	German

Arm-level characteristics

Characteristic	Fatigue Management Program (N = 139)	Control (N = 136)
% Female Sample size	n = 114 ; % = 82	n = 108 ; % = 79
Disease duration Mean (SD)	8.91 (7.5)	9.19 (7.4)
Relapsing remitting MS Sample size	n = 98 ; % = 70.5	n = 102 ; % = 75

Characteristic	Fatigue Management Program (N = 139)	Control (N = 136)
Patient determined disease step mild impairment Sample size	n = 51 ; % = 37	n = 49 ; % = 37

Outcomes

Study timepoints

- 12 week (End of treatment)
- 24 week (Follow up)

Chandler Fatigue Scale

Outcome	Fatigue Management Program vs Control, 12 week, N2 = 139, N1 = 136	Fatigue Management Program vs Control, 24 week, N2 = 139, N1 = 136
Chandler Fatigue Scale Mean (95% CI)	-2.74 (-4.32 to -1.16)	-2.19 (-3.82 to -0.57)
Hamilton Anxiety and Depression Scale-A Mean (95% CI)	-0.64 (-1.25 to -0.03)	-0.71 (-1.43 to 0.01)
HADS-D Mean (95% CI)	-0.33 (-0.96 to 0.29)	-0.5 (-1.18 to 0.18)
Fatigue Scale Motor and Cognition (FSMC)	-3.47 (-5.79 to -1.15)	-3.47 (-5.89 to -1.05)

Outcome	Fatigue Management Program vs Control, 12 week, N2 = 139, N1 = 136	Fatigue Management Program vs Control, 24 week, N2 = 139, N1 = 136
Mean (95% CI)		
FSMC-Cognition Mean (95% CI)	-1.78 (-3.12 to -0.44)	-2.01 (-3.38 to -0.64)
FSMC-motor Mean (95% CI)	-1.71 (-2.94 to -0.48)	-1.49 (-2.74 to -0.23)
Multiple Sclerosis Neuropsychological Screening Questionnaire Mean (95% CI)	-1.45 (-3.13 to 0.22)	-0.27 (-2.21 to 1.66)

Chandler Fatigue Scale - Polarity - Lower values are better

Hamilton Anxiety and Depression Scale-A - Polarity - Lower values are better

HADS-D - Polarity - Lower values are better

Fatigue Scale Motor and Cognition (FSMC) - Polarity - Lower values are better

FSMC-Cognition - Polarity - Lower values are better

FSMC-motor - Polarity - Lower values are better

Multiple Sclerosis Neuropsychological Screening Questionnaire - Polarity - Lower values are better

This questionnaire assesses severity of physical and mental fatigue and is not disease specific. The scale contains 11 items covering physical fatigue (items 1-7) and mental fatigue (items 8-11).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Chandler Fatigue Scale 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

HADS-A

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Chandler Fatigue Scale 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

HADS-A 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

HADS-D 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

HADS-D 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

FSMC 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

FSMC 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

FSMC-Cognition 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

FSMC-Motor 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

FSMC-Motor 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MSNSQ 12 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

MSNSQ 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Rahimi, 2020

Bibliographic Reference	**Rahimi, H.; Mehrpooya, N.; Nahayati, M. A.; Vagharseyyedin, S.; Izadpanahi, A. M.; Rezaee, Z.; Self-acupressure for multiple sclerosis-related depression and fatigue: A feasibility randomized controlled trial; Journal of Advances in Medical and Biomedical Research; 2020; vol. 28 (no. 130); 276-283**

Study details

Trial name / registration number	IRCT20190515043601N5
Study location	Iran
Study setting	Outpatient
Study dates	Data collection between November 2019 and April 2020
Sources of funding	Not reported
Inclusion criteria	between 20 to 45 years old; having remitting-relapsing MS; having a minimum six-month history of MS diagnosis; obtaining a score between 0 and 5.5 on the EDSS; lack of any history of psychotic disorders, addiction to drugs, stimulants, and smoking; a lack of regular use of sedatives; a lack of skin lesions in acupressure or sham points; and not being pregnant.
Exclusion criteria	lack of willingness to continue participating in the research and exacerbation of MS symptoms during the intervention.
Recruitment / selection of participants	Selected using convenience sampling method
Intervention(s)	Self-acupressure: three training sessions of 30-40 min for participants. Number of participants per group was 8-10. First session involved discussion psychological and physical complications of MS and explaining the designed intervention. Second session involved teaching participants location of acupoints (left and right Shenmen, and Yin Tang - Shenmen

	located in ulnar, the end of the transverse crease of the wrist, and in the small depression between ulna and pisiform bones and Yin Tang located midway between medial/inner ends of two eyebrows). In the second session participants also explained method and amount of pressure on the acupoints, with pressure to be applied using pulp of the thumb. Asked to press each acupoint for 30 seconds and gradually increase pressure to feel warmth and tingling in target areas. Then asked to hold the weight for 4 minutes and release hand pressure for 30 seconds. Each acupoint pressed individually and then this was repeated on another acupoint. Intervention to be conducted at home every day between 9.00 and 10.00 am for 15 min (5 min per acupoint). In the third session a CD containing acupressure video was presented to participants. Intervention lasted for 1 month, during which researchers reminded participants to perform between 9 and 10 am by auto SMS reminder
Population subgroups	None
Comparator	Sham group: taught to use the pulp of the thumb to press 2.5 cm below Shenmen point (to the forearm) and 3 cm above the Yin Tang acupoint. Length and frequency of the intervention was the same as the self-acupressure group. 1 month duration.
Number of participants	106 randomised, 86 analysed at end of intervention (1 month)
Duration of follow-up	1 month - end of intervention
Indirectness	outcome - reported at time-point <3-month minimum specified in the protocol
Additional comments	Appears to be modified intention to treat with those without data not analysed

Study arms

Self-acupressure (N = 53)

Sham treatment (N = 53)

Characteristics

Arm-level characteristics

Characteristic	Self-acupressure (N = 53)	Sham treatment (N = 53)
% Female Sample size	n = 33 ; % = 75	n = 30 ; % = 71.4
20-25 years Sample size	n = 8 ; % = 18.2	n = 9 ; % = 21.4
26-30 years Sample size	n = 10 ; % = 22.7	n = 9 ; % = 21.4
31-35 years Sample size	n = 10 ; % = 22.7	n = 10 ; % = 23.8
36-45 years Sample size	n = 16 ; % = 36.4	n = 14 ; % = 33.3
Ethnicity Custom value	NR	NR
Comorbidities	NR	NR

Characteristic	Self-acupressure (N = 53)	Sham treatment (N = 53)
Custom value		
6-12 months Sample size	n = 8 ; % = 18.18	n = 10 ; % = 26.19
13-19 months Sample size	n = 19 ; % = 43.18	n = 17 ; % = 40.47
20-26 months Sample size	n = 6 ; % = 13.63	n = 9 ; % = 21.42
0.5-1.5 Sample size	n = 7 ; % = 15.9	n = 9 ; % = 21.42
1.6-2.6 Sample size	n = 12 ; % = 27.27	n = 15 ; % = 35.71
2.7-3.7 Sample size	n = 16 ; % = 36.36	n = 14 ; % = 33.33
3.8-4.5 Sample size	n = 9 ; % = 20.47	n = 4 ; % = 9.54

Note that patient characteristics are given for those analysed (n=44 in intervention and n=42 in control), rather than those randomised

Outcomes

Study timepoints

Baseline

1 month (1-month (30 days) - end of intervention period)

Results - raw data

Outcome	Self-acupressure, Baseline, N = 44	Self-acupressure, 1 month, N = 44	Sham treatment, Baseline, N = 42	Sham treatment, 1 month, N = 42
Fatigue Severity Scale Scale 1-7 Mean (SD)	4.26 (1.61)	3.85 (1.48)	4.02 (1.62)	4.01 (1.59)
Depression - DASS-42 Depression subscale of Depression Anxiety Stress Scales. Scale 0-42. Mean (SD)	11.48 (3.1)	9.66 (2.5)	11.45 (3.57)	11.36 (3.58)

Fatigue Severity Scale - Polarity - Lower values are better

Depression - DASS-42 - Polarity - Lower values are better

Note that despite 53 being randomised to each group, appears results even at baseline have only been given for those analysed at follow-up (n=44 and n=42, respectively)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results Fatigue Severity Scale 1 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 month minimum specified in the protocol)*

Results Depression DASS-42 1 month

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point <3 month minimum specified in the protocol)*

Razazian, 2016

Bibliographic Reference	**Razazian, N.; Yavari, Z.; Farnia, V.; Azizi, A.; Kordavani, L.; Bahmani, D. S.; Holsboer-Trachsler, E.; Brand, S.; Exercising Impacts on Fatigue, Depression, and Paresthesia in Female Patients with Multiple Sclerosis; Medicine & Science in Sports & Exercise; 2016; vol. 48 (no. 5); 796-803**

Study details

Secondary publication of another included	No additional information

study- see primary study for details	
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	Community
Study dates	Fall 2014
Sources of funding	Financial support was received from the Research Council of the medical Sciences University of Kermanshah (Iran) (research no. 44854).
Inclusion criteria	Diagnosed and approved diagnosis of multiple sclerosis, as ascertained by neurologists, patients' reports, and medical records; female; age between 25 and 50 year; Expanded Disability Status Scale of no more than 6; one of the following types of multiple sclerosis, as ascertained by a neurologists no otherwise involved in the study: primary-progressive, secondary-progressive, relapsing-remitting, progressive-relapsing; stable, regular and monitored pharmacological treatment of multiple sclerosis (immune modulatory treatments).
Exclusion criteria	Not meeting the inclusion criteria as described above; unable or unwilling to follow the intervention; psychiatric disorder such as severe depression, substance abuse, eating disorders, and similar; being pregnant or breastfeeding, or willing to become pregnant during the study; being treated with psychopharmaceuticals such as antidepressants, stimulants, mood

	stabilizers, antipsychotics, narcotics, or similar; relapse/MS attack within the last 2 months; possible risk of relapse during the study; being currently under treatment involving yoga or any other kind of physical activity; being currently under psychotherapeutic treatment; known somatic issues such as cardiovascular disease, arthritis, diabetes, or orthopaedic issues, which would have impeded participation in a physical activity program.
Recruitment / selection of participants	People attending the MS center of the Imam Reza hospital of Kermanshah (Iran).
Intervention(s)	Yoga Yoga sessions took place in the gym hall of the hospital. Sessions took place three times a week for about 60 minutes for eight consecutive weeks under the supervision of a certified yoga instructor (Hatha yoga). During the sessions, when appropriate, participants could talk to each other. Yoga sequences for beginners were instructed; a typical session consisted of centering; breathing exercises, mediation; sun salute; different and increasingly demanding standing postures; supported head and shoulder stands; different twists and bends; corpse pose at the end of the session. Resistance training (aquatic exercising) Aquatic exercising took place in the rehabilitation center of the hospital. The exercise program for the aquatic training group included a series of water activities undertaken for a period of 8 weeks with three sessions per week and 1 hour per session (water 28 degrees C-30 degrees C). Generally, sessions were organized and supervised by a certified instructor not otherwise involved in the study as follows: warming up, 10-min walking, stretching, and gymnastic; 40-min power endurance activities such as relay races, crossing the pool alone or as team competition, strength training and similar; 10-min cooling down, relaxing, stretching and breathing exercises. During the session, participants were free to chat to each other. Concomitant therapy: Not stated/unclear. All people required to be receiving disease-modifying treatment for MS.

	Intervention subgroups: Group vs. individual: Group Remote vs. in person: In person
Population subgroups	According to type: See participants characteristics table. Mixed. According to disability: EDSS of no more than 6. See participants characteristics table. Disease modifying treatment status: All people were receiving disease modifying treatment.
Comparator	To each other (yoga compared to resistance training) Control/usual care Participants in the nonexercise condition met two to three times a week in the hospital for about 60 to 90 minutes. They were free to talk to physicians and hospital staff, to complete everyday duties, to participate in occupational therapy and to meet and to talk to other patients. In establishing and emphasizing components of attention and social contact for patients in the nonexercise condition, we ensured that possible effects of exercise could not be explained in terms of differences in extent of social contacts with other patients, experts or hospital staff.
Number of participants	54
Duration of follow-up	8 weeks (this is less than 3 months and so will be downgraded for indirectness)
Indirectness	Outcome indirectness - Follow up is at 8 weeks. This is less than 3 months and so will be downgraded due to indirectness.
Additional comments	Available case analysis.

Study arms

Yoga (N = 18)

Yoga sessions took place in the gym hall of the hospital. Sessions took place three times a week for about 60 minutes for eight consecutive weeks under the supervision of a certified yoga instructor (Hatha yoga). During the sessions, when appropriate, participants could talk to each other. Yoga sequences for beginners were instructed; a typical session consisted of centering; breathing exercises, mediation; sun salute; different and increasingly demanding standing postures; supported head and shoulder stands; different twists and bends; corpse pose at the end of the session.

Resistance training (aquatic exercising) (N = 18)

Aquatic exercising took place in the rehabilitation center of the hospital. The exercise program for the aquatic training group included a series of water activities undertaken for a period of 8 weeks with three sessions per week and 1 hour per session (water 28 degrees C-30 degrees C). Generally, sessions were organized and supervised by a certified instructor not otherwise involved in the study as follows: warming up, 10-min walking, stretching, and gymnastic; 40-min power endurance activities such as relay races, crossing the pool alone or as team competition, strength training and similar; 10-min cooling down, relaxing, stretching and breathing exercises. During the session, participants were free to chat to each other.

Control/usual care (N = 18)

Participants in the nonexercise condition met two to three times a week in the hospital for about 60 to 90 minutes. They were free to talk to physicians and hospital staff, to complete everyday duties, to participate in occupational therapy and to meet and to talk to other patients. In establishing and emphasizing components of attention and social contact for patients in the nonexercise condition, we ensured that possible effects of exercise could not be explained in terms of differences in extent of social contacts with other patients, experts or hospital staff.

Characteristics

Arm-level characteristics

Characteristic	Yoga (N = 18)	Resistance training (aquatic exercising) (N = 18)	Control/usual care (N = 18)
% Female Sample size	n = 18 ; % = 100	n = 18 ; % = 100	n = 18 ; % = 100
Mean age (SD) Mean (SD)	33.33 (7.4)	35.39 (6.89)	33.11 (6.6)
Ethnicity Nominal	NR	NR	NR
Comorbidities Nominal	NR	NR	NR
EDSS Mean (SD)	3.89 (1.02)	3.44 (0.95)	3.25 (1.24)
Primary-progressive Nominal	0	0	0
Secondary-progressive Nominal	1	2	2
Relapsing-remitting Nominal	13	11	12
Progressive-relapsing	4	5	4

Characteristic	Yoga (N = 18)	Resistance training (aquatic exercising) (N = 18)	Control/usual care (N = 18)
Nominal			

Outcomes

Study timepoints

- Baseline
- 8 week (Follow up is at 8 weeks. This is less than 3 months and so will be downgraded due to indirectness.)

Yoga compared to resistance training compared to usual care at 3-6 months - continuous outcomes (final values)

Outcome	Yoga, Baseline, N = 18	Yoga, 8 week, N = 18	Resistance training (aquatic exercising), Baseline, N = 18	Resistance training (aquatic exercising), 8 week, N = 18	Control/usual care, Baseline, N = 18	Control/usual care, 8 week, N = 18
Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) Scale range: 7-63 Mean (SD)	38.94 (13.63)	16.22 (9.6)	48.72 (11.46)	25.28 (11.71)	39.56 (14.68)	41.22 (13.52)
Psychological symptoms (Beck depression scale) Scale range: 0-63 Mean (SD)	19.72 (7.04)	5.06 (2.92)	19.17 (7.83)	4.78 (3.42)	20.78 (6.22)	21.33 (6.88)

Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) - Polarity - Lower values are better

Psychological symptoms (Beck depression scale) - Polarity - Lower values are better

Follow up is at 8 weeks. This is less than 3 months and so will be downgraded due to indirectness.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Yoga compared to resistance training compared to usual care at 3-6 months – continuous outcomes (final values) - Patient-reported outcome measures to assess MS fatigue (Fatigue Severity Scale) – Mean SD-Yoga-Resistance training (aquatic exercising)-Control/usual care-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up is at 8 weeks. This is less than 3 months and so will be downgraded due to indirectness.)*

Yoga compared to resistance training compared to usual care at 3-6 months – continuous outcomes (final values) -Psychological symptoms (Beck depression scale) – Mean SD – Yoga - Resistance training (aquatic exercising)-Control/usual care-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Follow up is at 8 weeks. This is less than 3 months and so will be downgraded due to indirectness.)*

Razeghi-Jahromi, 2020

Bibliographic Reference	**Razeghi-Jahromi, S.; Doosti, R.; Ghorbani, Z.; Saeedi, R.; Abolhasani, M.; Akbari, N.; Cheraghi-Serkani, F.; Moghadasi, A. N.; Azimi, A.; Togha, M.; et, al.; A randomized controlled trial investigating the effects of a mediterranean-like diet in patients with multiple sclerosis-associated cognitive impairments and fatigue; Current journal of neurology; 2020; vol. 19 (no. 3); 112-121**

Study details

Trial name / registration number	Not reported
Study location	Iran
Study setting	Possibly outpatient
Study dates	Not reported
Sources of funding	Not reported

Inclusion criteria	Relapsing-remitting MS based on 2010 McDonald criteria; undergoing beta-interferon treatment (to rule out effects of different treatment modalities and various drug types that could be a source of bias in results); EDSS <5.5; aged 18-55 years; BMI 18-30 kg/m2; and in the remitting phase of MS with no relapse in the past 3 months.
Exclusion criteria	Changes in disease-modifying treatment within the study; consumption of cytotoxic medications, antipsychotic drugs and cortisone; history of drug abuse; following any special diet because of medical reasons; suffering from any neurological condition other than MS; psychologic or chronic disorders including head trauma, tumours, eating disorder, major depression, cardiovascular disease, as well as endocrine, metabolic, liver or kidney impairment; and pregnancy, breastfeeding or planning pregnancy.
Recruitment / selection of participants	Recruited from MS clinic of Sina University Hospital, Tehran University of Medical Sciences, Iran.
Intervention(s)	Mediterranean-based diet: patients interviewed by a dietician. Data on usual dietary intake collected using 24 h diet recall for 3 days to prescribe specific diet for each subject taking into account their usual dietary habits and preferences. Energy requirement calculated at first visit according to anthropometric assessments. Nutritional needs and macronutrient needs estimated. Distribution of macronutrients for patients in both groups was 18-20% protein, 30% lipid and 50-52% for carbohydrate. Patients visited by same dietician monthly until end of study. Prescribed diet adjusted according to new weight assessments. Energy needs and macronutrients proportional to age, sex and BMI. Generally, diet was modified in accordance with Mediterranean diet apart from wine and other unspecified foods. Advice focused on encouraging increased consumption of healthy oils (especially olive and olive oil), whole grains, vegetables, fruits and raw and unroasted nuts and seeds, legumes, and healthy plant based foods. Consumption of fish and seafood (~2 times weekly), poultry, eggs, and low fat or skimmed dairy (daily to weekly) was recommended. Participants also instructed to limit the intake of red meat, fried foods, and refined grains and to minimise the consumption of simple sugar, sugary foods and beverages, processed meat, and animal based fats to as low amounts as possible. The main modification that was made to the original Mediterranean diet included eliminating wine and some types of foods according to the Iranian culture based on religious beliefs. Patients in both groups advised to have five meals daily and were not aware of whether they had received the intervention or control diet. 1-year intervention.
Population subgroups	None

Comparator	Standard healthy diet: nutritionist-aided diet in accordance with US Department of Agriculture dietary guidelines for Americans, 2010. Guidelines customised to be proportionate to age, sex and BMI. Propose food-based recommendations for promoting public health, aiming to ensure dietary requirements are met and to prevent development and progression of chronic disease. Patients in both groups advised to have five meals daily and were not aware of whether they had received the intervention or control diet. 1-year intervention.
Number of participants	80 randomised, 56-72 analysed at follow-up
Duration of follow-up	1 year - end of intervention
Indirectness	None
Additional comments	Modified intention to treat as those without data excluded

Study arms

Mediterranean-like diet (N = 40)

Standard healthy diet (N = 40)

Characteristics

Arm-level characteristics

Characteristic	Mediterranean-like diet (N = 40)	Standard healthy diet (N = 40)
% Female Sample size	n = 31 ; % = 91.2	n = 33 ; % = 86.8
Mean age (SD) Mean (SD)	34 (8)	34 (9)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
MS disease duration (years) Mean (SD)	8 (5)	8 (5)
EDSS score Mean (SD)	2.27 (1.14)	2.4 (1.07)

Note that patient characteristics are given for those analysed for fatigue at follow-up (n=34 and n=38, respectively), not those randomised (n=40 per group)

Outcomes

Study timepoints

- Baseline

- 1 year

Results - raw data adjusted using ANCOVA

Outcome	Mediterranean-like diet, Baseline, N = 34	Mediterranean-like diet, 1 year, N = 34	Standard healthy diet, Baseline, N = 38	Standard healthy diet, 1 year, N = 38
Modified fatigue impact scale Scale 0-84. Result adjusted for age, MS disease duration, changes in Mediterranean-like diet adherence score, changes in BMI levels and baseline fatigue score. Mean (SD) or adjusted mean (95% CI)	40.05 (4.22)	33.93 (32.97-34.89)	38.19 (4.01)	37.98 (36.99-38.97)
PASAT Measure of cognition. Paced Auditory Serial Addition test. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	41.07 (16.67)	42.68 (39.89-45.47)	41. 18 (16.86)	42.37 (39.73-45.01)
PASAT Measure of cognition. Paced Auditory Serial Addition test. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29
SDMT Measure of cognition. Symbol Digit Modalities Test. Adjusted	44.96 (13.07)	43.37 (40.70-46.04)	43.0 (11.44)	45.89 (43.37-48.42)

Outcome	Mediterranean-like diet, Baseline, N = 34	Mediterranean-like diet, 1 year, N = 34	Standard healthy diet, Baseline, N = 38	Standard healthy diet, 1 year, N = 38
for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)				
SDMT Measure of cognition. Symbol Digit Modalities Test. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29
CVLT-II delayed recall Measure of cognition. California Verbal Learning Test-II. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	10.39 (2.98)	11.50 (10.31-12.69)	11.0 (3.11)	10.12 (8.96-11.28)
CVLT-II delayed recall Measure of cognition. California Verbal Learning Test-II. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29

Outcome	Mediterranean-like diet, Baseline, N = 34	Mediterranean-like diet, 1 year, N = 34	Standard healthy diet, Baseline, N = 38	Standard healthy diet, 1 year, N = 38
CVLT-II total learning Measure of cognition. California Verbal Learning Test-II. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	49.39 (9.32)	50.79 (47.08-54.49)	50.62 (8.90)	50.94 (47.24-54.64)
CVLT-II total learning Measure of cognition. California Verbal Learning Test-II. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29
Judgement of Line Orientation test Measure of cognition. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	20.29 (5.14)	18.62 (17.27-19.97)	18.13 (5.10)	19.57 (18.30-20.85)
Judgement of Line Orientation test Measure of cognition. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29

Outcome	Mediterranean-like diet, Baseline, N = 34	Mediterranean-like diet, 1 year, N = 34	Standard healthy diet, Baseline, N = 38	Standard healthy diet, 1 year, N = 38
BVMT-R Measure of cognition. Brief Visuospatial Memory Test-Revised. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	21.96 (8.55)	20.56 (18.60-22.51)	22.22 (7.39)	23.73 (21.88-25.57)
BVMT-R Measure of cognition. Brief Visuospatial Memory Test-Revised. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29
North American Adult Reading Test Measure of cognition. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	43.00 (5.00)	41.52 (40.21-42.83)	42.00 (6.25)	40.95 (39.71-42.19)
North American Adult Reading Test Measure of cognition. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29

Outcome	Mediterranean-like diet, Baseline, N = 34	Mediterranean-like diet, 1 year, N = 34	Standard healthy diet, Baseline, N = 38	Standard healthy diet, 1 year, N = 38
COWAT Measure of cognition. Controlled Oral Word Association Test. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	9.37 (3.52)	8.82 (8.02-9.61)	7.99 (3.08)	8.63 (7.89-9.38)
COWAT Measure of cognition. Controlled Oral Word Association Test. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29
D-KEFS descrption score Measure of cognition. Delis-Kaplan Executive Function System description. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	13.70 (4.92)	10.97 (9.45-12.49)	12.56 (5.38)	11.69 (10.25-13.12)
D-KEFS descrption score Measure of cognition. Delis-Kaplan Executive Function System description. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test.	27	27	29	29

Outcome	Mediterranean-like diet, Baseline, N = 34	Mediterranean-like diet, 1 year, N = 34	Standard healthy diet, Baseline, N = 38	Standard healthy diet, 1 year, N = 38
Number analysed				
D-KEFS total scoring Measure of cognition. Delis-Kaplan Executive Function System description. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Mean (SD) or adjusted mean (95% CI)	3.68 (1.31)	2.92 (2.48-3.36)	3.39 (1.37)	3.39 (2.98-3.81)
D-KEFS total scoring Measure of cognition. Delis-Kaplan Executive Function System description. Adjusted for age, MS disease duration, changes in the Mediterranean-like diet adherence score, changes in BMI levels, and baseline score of test. Number analysed	27	27	29	29
Adherence to intervention Scale 0-14. Mean (SD)	NR (NR)	9.45 (2.49)	NR (NR)	7 (2.54)

Modified fatigue impact scale - Polarity - Lower values are better

PASAT - Polarity - Higher values are better

SDMT - Polarity - Higher values are better

CVLT-II delayed recall - Polarity - Higher values are better

CVLT-II total learning - Polarity - Higher values are better

Judgement of Line Orientation test - Polarity - Higher values are better

BVMT-R - Polarity - Higher values are better

North American Adult Reading Test - Polarity - Higher values are better

COWAT - Polarity - Higher values are better

D-KEFS descrption score - Polarity - Higher values are better

D-KEFS total scoring - Polarity - Higher values are better

Adherence to intervention - Polarity - Higher values are better

Note that although n=40 were randomised to each group, baseline values in the paper are given only for those analysed at the end of the intervention. Note that numbers analysed are n=27 and n=29 for the cognitive outcomes.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results MFIS 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results PASAT 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results SDMT 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CVLT-II delayed recall 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results CVLT-II total learning 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results Judgement of Line Orientation test 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results BVMT-R 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results North American Adult Reading Test 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results COWAT 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results D-KEFS description score 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results D-KEFS total scoring 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence to intervention 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Rietberg, 2014

Bibliographic Reference	**Rietberg, M. B.; van Wegen, E. E.; Eyssen, I. C.; Kwakkel, G.; group, M. S. study; Effects of multidisciplinary rehabilitation on chronic fatigue in multiple sclerosis: a randomized controlled trial; PLoS ONE [Electronic Resource]; 2014; vol. 9 (no. 9); e107710**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with	NR

this study included in review	
Trial name / registration number	NR
Study location	Netherlands
Study setting	VU University Medical Centre outpatient department
Study dates	Jan 2006 - Dec 2009
Sources of funding	This study was supported by the Dutch MS Research Foundation 'Stichting (project number 04-553 MS) http://msresearch.nl/. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Inclusion criteria	(1) older than 18 years; (2) diagnosed with MS according to the McDonald criteria [22]; (3) suffering from chronic fatigue according to the MSCCPG definition; and (4) able to walk.
Exclusion criteria	(1) current MS relapse, (2) pregnancy, (3) current infection (cystitis), (4) alcohol or substance abuse, (5) physical conditions like muscle spasm or pain contributing to sleep problems, (6) pharmacological treatment for fatigue that was started in the past 3 months, or (7) depressive symptomatology importantly contributing to fatigue according to the Hospital Anxiety and Depression Scale (HADS). A score of 8 or higher on the depression scale was classified as depression.
Recruitment / selection of participants	Eligible patients were screened for the inclusion and exclusion criteria by a neurologist. Due to slow recruitment we were not able to keep our original time frame for inclusion of patients between 2005 and 2008. Recruitment started in January 2006 and the last follow-up assessment was performed in December 2009. Before patients were allocated to a treatment group, the neurologist completed a standardized fatigue screening questionnaire.
Intervention(s)	Before patients were allocated to a treatment group, the neurologist completed a standardized fatigue screening questionnaire. It is a structured approach which starts with identification of the most important daily problems related to

	fatigue as perceived by the patient, such as dividing time between rest and activity, improving or maintaining physical condition and coping with MS symptoms. Moreover, patients were asked to indicate their preferences regarding the sequence in treatment for their individual identified problems. Subsequently, a multidisciplinary team, consisting of a neurologist, rehabilitation doctor, occupational therapist, physiotherapist, social worker, MS nurse and medical psychologist, discussed the results of the fatigue screening by the neurologist and a tailored pathway of referral was determined for each individual patient. Then, patients were randomly allocated to MDR or to NC. Patients to MDR were referred to one or more disciplines that were professionally linked to the fatigue management problems of interest to each patient. Multidisciplinary Rehabilitation programme (MDR). Patients assigned to MDR received an individually tailored programme that focussed on optimising self management behaviour in daily life activities on the domains of physical fitness, behaviours or cognitions that perpetuate fatigue, and energy conservation. For addressing this therapy goals participants received physical therapy (PT), or occupational therapy (OT), or social work (SW), or any combination of these treatments. For PT, the number of treatment sessions was predefined, whereas for the other intervention types, the number of sessions was on an as-needed basis, with a minimum of 2 sessions. In addition to the outpatient treatment sessions, the MS patients were given homework assignments. The participating disciplines treated MS-related fatigue according to specific treatment programmes, as described below. Physiotherapy - The 12-week training programme consisted of two 45- minute sessions a week of supervised aerobic training in circuit style, performed individually or in classes. Maximal aerobic capacity of each participant was estimated by means of a submaximal bicycle ergometer test. Moderate intensity was defined as 50–70% VO2-peak steady-state endurance training. Various fitness devices (e.g. bicycle ergometer, rowing ergometer, stair walker) were used in blocks of six minutes, in order to offer a total body work-out. Occupational therapy (OT) Patients were referred to occupational therapy to address the factors of ‘dividing time between rest and activity’, ‘work, education, leisure time and social contacts’, ‘sitting and walking’ and ‘personal care’. During a one-hour session, intervention goals were set, which were evaluated in follow-up consultations. Fatigue management skills were taught to help with the application of coping strategies, energy conservation, time management, efficient body mechanics and task performance.

	Social work (SW) Patients were referred to social work to address the factors of 'support from the environment', 'conflicts at work or with social services', and 'coping with MS'. The social worker provided psychosocial support through counselling and practical assistance. Goals were set during a one-hour session, and subsequently evaluated in follow up consultations. The psychosocial support, used the techniques of skilled listening, encouragement to ventilate feelings, normalization of feelings and advice regarding coping strategies, coupled with practical help to enable both patient and family to cope with difficult circumstances identified.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - NR · Group vs individual - mixed · Delivered remotely vs in person - in person
Comparator	Before patients were allocated to a treatment group, the neurologist completed a standardized fatigue screening questionnaire. It is a structured approach which starts with identification of the most important daily problems related to fatigue as perceived by the patient, such as dividing time between rest and activity, improving or maintaining physical condition and coping with MS symptoms. Moreover, patients were asked to indicate their preferences regarding the sequence in treatment for their individual identified problems. Subsequently, a multidisciplinary team, consisting of a neurologist, rehabilitation doctor, occupational therapist, physiotherapist, social worker, MS nurse and medical psychologist, discussed the results of the fatigue screening by the neurologist and a tailored pathway of referral was determined for each individual patient. Then, patients were randomly allocated to MDR or to NC. Patients to MDR were referred to one or more disciplines that were professionally linked to the fatigue management problems of interest to each patient. Patients allocated to the NC group received consultation according to the Nursing Intervention Classification. Goals were set during a one-hour session, and subsequently evaluated in follow-up consultations every three weeks. The nurse discussed general principles of planning of activities, priority setting, energy conservation, accepting help from others with

	daily life activities or use of devices. Physical activity was recommended. Patients were advised on nutrition and alcohol and drug intake. In addition to the consultation sessions, the patients were given homework assignments.
Number of participants	48
Duration of follow-up	6 months
Additional comments	NR

Study arms

multidisciplinary outpatient rehabilitation (N = 23)

MS–nurse consultation (N = 25)

Characteristics

Study-level characteristics

Characteristic	Study (N = 48)
% Female Nominal	31

Arm-level characteristics

Characteristic	multidisciplinary outpatient rehabilitation (N = 23)	MS–nurse consultation (N = 25)
Age Mean (SD)	45 (9.9)	47 (8.6)

Outcomes

Study timepoints

6 month (3-6 month change score)

3 month (0-3 month change score)

change scores at 0-3 months and 3-6 months

Outcome	multidisciplinary outpatient rehabilitation, 6 month, N = 21	multidisciplinary outpatient rehabilitation, 3 month, N = 22	MS–nurse consultation, 6 month, N = 23	MS–nurse consultation, 3 month, N = 24
CIS-20R - total change score Mean (SD)	3.4 (8.8)	-0.8 (7.1)	-1 (8.8)	2.2 (10.3)
CIS-20R - subjective feeling change score 12-24 weeks	2.1 (5.1)	0.6 (3.2)	-0.6 (6.1)	1.7 (5)

Outcome	multidisciplinary outpatient rehabilitation, 6 month, N = 21	multidisciplinary outpatient rehabilitation, 3 month, N = 22	MS–nurse consultation, 6 month, N = 23	MS–nurse consultation, 3 month, N = 24
Mean (SD)				
CIS-20R - concentration change score - 12-24 weeks Mean (SD)	1.3 (3.7)	-1.1 (3.8)	-0.2 (3)	-0.3 (3.3)
CIS-20R - motivation change score - 12-24 weeks Mean (SD)	0.1 (3.3)	-0.6 (3.1)	0 (2.8)	0.3 (3.3)
CIS-20R - physical activity change score - 12-24 weeks Mean (SD)	0.3 (2.5)	0.3 (2.1)	-0.3 (2.1)	0.6 (2.9)
FSS change score 12-24 weeks Mean (SD)	0.5 (7.9)	-1.6 (7.1)	-1.3 (7.8)	0.3 (8.5)

Outcome	multidisciplinary outpatient rehabilitation, 6 month, N = 21	multidisciplinary outpatient rehabilitation, 3 month, N = 22	MS–nurse consultation, 6 month, N = 23	MS–nurse consultation, 3 month, N = 24
MFIS total change score 12-24 weeks Mean (SD)	1.9 (11.2)	1.2 (9.5)	3.9 (11.9)	-0.6 (13.8)
MFIS - physical change score - 12-24 Mean (SD)	1 (4.6)	1.1 (4.4)	2.2 (5.7)	-0.6 (6.3)
MFIS - cognitive change score 12-24 weeks Mean (SD)	0.6 (7.7)	-0.1 (6.3)	1.4 (9.7)	0.1 (7.4)
MFIS - psycho social change score - 12 - 24 weeks Mean (SD)	0.3 (1.6)	0.1 (1.5)	0.3 (1.6)	-0.1 (1.9)
functional independance measure change score - 12-24 weeks Mean (SD)	1 (4)	2 (4)	-1 (9)	-1 (5)

Outcome	multidisciplinary outpatient rehabilitation, 6 month, N = 21	multidisciplinary outpatient rehabilitation, 3 month, N = 22	MS–nurse consultation, 6 month, N = 23	MS–nurse consultation, 3 month, N = 24
MSIS physical change score - 12-24 weeks Mean (SD)	-3 (14)	1 (7)	1 (9)	2 (9)
MSIS psychological change score 12-24 weeks Mean (SD)	0 (6)	0 (6)	0 (7)	1 (5)
adherence to homework tasks (%) Nominal	96	*empty data*	89	*empty data*

CIS-20R - total - Polarity - Lower values are better

CIS-20R - subjective feeling - Polarity - Lower values are better

CIS-20R - concentration - Polarity - Lower values are better

CIS-20R - motivation - Polarity - Lower values are better

CIS-20R - physical activity - Polarity - Lower values are better

FSS - Polarity - Lower values are better

MFIS total - Polarity - Lower values are better

MFIS - physical - Polarity - Lower values are better

MFIS - cognitive - Polarity - Lower values are better

MFIS - psycho social - Polarity - Lower values are better

functional independance measure - Polarity - Lower values are better

MSIS physical - Polarity - Lower values are better

MSIS psychological - Polarity - Lower values are better

adherence to homework tasks - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

changescoresat0-3monthsand3-6months-CIS-20R-total-MeanSD-multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS – 20 R-total – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS – 20 R – subjective feeling – Mean SD – multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS – 20 R – subjective feeling – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS – 20 R – concentration – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS – 20 R – concentration – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS – 20 R – motivation – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS - 20R – motivation – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS - 20R – physical activity – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – CIS - 20R – physical activity – Mean SD - multidisciplinary outpatient rehabilitation - MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – FSS – Mean SD - multidisciplinary outpatient rehabilitation – MS – nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – FSS – Mean SD - multidisciplinary outpatient rehabilitation – MS – nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS total – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS total – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS – physical – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS – physical – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS – cognitive – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS – cognitive – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS – psychosocial – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MFIS – psychosocial – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MSIS psychological – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MSIS psychological – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MSIS physical – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – MSIS physical – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – functional independence measure – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – functional independence measure – Mean SD - multidisciplinary outpatient rehabilitation-MS–nurse consultation-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Change scores at 0-3 months and 3-6 months – adherence to homework tasks - Nominal-multidisciplinary outpatient rehabilitation-MS–nurse consultation-t6

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Sabapathy, 2011

Bibliographic Reference	**Sabapathy, N. M.; Minahan, C. L.; Turner, G. T.; Broadley, S. A.; Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study; Clin Rehabil; 2011; vol. 25 (no. 1); 14-24**

Study details

Trial name / registration number	None reported
Study location	Australia
Study setting	Community
Study dates	None reported
Sources of funding	MS Society of Queensland
Inclusion criteria	Subjects with multiple sclerosis were included in the study if they could ambulate independently either with or without the use of walking aid.
Exclusion criteria	None reported
Recruitment / selection of participants	Individuals with multiple sclerosis responded to a “call for volunteers” flyer displayed at local Community Health Centres and were accepted to participate in the program
Intervention(s)	Both the endurance- and resistance-exercise training programs were 8 weeks in duration and consisted of two exercise sessions per week. All training sessions were supervised by two Exercise Physiologists. Before all training sessions, subjects completed a 5-min warm-up comprised of walking at a self-selected speed. The training sessions were concluded with15-20 min of supervised static and dynamic stretching of the major upper- and lower-body muscle groups. The endurance-exercise training program involved a circuit of eight exercise stations comprising of six different activities. Subjects exercised for 5 min at each station and rested for 2 min every 10 min (i.e. after the completion of every two activities). The eight exercise stations were: 1) step ups (step height 10-20 cm), 2) arm cranking (ADPE Duo Bike), 3) upright cycling (Tunturi F35 Competence or York Magnaforce 5000 HRC), 4) arm cranking, 5) recumbent cycling (Vision Fitness R2250 HRT), 6) cross-trainer (Octance Fitness Q35), 7) treadmill walking (Elite DX726 or Pacer 3701), and 8) arm cranking. The exercise-intensity of each activity was increased throughout the program by adjusting resistance and/or

	cadence. Additionally exercise time was progressively increased over the 8- week endurance-exercise training program for those subjects who initially were unable to complete 5 min of continuous activity.
Population subgroups	None
Comparator	The resistance-exercise training program consisted of three upper-body and three lower-body exercises as well as one core-strength, and one stability exercise. For each exercise, subjects commenced and progressed through a series of exercises dependent upon the individual's initial level of strength and rate of improvement. Subjects performed 2-3 sets, comprised of 6- 10 repetitions of each exercise per set. Subjects were instructed to have a minimum of 30-60 s rest between each exercise set. Progression through the resistance-exercise training program was facilitated by increasing the resistance of Therabands and/or weights used on applicable exercises and by progressing through a series of exercises
Number of participants	16
Duration of follow-up	8 weeks
Indirectness	None

Study arms

Endurance exercise (N = 16)

The endurance-exercise training program involved a circuit of eight exercise stations comprising of six different activities.

Resistance-exercise (N = 16)

The resistance-exercise training program consisted of three upper-body and three lower-body exercises as well as one core-strength, and one stability exercise

Characteristics

Study-level characteristics

Characteristic	Study (N =)
% Female Sample size	n = 12 ; % = 75
Mean age (SD) Mean (SD)	55 (7)
Ethnicity Custom value	Australian
Relapsing remitting MS Sample size	n = 10 ; % = 62.5

Outcomes

Study timepoints

- 8 week (Post treatment)

Post training

Outcome	Endurance exercise, 8 week, N = 16	Resistance-exercise , 8 week, N = 16
Modified Fatigue Impact Scale Physical Scale Change score Mean (SD)	-2.7 (5.3)	-1.6 (3.3)
MFIS Psychosocial scale Change score Mean (SD)	-0.8 (1.4)	-1.6 (11.6)
MFIS Cognitive scale Change score Mean (SD)	-2.3 (6)	-3.3 (7.8)
SF-36 Physical Change score Mean (SD)	-0.2 (6.8)	3.7 (7)
SF-36 Mental Change score Mean (SD)	2.3 (10.6)	-1.9 (9.7)
Beck Depression Inventory Change score Mean (SD)	0.6 (3.9)	-2.3 (5.4)
Adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0

Modified Fatigue Impact Scale Physical Scale - Polarity - Lower values are better

MFIS Psychosocial scale - Polarity - Lower values are better

MFIS Cognitive scale - Polarity - Lower values are better

SF-36 Physical - Polarity - Higher values are better

SF-36 Mental - Polarity - Higher values are better

Beck Depression Inventory - Polarity - Lower values are better

Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

MFIS physical 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

MFIS Psychosocial 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

MFIS Cognitive 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

SF-36 Physical

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

SF-36 Mental

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

BDI 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)	Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)	High
Domain 3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness < 3 mths follow up)*

Sadeghi Bahmani, 2019

Bibliographic Reference	**Sadeghi Bahmani, D.; Razazian, N.; Farnia, V.; Alikhani, M.; Tatari, F.; Brand, S.; Compared to an active control condition, in persons with multiple sclerosis two different types of exercise training improved sleep and depression, but not fatigue, paresthesia, and intolerance of uncertainty; Multiple Sclerosis and Related Disorders; 2019; vol. 36; 101356**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with	NR

this study included in review	
Trial name / registration number	NR
Study location	Iran
Study setting	Farabi University-Hospital of the Kermanshah University of Medical Sciences (KUMS; Kermanshah, Iran)
Study dates	NR
Sources of funding	The entire study was performed without external funding
Inclusion criteria	1. Age between 18 and 65 years; 2. Status of MS, ascertained by a trained neurologist and based on Mc Donald's criteria; 3. EDSS score < 6; 4. Willing and able to comply with the study conditions; 5. Signed written informed consent.
Exclusion criteria	1. Other neurological disease; 2. Severe psychiatric issues such as major depressive disorders, bipolar disorders, substance use disorder, anxiety disorders, post-traumatic stress disorders, attention-deficit-hyperactivity disorders, based on a thorough clinical psychiatric interview (Sheehan et al., 1998); 3. Acute suicidality; 4. Musculoskeletal issues which did not allow regular PA; 5. Participants missed more than 3 sessions; 6. The principle investigator excluded participants from the study, if a participant showed adverse events, which might have been associated with the interventions. 7. Undergoing further PA, psychotherapy, or undergoing surgery; 8. Pregnancy and/or breast feeding
Recruitment / selection of participants	Female PwMS of the MS Society of Kermanshah province, located in the Farabi University-Hospital of the Kermanshah University of Medical Sciences (KUMS; Kermanshah, Iran) were approached to participate in the present intervention study. Eligible participants were fully informed about the aims of the study and the confidential nature of the data handling. Thereafter, participants signed the written informed consent.
Intervention(s)	**Group 1 -Endurance training** condition lasted for eight consecutive weeks and consisted of three weekly supervised and guided group sessions (30–45 min/each). After 5 min of warming-up and stretching, participants exercised for 25–35 min on

	treadmill, exercise bicycles or walking/jogging with individual pauses of 1–2 min, followed by 5 min of cooling down. At the end of a session, participants should have had the feeling to be slightly exhausted, but not severely exhausted. Professional instructors monitored the sessions and participants' level of performance and exhaustion. In this view, Meyer et al. (2016) showed that compared to a preferred exercise duration and intensity, keeping a prescribed exercise duration and intensity improved mood among individuals with major depressive disorders. **Group 2 -Coordinative training** lasted for eight consecutive weeks, and three supervised and guided group sessions the week for 30–45 min/session. After 5 min of warming up, exercises focused on CT such as balancing on a small bar, mirroring and imitating instructors' movements (such as dancing steps), balancing balls, mirroring participants' bouncing with the balls of different size, surface and weight, 'football-tennis', balancing with closed eyes on a rope on the floor and similar exercises. The CT required a higher level of object control and locomotor skills as well as interactions with other participants. Such exercise characteristics are suggested to increase coordinative demands and cognitive engagement (. At the end of a session, participants should have had the feeling to be slightly exhausted, but not severely exhausted. Professional instructors monitored the sessions and participants' level of performance and exhaustion. Cooling down lasted for about 5 min.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - NR · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - NR · Group vs individual - group · Delivered remotely vs in person - in person
Comparator	**Active control.** For eight consecutive weeks, participants of the ACC met three times/week for 30–45 min/session at the hospital centre to ensure that frequency, duration, and the degree social contacts of the control condition were identical to the endurance and resistance training conditions. The control condition was not a 'bona fide' condition, which would have been actually intended to elicit change in cognitive and emotional dysfunctional consequences (Goyal et al., 2014; Wampold et al., 1997; Jasbi et al., 2018). Most importantly, in the control condition, topics such as successful coping

	strategies were not treated and not proactively proposed by the clinical psychologist responsible to monitor the content of the control conditions. Rather, participants were encouraged to proposing and exchanging daily life experiences.
Number of participants	92
Duration of follow-up	8 weeks
Indirectness	marked down as FU period <3 months
Additional comments	NR

Study arms

Endurance training (N = 31)

Coordinative training (N = 30)

active control (N = 31)

Characteristics

Study-level characteristics

Characteristic	Study (N = 92)
% Female Nominal	92

Arm-level characteristics

Characteristic	Endurance training (N = 31)	Coordinative training (N = 30)	active control (N = 31)
Age Mean (SD)	39.17 (8.66)	37.96 (8.69)	37.9 (9.91)

Outcomes

Study timepoints

- 8 week

8 week outcomes

Outcome	Endurance training, 8 week, N = 26	Coordinative training, 8 week, N = 24	active control, 8 week, N = 21
Fatigue Severity Scale (FSS) 9-63 Mean (SD)	39.31 (17.23)	34.08 (15.15)	45.05 (11.77)

Outcome	Endurance training, 8 week, N = 26	Coordinative training, 8 week, N = 24	active control, 8 week, N = 21
EDSS = Expanded Disability Status Scale Mean (SD)	2.27 (1.64)	3.1 (1.86)	1.98 (1.7)
Insomnia Severity Index (ISI) (0-28) Mean (SD)	8.81 (5.41)	10.13 (4.92)	11.14 (5.39)
Beck Depression Inventory-Fast Screen (BDI-FS) Scale 0-21 Mean (SD)	5.12 (4.65)	5.29 (5.75)	6.52 (4.91)

Fatigue Severity Scale (FSS) - Polarity - Lower values are better

EDSS = Expanded Disability Status Scale - Polarity - Lower values are better

Insomnia Severity Index (ISI) - Polarity - Lower values are better

Beck Depression Inventory-Fast Screen (BDI-FS) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

8 week outcomes – Fatigue Severity Scale (FSS) – Mean SD-Endurance training-Coordinative training-active control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(over 10% missing overall and more than 10% difference in missingness between control and intervention groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(FU period is less than 3 months)*

8 week outcomes – Insomnia Severity Index (ISI) – Mean SD-Endurance training-Coordinative training-active control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(over 10% missing overall and more than 10% difference in missingness between control and intervention groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(FU period is less than 3 months)*

8 week outcomes – Beck Depression Inventory – Fast Screen (BDI-FS) – Mean SD-Endurance training-Coordinative training-active control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(over 10% missing overall and more than 10% difference in missingness between control and intervention groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(FU period is less than 3 months)*

8 week outcomes – EDSS = Expanded Disability Status Scale – Mean SD - Endurance training-Coordinative training-active control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(over 10% missing overall and more than 10% difference in missingness between control and intervention groups)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(FU period is less than 3 months)*

Sajadi, 2020

Bibliographic Reference	**Sajadi, M.; Davodabady, F.; Ebrahimi-Monfared, M.; The effect of foot reflexology on fatigue, sleep quality and anxiety in patients with multiple sclerosis: A randomized controlled trial; Archives of Neuroscience; 2020; vol. 7 (no. 3); 1-8**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	Iran
Study setting	multiple sclerosis society of Arak City, Markazi Province, Iran
Study dates	May 2018 to May 2019
Sources of funding	This study was funded by Vice Chancellor for Research and Technology, Arak University of Medical Sciences, Arak, Iran
Inclusion criteria	(1) age range of 18 - 50 years; (2) Expanded Disability Status scale (EDSS), the score of ≤ 4 according to the neurologist; and (3) patients with relapsing-remitting MS.
Exclusion criteria	(1) deformities, wounds, or skin diseases of the lower extremity; (2) use of sleep medications and antidepressants; and (3) use of other CAM currently or during the last 6 months

Recruitment / selection of participants	After making an official announcement at the Arak MS Association, patients who were willing to participate in the study, were invited via written letters. 76 patients agreed to participate in the study. Nevertheless, 6 volunteers were excluded according to the initial screening characteristics (e.g., inclusion and exclusion criteria and past medical history). The research methodology and objectives were explained to all the participants, and then, informed consent was obtained.
Intervention(s)	The Rwo Shur method of reflexology was used in this study. In the reflexology group, the patients participated in reflexology sessions (n = 8) in the afternoon twice a week for four weeks. The intervention was conducted independently for each participant in a private room with appropriate lighting and temperature. During the intervention, the participant and reflexologist (first author, who is the qualified reflexologist) were alone in the room. Before each session, the feet were washed, and the patient was seated on a comfortable reclining chair; to prevent fatigue, a small pillow was placed under the knees. Also, to decrease friction, scent-free moisturizing oil was used. First, the general massage of the right foot began for five minutes by applying controlled pressure. Then, specialized massage was applied to the pituitary gland, hypothalamus, pineal gland (the reflex points that help to reduce fatigue, anxiety, and improving sleep quality), and, finally, the solar plexus reflex points for 10 - 15 minutes. The left foot was massaged in the same manner. At the end of the sessions, the patient was asked to take a glass of water to remove toxins from the body. Each session continued for 30 - 40 minutes on average.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - only RR · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - NR · Group vs individual - individual · Delivered remotely vs in person - in person
Comparator	To eliminate the effects of reflexologist’s presence and other environmental factors on the parameters under measurement, the subjects in the control group also participated in eight sessions of non-specialized foot massage twice a week in the afternoon for four weeks. The control group, under the same conditions as the reflexology group, received sham massage on foot, without applying pressure on any particular reflex points.

Number of participants	63
Duration of follow-up	4 weeks
Indirectness	marked down for FU being <3 months
Additional comments	NR

Study arms

Reflexology group (N = 35)

Sham reflexology (N = 35)

Characteristics

Study-level characteristics

Characteristic	Study (N = 63)
% Female Nominal	93
Mean age (SD)	20 to 49

Characteristic	Study (N = 63)
Range	

Outcomes

Study timepoints

4 week

4 week outcomes

Outcome	Reflexology group, 4 week, N = 33	Sham reflexology, 4 week, N = 30
Fatigue Impact Scale - total score 0-160 Mean (SD)	67.76 (32.24)	81.33 (38.56)
FIS - Cognitive subscale fatigue 0-160 Mean (SD)	17.55 (9.23)	19.53 (11.09)
FIS - Physical subscale fatigue 0-160 Mean (SD)	17.24 (8.12)	22.3 (11.06)
FIS - Social subscale fatigue 0-160	33.27 (17.08)	40.1 (20.59)

Outcome	Reflexology group, 4 week, N = 33	Sham reflexology, 4 week, N = 30
Mean (SD)		
Pittsburgh Sleep Quality Index (0-21) Mean (SD)	5.76 (2.56)	10.03 (7.96)
State-Trait Anxiety Inventory 20-80 Mean (SD)	43.3 (2.06)	49.5 (2.35)

Fatigue Impact Scale - total score - Polarity - Lower values are better

FIS - Cognitive subscale fatigue - Polarity - Lower values are better

FIS - Physical subscale fatigue - Polarity - Lower values are better

FIS - Social subscale fatigue - Polarity - Lower values are better

Pittsburgh Sleep Quality Index - Polarity - Lower values are better

State-Trait Anxiety Inventory - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

4 week outcomes – Fatigue Impact Scale – total score – Mean SD - Reflexology group-Sham reflexology-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

4 week outcomes – FIS – Cognitive subscale fatigue – Mean SD - Reflexology group-Sham reflexology-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

4 week outcomes – FIS – Physical subscale fatigue – Mean SD - Reflexology group-Sham reflexology-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

4 week outcomes – FIS – Social subscale fatigue – Mean SD - Reflexology group-Sham reflexology-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

4 week outcomes – Pittsburgh Sleep Quality Index – Mean SD - Reflexology group-Sham reflexology-t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

4 week outcomes – State – Trait Anxiety Inventory – Mean SD – Reflexology group – Sham reflexology -t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Indirectly applicable

Sangelaji, 2014

Bibliographic Reference	**Sangelaji, B.; Nabavi, S. M.; Estebsari, F.; Banshi, M. R.; Rashidian, H.; Jamshidi, E.; Dastoorpour, M.; Effect of combination exercise therapy on walking distance, postural balance, fatigue and quality of life in multiple sclerosis patients: a clinical trial study; Iranian Red Crescent Medical Journal; 2014; vol. 16 (no. 6); e17173**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR

Trial name / registration number	NR
Study setting	Iran's Multiple Sclerosis Society (located in Tehran, Iran)
Study dates	September 2012 to December 2013
Sources of funding	The study is self-funded
Inclusion criteria	Suffering from recurrent and improving type of MS, 18 to 50 years old, not having had any MS attack in the last three months and consuming various types of interferon for prevention of MS attacks. Also, these patients had to have EDSS scores of 0-4, and higher scores excluded the patient from the research.
Exclusion criteria	EDSS >4
Recruitment / selection of participants	The participants consisted of 147 patients with multiple sclerosis which enrolled in this study based on convenience sampling method who were referred by neurologists to physiotherapy clinic of Iran's Multiple Sclerosis Society.
Intervention(s)	10 weeks of combination exercises including stretching and aerobics exercises, strengthening exercises with spring, and balancing exercises with tilt board and cerebral palsy ball. Three exercise sessions per week with a total number of 30 sessions were considered for the patients. The time of aerobics exercises was divided equally between bicycle and treadmill. The difficulty level in every session started from a low point and gradually reached to the climax and once again decreased and returned to the starting point. In every treatment session, patients did strengthening exercises with a spring for strengthening their quadriceps, gluteal, and cuff muscles. Exercise regimen for these muscles started many cycles of low intensity exercise and took nearly 10-15 minutes. In every session, patients did various balancing exercises with circular and rectangular tilt boards and also cerebral palsy ball. These exercises took 10 minutes at the beginning and gradually increased to 20 minutes. Thus, every session started with one active hour and gradually, depending on patients' endurance, increased to nearly 90 minutes. Patients were allowed to take enough rest between exercises to refresh themselves and overcome their fatigue. Whenever possible they were offered proper fruit

	juice, biscuits, and dates. It must also be noted that patients received sufficient explanation about the methods, principles, and benefits of exercises for MS patients and were encouraged to do exercises on a regular and long-term basis.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - NR · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - using interferon drugs · Group vs individual - group · Delivered remotely vs in person - in person
Comparator	Wait list control. no details but assuming usual care.
Number of participants	72
Duration of follow-up	End of intervention (no specific time frame given but >10 weeks)
Indirectness	marked down for indirectness as < 3 month FU period
Additional comments	NR

Study arms

combination exercise therapy (N = 42)

control group (N = 42)

Characteristics

Study-level characteristics

Characteristic	Study (N = 61)
% Female Nominal	39

Arm-level characteristics

Characteristic	combination exercise therapy (N = 42)	control group (N = 42)
Age Mean (SD)	33.05 (7.68)	32.05 (6.35)

Outcomes

Study timepoints

- Baseline
- 11 week (11 weeks - 1 week after end of 10-week programme)
- 1 year (12 months - 12 months after start of intervention.)

Change score vs. baseline in intervention group relative to control group

Outcome	combination exercise therapy vs control group, 11 week vs Baseline, N2 = 22, N1 = 39	combination exercise therapy vs control group, 1 year vs Baseline, N2 = 20, N1 = 35
Fatigue Severity Scale Scale usually 9-63. P-value	0.02	0.004
Fatigue Severity Scale Scale usually 9-63. Mean (SD)	-6.9 (2.82)	-10.2 (3.42)
MS-specific quality of life, mental domain - name of scale not provided. Name of measurement and therefore scale unclear. P-value	0.001	0.02
MS-specific quality of life, mental domain - name of scale not provided. Name of measurement and therefore scale unclear. Mean (SD)	16.36 (4.46)	13.54 (5.37)
MS-specific quality of life, physical domain - name of scale not provided. Name of measurement and therefore scale unclear. P-value	0.001	0.02

Outcome	combination exercise therapy vs control group, 11 week vs Baseline, N2 = 22, N1 = 39	combination exercise therapy vs control group, 1 year vs Baseline, N2 = 20, N1 = 35
MS-specific quality of life, physical domain - name of scale not provided. Name of measurement and therefore scale unclear. Mean (SD)	12.17 (3.62)	10.9 (4.55)
EDSS Scale 0-10 usually. P-value	0.60	0.35
EDSS Scale 0-10 usually. Mean (SD)	-0.13 (0.23)	-0.28 (0.29)

Fatigue Severity Scale - Polarity - Lower values are better

MS-specific quality of life, mental domain - name of scale not provided. - Polarity - Higher values are better

MS-specific quality of life, physical domain - name of scale not provided. - Polarity - Higher values are better

EDSS - Polarity - Lower values are better

Changes appear to be given for 11 weeks vs. baseline (n=39 vs. n=22) and 1 year vs. baseline (n=35 vs. n=20)

Results - raw data

Outcome	combination exercise therapy, Baseline, N = 42	combination exercise therapy, 11 week, N = 41	combination exercise therapy, 1 year, N = NA	control group, Baseline, N = 42	control group, 11 week, N = 23	control group, 1 year, N = NA
Adverse events leading to withdrawal Based on information reported in text about reasons for leaving the study No of events	n = NA ; % = NA	n = 2 ; % = 4.9	n = NA ; % = NA	n = NA ; % = NA	n = 1 ; % = 4.3	n = NA ; % = NA

Available case analysis extracted based on information within the text.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 11 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(just under minimum of 3 months in protocol)*

Results FSS 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results QOL mental 11 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(just under minimum of 3 months in protocol)*

Results QOL mental 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results QOL physical 11weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(just under minimum of 3 months in protocol)*

Results QOL physical 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results EDSS 11 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(just under minimum of 3 months in protocol)*

Results EDSS 1 year

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results withdrawal due to adverse events 11 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(just under minimum of 3 months in protocol)*

Schulz, 2004

Bibliographic Reference	**Schulz, K. H.; Gold, S. M.; Witte, J.; Bartsch, K.; Lang, U. E.; Hellweg, R.; Reer, R.; Braumann, K. M.; Heesen, C.; Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis; J Neurol Sci; 2004; vol. 225 (no. 12); 11-8**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR

Study location	Germany
Study setting	NR
Study dates	NR
Sources of funding	This research was supported by grants from the Gemeinnqtzige Hertie Stiftung (Grant No. 1.319.110-01- 06 and Grant No. 1.319.120-01-01).
Inclusion criteria	Definitive multiple sclerosis according to Poser criteria, Expanded Disability Status Scale (EDSS) <5.0, and without steroid or immunosuppressive therapy within the past 4 weeks. Patients on immunomodulatory treatment (i.e. interferons, glatiramer acetate) were included in the study.
Exclusion criteria	Patients were not eligible for participation if they had received interferon the day prior to the session of the 30-min endurance test. Patients were also excluded if their diagnosis was not clearly established, they were suffering from an acute relapse or severe cognitive deficits, or had signs of any psychiatric disease. Furthermore, patients who were not able to perform the whole 30-min bicycle test were excluded from the immune-endocrine study.
Recruitment / selection of participants	The study recruited a group of MS patients (n=46) who underwent an inclusion test and were randomized later to an exercise or a control group.
Intervention(s)	After determination of the individual level of fitness, all subjects were randomized to either an 8- week bicycle ergometry training program tailored to their individual capabilities or to a waitlist control group. All subjects completed a 30-min endurance test, standardized tests of coordinative function, and a set of psychological questionnaires before and after the 8 weeks. In order to determine the individual levels of fitness, participants were subjected to a stepwise incremental cycle ergometry test. Based on the VO2max recorded during this exercise test, an individually adjusted 30-min constant load ergometry test was performed 1 week later. Fifteen patients in the training group underwent an 8- week training program tailored to their individual levels of fitness as measured by the fitness test prior to the training. For 8 weeks they exercised twice a week (mostly in the early evening) with

	an interval-training schedule for 30 min at a maximal intensity of 75% of the maximal watts taken from the ergometry results.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed but mostly RR · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - mixed · Group vs individual - NR · Delivered remotely vs in person - NR
Comparator	After determination of the individual level of fitness, all subjects were randomized to either an 8- week bicycle ergometry training program tailored to their individual capabilities or to a waitlist control group. All subjects completed a 30-min endurance test, standardized tests of coordinative function, and a set of psychological questionnaires before and after the 8 weeks. The subjects in the waitlist control group were offered the training program after the completion of the study.
Number of participants	28
Duration of follow-up	8 weeks
Indirectness	marked down as FU less than 3 months
Additional comments	NR

Study arms

aerobic training (N = 15)

wait list control (N = 13)

Characteristics

Study-level characteristics

Characteristic	Study (N = 28)
% Female Nominal	19

Arm-level characteristics

Characteristic	aerobic training (N = 15)	wait list control (N = 13)
Age Mean (SD)	39 (9)	40 (11)

Outcomes

Study timepoints

- 8 week

8 week outcomes

Outcome	aerobic training, 8 week, N = 15	wait list control, 8 week, N = 13
Multiple Sclerosis Fatigue Impact Scale (MFIS) - total Mean (SD)	21.1 (15)	30.3 (13.3)
Multiple Sclerosis Fatigue Impact scale - physical Mean (SD)	9.7 (6.8)	14.5 (6.4)
Multiple Sclerosis Fatigue Impact Scale (MFIS) - cognitive Mean (SD)	9.7 (7.5)	14 (6.2)
Multiple Sclerosis Fatigue Impact Scale (MFIS) - social Mean (SD)	1.7 (1.5)	1.8 (1.7)
Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - Fatigue/thinking Mean (SD)	1.9 (0.9)	2.7 (1)
Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - total Mean (SD)	1.6 (0.3)	2 (0.5)

Outcome	aerobic training, 8 week, N = 15	wait list control, 8 week, N = 13
Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - mood Mean (SD)	1.7 (0.5)	2.1 (0.7)
Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - social function Mean (SD)	1.8 (0.7)	1.9 (0.6)
SF-36, POMS, SES, HADS narrative data narrative data Custom value	None of the scales of the generic QoL measure SF-36 showed a significant training effect.	None of the scales of the generic QoL measure SF-36 showed a significant training effect.
SF-36, POMS, SES, HADS narrative data narrative data Custom value	No significant effects of the training program were found in the depression and anxiety subscale of	No significant effects of the training program were found in the depression and anxiety subscale of
SF-36, POMS, SES, HADS narrative data narrative data Custom value	Furthermore, no effects were seen on the self-efficacy scale (SES) and the POMS	Furthermore, no effects were seen on the self-efficacy scale (SES) and the POMS

Multiple Sclerosis Fatigue Impact Scale (MFIS) - total - Polarity - Lower values are better

Multiple Sclerosis Fatigue Impact scale - physical - Polarity - Lower values are better

Multiple Sclerosis Fatigue Impact Scale (MFIS) - cognitive - Polarity - Lower values are better

Multiple Sclerosis Fatigue Impact Scale (MFIS) - social - Polarity - Lower values are better

Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - Fatigue/thinking - Polarity - Lower values are better

Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - total - Polarity - Lower values are better

Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - mood - Polarity - Lower values are better

Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - social function - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

8 week outcomes – Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) – total – Mean SD-aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was*

Section	Question	Answer
		distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Multiple Sclerosis Fatigue Impact Scale (MFIS) – total – Mean SD-aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18*

Section	Question	Answer
		subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Multiple Sclerosis Fatigue Impact scale – physical – Mean SD - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Low

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Multiple Sclerosis Fatigue Impact Scale (MFIS) – cognitive – Mean SD - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Multiple Sclerosis Fatigue Impact Scale (MFIS) – social – Mean SD - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) - Fatigue/thinking – Mean SD-aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) – mood – Mean SD - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes – Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS) – social function – Mean SD - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was*

Section	Question	Answer
		distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes - SF-36, POMS, SES, HADS narrative data – Custom Value 0 - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18*

Section	Question	Answer
		subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes - SF-36, POMS, SES, HADS narrative data – Custom Value 1 - aerobic training-wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Low

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

8 week outcomes - SF-36, POMS, SES, HADS narrative data – Custom Value 2 - aerobic training - wait list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(MS patients (n=46) underwent an inclusion test and were randomized to an exercise or a control group. From the original sample of 46 MS patients, 18 subjects had to be excluded from the immune-endocrine study, as they did not reach at least 100 W or interrupted the endurance test more than 5 min earlier than required. Therefore nearly 1/3 pts unable to participate in study and unclear if this was pre or post randomisation so unsure how this was distributed across groups. Also left bias sample of pts more likely to tolerate the exercise regime)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(self reported pt outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(marked down as only 8 week FU)*

Sgoifo, 2017

Bibliographic Reference	**Sgoifo, A.; Bignamini, A.; La Mantia, L.; Celani, M. G.; Parietti, P.; Ceriani, M. A.; Marazzi, M. R.; Proserpio, P.; Nobili, L.; Protti, A.; Agostoni, E. C.; Integrated Imaginative Distention Therapy to Cope with Fatigue. DIMMI SI Study: The First Randomized Controlled Trial in Multiple Sclerosis; Neurology & Therapy; 2017; vol. 6 (no. 2); 213-223**

Study details

Secondary publication of another included study- see primary study for details	No additional information.
Other publications associated with this study included in review	No additional information.
Trial name / registration number	ClinicalTrials.gov registry - NCT02290990.
Study type	Randomised controlled trial (RCT)
Study location	Italy.
Study setting	Outpatient.
Study dates	September 2014-September 2015.
Sources of funding	No funding or sponsorship was received for this study or publication of this article.

Inclusion criteria	MS diagnosis and 1 month relapse free in people with MS. 18-75 years of age.
Exclusion criteria	Presence of severe co-morbidities; inability to practice Italian language; inability to provide informed consent.
Recruitment / selection of participants	Enrollment took place at Niguarda Hospital, Milan, Italy. Outpatients afferent to the specialised ms and Sleep Disorders Centres had been informed about the study through an unselective proposal by the neurologist who was able to verify the criteria for inclusion/exclusion.
Intervention(s)	Integrated Imaginative Distention (IID) is a therapy combining muscular and imaginative relaxation- IID was delivered by a single skilled psychotherapist through eight weekly training group sessions in 2 months. Each session lasted 60 min and involved eight people, homogeneous for condition. IID training consists of four practical steps, twice repeated: a selection of Jacobson relaxation exercises with breath awareness, motor imaging, body imaginative scan, imaginative experience. The study includes participants with insomnia and healthcare professionals. These groups are reported separately and so will not be included in the number of participants. Concomitant therapy: Not stated/unclear Intervention subgroups: Group vs. individual - Group Delivered remotely vs. in person - In person
Population subgroups	According to type: Not stated/unclear. According to disability: Not stated/unclear. Disease modifying treatment status: Not stated/unclear.
Comparator	Waiting list control.

Number of participants	48. The study includes participants with insomnia and healthcare professionals. These groups are reported separately and so will not be included in the number of participants.
Duration of follow-up	8 weeks (2 months). This is less than 3 months and so outcomes will be downgraded for indirectness.
Indirectness	Outcome indirectness due to short follow up period (<3 months).
Additional comments	Intention to treat. They report available case analysis data in the supplementary data where the outcomes are taken from.

Study arms

Relaxation (Integrated Imaginative Distention) (N = 24)

Integrated Imaginative Distention (IID) is a therapy combining muscular and imaginative relaxation- IID was delivered by a single skilled psychotherapist through eight weekly training group sessions in 2 months. Each session lasted 60 min and involved eight people, homogeneous for condition. IID training consists of four practical steps, twice repeated: a selection of Jacobson relaxation exercises with breath awareness, motor imaging, body imaginative scan, imaginative experience. The study includes participants with insomnia and healthcare professionals. These groups are reported separately and so will not be included in the number of participants.

Waiting list control (N = 24)

Waiting list control. The study includes participants with insomnia and healthcare professionals. These groups are reported separately and so will not be included in the number of participants.

Characteristics

Arm-level characteristics

Characteristic	Relaxation (Integrated Imaginative Distention) (N = 24)	Waiting list control (N = 24)
% Female No of events	n = 17 ; % = 70.8	n = 17 ; % = 70.8
Mean age (SD) Mean (SD)	43.5 (9.3)	47.9 (9.7)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 8 week (Outcome indirectness due to short follow up period (<3 months).)

Relaxation compared to waitlist control at 3-6 months - continuous outcomes (final values)

Outcome	Relaxation (Integrated Imaginative Distention), Baseline, N = 24	Relaxation (Integrated Imaginative Distention), 8 week, N = 22	Waiting list control, Baseline, N = 24	Waiting list control, 8 week, N = 23
Patient-reported outcome measure for MS fatigue (MFIS) Scale range: 0-84. Mean (SD)	40 (19.5)	34.3 (16.8)	39.3 (12)	38.1 (14.3)

Patient-reported outcome measure for MS fatigue (MFIS) - Polarity - Lower values are better

Outcome indirectness due to short follow up period (<3 months).

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Relaxation compared to wait list control at 3-6 months – continuous outcomes (final values) - Patient-reported outcome measure for MS fatigue (MFIS) – Mean SD - Relaxation (Integrated Imaginative Distention)-Waiting list control-t8

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness due to short follow up period (<3 months).)*

Straudi, 2014

Bibliographic Reference	**Straudi, S.; Martinuzzi, C.; Pavarelli, C.; Sabbagh Charabati, A.; Benedetti, M. G.; Foti, C.; Bonato, M.; Zancato, E.; Basaglia, N.; A task-oriented circuit training in multiple sclerosis: a feasibility study; BMC Neurology; 2014; vol. 14; 124**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with	NR

this study included in review	
Trial name / registration number	NR
Study location	Italy
Study setting	outpatient clinic of the Physical Medicine and Rehabilitation Department (Ferrara University Hospital)
Study dates	NR
Sources of funding	CM was supported by the Multiple Sclerosis Italian Society (grant 2010/R/6). CP and ASC were supported by Emilia Romagna region (grant 1786/2012).
Inclusion criteria	males and females, age 18 to 75, diagnosis of MS (primary or secondary progressive, relapsing-remitting), without relapses in the preceding 3 months, mild to moderate gait impairments referred to Expanded Disability Status Scale (EDSS) score between 4 and 5.5. Subjects were able to walk for at least 100 meters with no constant assistance (cane, crutch or brace) required.
Exclusion criteria	other conditions that may affect motor function, impaired cognitive functioning (Mini Mental Status Examination score less than 24).
Recruitment / selection of participants	Subjects were recruited at the outpatient clinic of the Physical Medicine and Rehabilitation Department (Ferrara University Hospital). Informed written consent was obtained from eligible subjects.
Intervention(s)	10 task-oriented training sessions (Monday-Friday) over 2 weeks; each session lasted 2 hours. Task-oriented circuit training included six different workstations in which subjects exercised for 5 minutes in each one (3 minutes of exercises and 2 minutes of rest). During each session, subjects underwent 2 laps that took about 60 minutes (6 workstation × 5 minutes × 2 laps), with 10 minutes of rest after each lap. In addition, walking endurance was trained by 30 minutes walking

	on the treadmill including rests if necessary. This was a progressive circuit and subjects while exercising received feedbacks (visual and auditory) by the physiotherapist. Rests were used to discuss about difficulties and to provide further feedbacks. One session included up to 3 patients and lasted 120 minutes, 5 days/week for 2 weeks. After the supervised 2 weeks, a home- exercise illustrated brochure was given to subjects so that they could independently train for the following 3 months. It included similar exercises that subjects learned during the 2 weeks, gait training (over ground or treadmill), stretching and strengthening exercises. pts were advised to perform an independent home training 3 times/week (60 minutes/each session). Subjects were asked to record in a diary the intensity and duration of exercise; they were allowed to call hospital to have further information and feedbacks.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - mixed · Group vs individual - group · Delivered remotely vs in person - both
Comparator	The control group (UC) did not receive any specific rehabilitation treatment for gait performance and mobility improvement. During the entire study, both groups were authorized, at will, to exercise in non-rehabilitative contexts.
Number of participants	24
Duration of follow-up	3 months
Indirectness	
Additional comments	NR

Study arms

task-oriented circuit class (N = 12)

usual care (N = 12)

Characteristics

Study-level characteristics

Characteristic	Study (N = 24)
% Female Nominal	17
Mean age (SD) Mean (SD)	52.58 (11.21)

Outcomes

Study timepoints

3 month

3 month outcomes

Outcome	task-oriented circuit class, 3 month, N = 12	usual care, 3 month, N = 12
FSS Mean (SD)	5.63 (0.78)	6.01 (0.91)
MSIS-29 - psychological 0-100 Mean (SD)	42.96 (16.2)	53.7 (16.43)
MSIS-29 PHYS score 0-100 Mean (SD)	49.16 (11)	53 (22.28)
Multiple Sclerosis Walking Scale – 12 0-100 Mean (SD)	65.42 (16.04)	71.11 (20.34)

FSS - Polarity - Lower values are better

MSIS-29 - psychological - Polarity - Higher values are better

MSIS-29 PHYS score - Polarity - Higher values are better

Multiple Sclerosis Walking Scale – 12 - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

3monthoutcomes-MultipleSclerosisWalkingScale–12-MeanSD-task-oriented circuit class-usual care-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3 month outcomes - MSIS-29 PHYS score – Mean SD - task-oriented circuit class-usual care-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3 month outcomes - MSIS-29 – psychological – MeanSD - task-oriented circuit class-usual care-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

3 month outcomes – FSS – Mean SD - task-oriented circuit class-usual care-t3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Thomas, 2014

Bibliographic Reference	**Thomas, P. W.; Thomas, S.; Kersten, P.; Jones, R.; Slingsby, V.; Nock, A.; Davies Smith, A.; Baker, R.; Galvin, K. T.; Hillier, C.; One year follow-up of a pragmatic multi-centre randomised controlled trial of a group-based fatigue management programme (FACETS) for people with multiple sclerosis; BMC Neurology; 2014; vol. 14; 109**

Study details

Secondary publication of another included	Thomas, S., Thomas, P. W., Kersten, P. et al. (2013) A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry 84(10): 1092-1099

study- see primary study for details	
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	UK
Study setting	FACETS was delivered in hotel meeting-room facilities, with the exception of one centre, where it was held in a rehabilitation hospital.
Sources of funding	Nr
Inclusion criteria	(1) clinically definite MS diagnosis, (2) fatigue impacting on daily life (Fatigue Severity Scale total score >4) and (3) ambulatory.
Exclusion criteria	(1) having taken part in a fatigue programme in the last year, (2) cognitive impairments (3) a relapse in the previous 3 months or (4) having started treatment with disease modifying or antidepressant drugs within the previous 3 months.
Recruitment / selection of participants	Participants were recruited in three UK centres (Poole, Bristol, Southampton/Portsmouth) from primary or secondary care, or via MS Society newsletters/websites. Recruitment took place from May 2008 to November 2009.
Intervention(s)	Applying Cognitive behavioural and Energy effectiveness Techniques to life Style (FACETS). Is a conceptual framework integrating elements from cognitive behavioural, social-cognitive, energy effectiveness, self-management and self-efficacy

	theories. The intervention consists of six sessions (90 min duration) held weekly and facilitated in groups of 6–12 by two health professionals (physios, nurses or OTs). Plus current local practice.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - NR · Disease modifying treatment status (currently using and not currently using) - NR · Group vs individual - group · Delivered remotely vs in person - in person
Comparator	current local practice only- This could have ranged from general advice and information provision about MS-fatigue to more detailed individualised management advice from a variety of health professionals
Number of participants	164
Duration of follow-up	1 year
Indirectness	Nil
Additional comments	NR

Study arms

FACETS (N = 81)

current local practice (N = 77)

Characteristics

Study-level characteristics

Characteristic	Study (N = 164)
% Female Nominal	119

Arm-level characteristics

Characteristic	FACETS (N = 81)	current local practice (N = 77)
Age Mean (SD)	48 (10.2)	50.1 (9.1)
Ethnicity - white english Nominal	68	69
Ethnicity - white british Nominal	7	5
Ethinicity - other Nominal	5	1
Ethinicity - other	5 (*empty data*)	*empty data*

Characteristic	FACETS (N = 81)	current local practice (N = 77)
Mean (SD)		
ethincity - not stated Nominal	4	5

Outcomes

Study timepoints

Baseline

1 year

5.5 month (5.5 months - some extra data reported in 2014 paper that was not reported in 2013 paper)

outcomes at 1 year

Outcome	FACETS, Baseline, N = NA	FACETS, 1 year, N = 62	FACETS, 5.5 month, N = NR	current local practice, Baseline, N =	current local practice, 1 year, N = 69	current local practice, 5.5 month, N = NR
Adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NR ; % = NR	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA
Dropout/no response - any reason	n = NA ; % = NA	n = 19 ; % = 23.46	n = NA ; % = NA	n = NA ; % = NA	n = 8 ; % = 10.3	n = NA ; % = NA

Outcome	FACETS, Baseline, N = NA	FACETS, 1 year, N = 62	FACETS, 5.5 month, N = NR	current local practice, Baseline, N =	current local practice, 1 year, N = 69	current local practice, 5.5 month, N = NR
No of events						

Adverse events - Polarity - Lower values are better

Dropout/no response - any reason - Polarity - Lower values are better

Note that for those with 'NA' at 5.5 months, this data was already reported in the 2013 evidence table and has not been re-extracted here. Only outcomes not reported in the 2013 paper at this time-point are extracted in this evidence table.

Difference in change from baseline between groups - 1 year

Outcome	FACETS vs current local practice, 5.5 month vs Baseline, N2 = 144, N1 = 159	FACETS vs current local practice, 1 year vs Baseline, N2 = 131, N1 = 159
Global fatigue severity (GFS) subscale of the FAI 1-7. Mean final values were 5.32 and 5.70 for FACETs and control at 1 year. Mean (95% CI)	NA (NA to NA)	-0.3 (-0.61 to 0.01)
Multiple Sclerosis Impact Scale-29 (MSIS-29) 0-100. Mean final values were 46.2 and 47.2 for FACETs and control at 1 year. Mean (95% CI)	NA (NA to NA)	-4.34 (-8.61 to -0.08)
MS Fatigue Self-Efficacy scale (MS-FSE) 10-100. Mean final values were 56.0 and 52.0 for FACETs and control at 1 year. Mean (95% CI)	NA (NA to NA)	6 (-1 to 12)

Outcome	FACETS vs current local practice, 5.5 month vs Baseline, N2 = 144, N1 = 159	FACETS vs current local practice, 1 year vs Baseline, N2 = 131, N1 = 159
Vitality subscale of the SF-36 0-100. Mean final values were 37.4 and 34.4 (5.5 months) and 47.70 and 32.43 (1 year) for FACETs and control. Mean (95% CI)	6.38 (0.45 to 12.32)	6.64 (0.84 to 12.44)
Multiple Sclerosis Impact Scale-29 (MSIS-29) - Physical subscale 0-100. Mean final values were 47.0 and 46.5 (5.5 months) and 47.4 and 50.5 (1 year) for FACETs and control. Mean (95% CI)	-0.81 (-5.91 to 4.28)	-4.74 (-9.4 to -0.08)

Global fatigue severity (GFS) subscale of the FAI - Polarity - Lower values are better

Multiple Sclerosis Impact Scale-29 (MSIS-29) - Polarity - Lower values are better

MS Fatigue Self-Efficacy scale (MS-FSE) - Polarity - Higher values are better

Vitality subscale of the SF-36 - Polarity - Higher values are better

Multiple Sclerosis Impact Scale-29 (MSIS-29) - Physical subscale - Polarity - Lower values are better

Note that for those with 'NA' at 5.5 months, this data was already reported in the 2013 evidence table and has not been re-extracted here. Only outcomes not reported in the 2013 paper at this time-point are extracted in this evidence table.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Outcomes at 1 year - Dropout/no response – any reason – No Of Events – FACETS - current local practice-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes at 1 year – Adverse events – No Of Events – FACETS - current local practice-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Outcomes at 1 year – Adverse events – Nominal – FACETS - current local practice-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – Global fatigue severity (GFS) subscale of the FAI -Mean Nine Five Percent CI-FACETS - current local practice-tBaseline-vs-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – Multiple Sclerosis Impact Scale – 29 (MSIS - 29) – Mean Nine Five Percent CI-FACETS - current local practice-tBaseline-vs-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – MS Fatigue Self-Efficacy scale (MS-FSE) – Mean Nine Five Percent CI-FACETS - current local practice-tBaseline-vs-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – Vitality subscale of the SF-36 – Mean Nine Five Percent CI-FACETS-current local practice-tBaseline-vs-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(only reports the secondary outcomes with significant difference which is the subdomain vitality of SF-26)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – Vitality subscale of the SF-36 – Mean Nine Five Percent CI-FACETS-current local practice-tBaseline-vs-t5.5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 5.5 months unclear if differs between groups as not reported)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(only reports the secondary outcomes with significant difference which is the subdomain vitality of SF-26)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – Multiple Sclerosis Impact Scale – 29 (MSIS-29) – Physical subscale-Mean Nine Five Percent CI-FACETS-current local practice-tBaseline-vs-t1

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 1 year 20% compared to 10% in control)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(only reports the secondary outcomes with significant difference which is the physical subscale)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Difference in change from baseline between groups – 1 year – Multiple Sclerosis Impact Scale – 29 (MSIS-29) – Physical subscale-Mean Nine Five Percent CI-FACETS-current local practice-tBaseline-vs-t5.5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(high rate of missing data in intervention group at 5.5 months and unclear if differed between groups as no details given)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(subjective pt reported outcomes with no blinding)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(only reports the secondary outcomes with significant difference which is the physical subscale)*
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Tramontano, 2018

Bibliographic Reference	**Tramontano, M.; Martino Cinnera, A.; Manzari, L.; Tozzi, F. F.; Caltagirone, C.; Morone, G.; Pompa, A.; Grasso, M. G.; Vestibular rehabilitation has positive effects on balance, fatigue and activities of daily living in highly disabled**

multiple sclerosis people: A preliminary randomized controlled trial; Restorative Neurology & Neuroscience; 2018; vol. 36 (no. 6); 709-718

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	Italy
Study setting	MS unit of Fondazione Santa Lucia, Italy
Study dates	April 2015- November 2016
Sources of funding	No financial support
Inclusion criteria	Clinical diagnosis of MS, age >20 and <65, EDSS 5-7, walking ability and minimal leg spasticity score of less than or equal to 1 on modified Ashworth scale.

Exclusion criteria	presence of neurological, orthopaedic, and severe cardiac co-morbidities and peripheral vestibular disorders, legal blindness in one or both eyes, documented MS-related exacerbation in the past 3 months and being involved in other research studies.
Recruitment / selection of participants	patients recruited and enrolled by consecutive sampling the the MS unit FSL between 2015 and 2016
Intervention(s)	Both groups performed 2 daily 40 min sessions 5x/wk for 4 weeks of conventional neuro rehabilitation for MS. The vestibular rehab group also performed an additional 20 min session 5x/wk for 4 wees to improve gaze stability and postural control. Patients were given gaze stability exercises by a physiotherapist for no more than 10 mins. They then performed blindfolded postural control exercises on a foam cushion supervised by a physiotherapist,.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - NR · According to disability (EDSS <6 and EDSS ≥6) - >6 · Disease modifying treatment status (currently using and not currently using) - NR · Group vs individual - individual · Delivered remotely vs in person - in person
Comparator	Control group performed 2 daily 40 min sessions 5x/wk for 4 weeks of conventional neuro rehabilitation for MS. This consisted of stretches, postural alignment, active assisted mobilisations and balance exercises.
Number of participants	30
Duration of follow-up	60 days
Indirectness	marked down as FU less than 3 months

Additional comments	NR

Study arms

Vestibular rehabilitation (N = 15)

Control - Neuro rehabilitation (N = 15)

Characteristics

Study-level characteristics

Characteristic	Study (N = 30)
% Female Nominal	17

Arm-level characteristics

Characteristic	Vestibular rehabilitation (N = 15)	Control - Neuro rehabilitation (N = 15)
Age Mean (SD)	50.64 (11.73)	45.77 (10.91)

Outcomes

Study timepoints

4 week

Outcomes at end of intervention 4 weeks

Outcome	Vestibular rehabilitation, 4 week, N = 13	Control - Neuro rehabilitation , 4 week, N = 10
FSS score 0-63 Mean (SD)	49.2 (7.6)	47.1 (11.9)
Barthel Index 0-20 Mean (SD)	84.5 (10.3)	81.3 (12.6)

FSS score - Polarity - Lower values are better

Barthel Index - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

outcomesatendofintervention4weeks-FSSscore-MeanSD-Vestibular rehabilitation-Control - Neuro rehabilitation -t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher missingness in the control group but both similar f2f intervention for same period of days/weeks so missingness likely by chance)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(subjective pt reported outcomes and pts were not blinded to intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable

Outcomes at end of intervention 4 weeks – Barthel Index – Mean SD -Vestibular rehabilitation-Control - Neuro rehabilitation -t4

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher missingness in the control group but both similar f2f intervention for same period of days/weeks so missingness likely by chance)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(subjective pt reported outcomes and pts were not blinded to intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable

van den Akker, 2017

Bibliographic Reference	**van den Akker, L. E.; Beckerman, H.; Collette, E. H.; Twisk, J. W.; Bleijenberg, G.; Dekker, J.; Knoop, H.; de Groot, V.; Group, Trefams-Ace Study; Cognitive behavioral therapy positively affects fatigue in patients with multiple sclerosis: Results of a randomized controlled trial; Multiple Sclerosis; 2017; vol. 23 (no. 11); 1542-1553**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	Van Kessel K, Moss-Morris R, Willoughby E, et al. A randomized controlled trial of cognitive behaviour therapy for multiple sclerosis fatigue. Psychosom Med 2008; 70(2): 205–213. Beckerman H, Blikman LJ, Heine M, et al. The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: The design of the TREFAMS-ACE programme. Trials 2013; 12(14): 250.
Trial name / registration number	TREFAMS-ACE Study Group
Study location	netherlands
Study setting	VU University Medical Center in Amsterdam, the Radboud University Medical Centre, and the St. Maartenskliniek in Nijmegen - 3 Dutch medical centres
Study dates	December 2011- December 2014
Sources of funding	The author(s) received no financial support for the research, authorship, and/or publication of this article
Inclusion criteria	Definitive diagnosis of MS, (b) experience of severe fatigue (CIS20r fatigue $\geqslant$35), (c) be ambulatory (Expanded Disability Status Scale (EDSS) score $\leqslant$6), (d) no signs of exacerbation, (e) no clinical depression (Hospital Anxiety and Depression

	Scale (HADS depression) score >11), and (f) no severe comorbid disorders (medical history taking and results of the blood draw).
Exclusion criteria	The exclusion criteria are: (a) depression; (b) primary sleep disorders; (c) severe co-morbidity; (d) current pregnancy or having given birth in the past 3 months; (e) pharmacological treatment for fatigue that was started in the past 3 months (for example, Amantadine, Modafinil, Ritalin, Pemoline); (f) non-pharmacological therapies for fatigue that took place in the past 3 months.
Recruitment / selection of participants	Participants were recruited in three Dutch centres (VU University Medical Centre in Amsterdam, the Radboud University Medical Centre, and the St. Maartenskliniek in Nijmegen), via referral from physicians at regional centres, personal invitation letters, advertisement via Internet and posters/pamphlets. Interested patients were invited for an intake interview to provide additional information about the trial and to test for eligibility. The intake consisted of a structured medical history taking, a structured physical examination, questionnaires, and a blood draw
Intervention(s)	12 sessions of individual face-to-face therapy spread over a 4-month period (8 sessions in the first 2months, 4 sessions in the last 2months). The CBT protocol consists of 10 modules: formulating goals, regulating sleep/wake pattern, changing beliefs regarding MS, changing beliefs regarding fatigue, reduce the focus on fatigue, regulation of physical, social, and mental activity, addressing the role of the environment, and handling pain. . After an intake session in which information was provided on the cognitive behavioural model of MS-related fatigue and CBT, patients started by formulating their treatment goals. The following sessions addressed the fatigue-maintaining cognitions and behaviours and were aimed at realizing the set treatment goals. The final therapy sessions focused on integrating the obtained skills into daily life and on how patients should handle relapses of fatigue. All CBT therapists were state-certified healthcare psychologists who received a 3-day course on how to deliver CBT according to the TREFAMS-CBT protocol.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) NR · Group vs individual - individual · Delivered remotely vs in person - in person

Comparator	protocolled treatment by an experienced MS nurse that included three consultations of 45minutes over a 4-month period, and intended. It was developed to control for attention from a MS-professional and information about fatigue, that is, to control for non-specific treatment effects, this should thus not be considered as an active or lower dose treatment. The study protocol did not allow the MS nurses to provide active advices or refer patients to a psychologist or other healthcare professionals for the treatment of fatigue. During the consultations, the patient received written and oral information about MS-related fatigue, and patients discussed their personal experiences in coping with fatigue and other fatigue-related issues. The consultations were guided by the questions that patients had about their fatigue and the provided booklet.
Number of participants	91
Duration of follow-up	16, 26 and 52 weeks post intervention
Indirectness	None
Additional comments	NR

Study arms

CBT (N = 44)

MS nurse control (N = 47)

Characteristics

Arm-level characteristics

Characteristic	CBT (N = 44)	MS nurse control (N = 47)
% Female Sample size	n = 31 ; % = 70.5	n = 39 ; % = 83
Mean age (SD) Mean (SD)	50.6 (8.3)	46.4 (11.6)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
Time since diagnosis (years) Median (IQR)	8.2 (2.9 to 14.2)	5.2 (2.1 to 15)
EDSS score Median (IQR)	3 (2.8 to 3.6)	2.5 (2.3 to 3)
Relapsing-remitting Sample size	n = 32 ; % = 72.7	n = 35 ; % = 74.5
Primary progressive Sample size	n = 6 ; % = 13.6	n = 4 ; % = 8.5
Secondary progressive	n = 5 ; % = 11.4	n = 7 ; % = 14.9

Characteristic	CBT (N = 44)	MS nurse control (N = 47)
Sample size		
Other Sample size	n = 1 ; % = 2.3	n = 0 ; % = 0
Unknown Sample size	n = 0 ; % = 0	n = 1 ; % = 2.1

Outcomes

Study timepoints

Baseline

16 week (end of treatment period)

52 week (~9 months after end of intervention)

16 week outcomes

Outcome	CBT, Baseline, N = 44	CBT, 16 week, N = 39	CBT, 52 week, N = 39	MS nurse control, Baseline, N = 46	MS nurse control, 16 week, N = 35	MS nurse control, 52 week, N = 35
CIS20r fatigue 8-56	42.9 (8.5)	34 (11.2)	38.9 (9.7)	44.2 (6)	40.3 (8.2)	39.5 (9)

Outcome	CBT, Baseline, N = 44	CBT, 16 week, N = 39	CBT, 52 week, N = 39	MS nurse control, Baseline, N = 46	MS nurse control, 16 week, N = 35	MS nurse control, 52 week, N = 35
Mean (SD)						
FSS score 1-7 Mean (SD)	5.4 (0.7)	4.5 (1.1)	5 (0.9)	5.5 (0.8)	5.2 (0.7)	5.1 (0.9)
MFIS total 0-84 Mean (SD)	47.3 (12.5)	38.7 (16.4)	42.5 (12.2)	47.7 (9.6)	41.2 (11.9)	39.1 (13.8)
MFIS physical subscore Scale 0-36 Mean (SD)	21.6 (5.7)	17.8 (7.3)	20.3 (6.1)	22.5 (5)	19.6 (6.3)	18.1 (6.8)
MFIS cognitive subscore Scale 0-40 Mean (SD)	21.5 (7.8)	17.4 (8.8)	18.6 (7.3)	20.8 (6.2)	18.1 (7.3)	17.6 (7.4)
MFIS psychosocial subscore Scale 0-8 Mean (SD)	4.3 (1.6)	3.4 (1.8)	3.6 (1.6)	4.3 (1.4)	3.4 (1.3)	3.4 (1.6)

Outcome	CBT, Baseline, N = 44	CBT, 16 week, N = 39	CBT, 52 week, N = 39	MS nurse control, Baseline, N = 46	MS nurse control, 16 week, N = 35	MS nurse control, 52 week, N = 35
SF-36 vitality (0 - 100) Mean (SD)	42.3 (13.4)	53.2 (17.2)	46.9 (16.6)	40.4 (14.7)	45.4 (12.3)	46.2 (17.1)
SF-36 physical functioning (0 - 100) Mean (SD)	55.8 (22.1)	58.2 (24.8)	55.9 (22.3)	62.2 (20.4)	61.3 (20.1)	60.3 (22)
SF-36 physical role functioning (0 - 100) Mean (SD)	20.5 (31.6)	48 (40.1)	28.8 (37.4)	16.3 (28.5)	32.4 (35.5)	38.5 (39.4)
SF-36 emotional role functioning (0 - 100) Mean (SD)	60.6 (41.5)	74.8 (36.3)	71.8 (36.3)	67.4 (41.9)	72.2 (39.4)	71.2 (42.4)
SF-36 social functioning (0 - 100) Mean (SD)	61.1 (18.5)	68.9 (21)	67.7 (19)	61.7 (18.9)	74.3 (16.8)	73.6 (20.6)
SF 36 mental health (0 - 100) Mean (SD)	64.5 (13.5)	71.7 (12.4)	68.3 (15.4)	68.8 (12.6)	71.7 (13.9)	71.1 (16.1)

Outcome	CBT, Baseline, N = 44	CBT, 16 week, N = 39	CBT, 52 week, N = 39	MS nurse control, Baseline, N = 46	MS nurse control, 16 week, N = 35	MS nurse control, 52 week, N = 35
SF-36 general health (0 - 100) Mean (SD)	49.5 (12.6)	46.5 (16.2)	48.6 (15.3)	53.8 (14.5)	48.2 (13.4)	50.3 (15.3)
SF-36 bodilly pain (0 - 100) Mean (SD)	68.8 (17.5)	73.3 (19.7)	70.4 (20.7)	66.7 (20.2)	68.6 (21.3)	70.5 (24.6)
CIS20r concentration Scale 5-35. Mean (SD)	22.7 (8.5)	20.1 (7.6)	20.8 (7)	22.1 (6.6)	21.3 (7.3)	20.4 (8)
Serious adverse events None reported to be directly related to intervention - MS relapse or surgery No of events	n = NA ; % = NA	n = 1 ; % = 2.6	n = 4 ; % = 10.3	n = NA ; % = NA	n = 2 ; % = 5.7	n = 3 ; % = 8.6
Compliance Custom value	NA	64% completed at least 10 sessions. Median (IQR) 10.5 (8.8-11.0) sessions	NA	NA	79% completed all three consultations, median (IQR) 3 (3-3).	NA
Improvement of at least 8 points on CIS20r fatigue	n = NA ; % = NA	n = 22 ; % = 56.4	n = NR ; % = NR	n = NA ; % = NA	n = 9 ; % = 25.7	n = NR ; % = NR

Outcome	CBT, Baseline, N = 44	CBT, 16 week, N = 39	CBT, 52 week, N = 39	MS nurse control, Baseline, N = 46	MS nurse control, 16 week, N = 35	MS nurse control, 52 week, N = 35
Established as clinically relevant change No of events						

CIS20r fatigue - Polarity - Lower values are better

FSS score - Polarity - Lower values are better

MFIS total - Polarity - Lower values are better

SF-36 vitality - Polarity - Higher values are better

SF-36 physical functioning - Polarity - Higher values are better

SF-36 physical role functioning - Polarity - Higher values are better

SF-36 emotional role functioning - Polarity - Higher values are better

SF-36 social functioning - Polarity - Higher values are better

SF 36 mental health - Polarity - Higher values are better

SF-36 general health - Polarity - Higher values are better

SF-36 bodilly pain - Polarity - Higher values are better

CIS20r concentration - Polarity - Lower values are better

Note baseline values given for n=44 and n=46, despite n=44 vs. n=47 being randomised.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

CIS20r fatigue 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS total 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 vitality 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 physical functioning 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 physical role functioning 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 emotional role functioning 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 social functioning 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 mental health 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 general health 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 general health 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 mental health 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 social functioning 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 emotional role functioning 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 physical role functioning 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 physical functioning 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 vitality 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS total 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

FSS score 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

CIS20r fatigue 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 bodily pain 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

SF-36 bodily pain 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
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Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS physical subscore 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS physical subscore 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS cognitive subscore 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
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Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS cognitive subscore 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS psychosocial subscore 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

MFIS psychosocial subscore 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

CIS20r concentration 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

CIS20r concentration 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(study reports assessors were blinded but main outcomes are pt self reported outcomes so may be bias due to unblinded pts and subjective outcomes)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events 52 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Compliance 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

CIS20r 8-point improvement 16 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(higher rate of missingness in the control group generally not related to intervention)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Wahls, 2021

Bibliographic Reference	**Wahls, T. L.; Titcomb, T. J.; Bisht, B.; Eyck, P. T.; Rubenstein, L. M.; Carr, L. J.; Darling, W. G.; Hoth, K. F.; Kamholz, J.; Snetselaar, L. G.; Impact of the Swank and Wahls elimination dietary interventions on fatigue and quality of life in relapsing-remitting multiple sclerosis: The WAVES randomized parallel-arm clinical trial; Multiple Sclerosis Journal Experimental Translational & Clinical; 2021; vol. 7 (no. 3); 20552173211035399**

Study details

Trial name / registration number	NCT02914964
Study location	USA
Study setting	Outpatient
Study dates	Recruitment took place from August 2016 to May 2019 and follow-up from February 2017 to January 2020
Sources of funding	Supported in part by the National Multiple Sclerosis Society grant RG-1506- 04312, the Institute for Clinical and Translational Science (ICTS) at the University of Iowa, and University of Iowa institutional funds. The ICTS is supported by the National Institutes of Health Clinical and Translational Science Award program. One author is a research trainee of the University of Iowa Fraternal Order of Eagles Diabetes Research Center and is supported by the Carter Chapman Shreve Family Foundation and the Carter Chapman Shreve Fellowship Fund for diet and lifestyle research conducted by the Wahls Research team at the University of Iowa. In-kind support was provided by the University of Iowa College of Public Health Preventive Intervention Center.
Inclusion criteria	aged 18-70 years; neurologist-confirmed RRMS based on the 2010 McDonald criteria; moderate to severe fatigue (Fatigue Severity Scale score of at least 4.0); an ability to walk 25 feet with unilateral or no support; were not pregnant or planning on becoming pregnant; and were willing to comply with all aspects of the study intervention and assessments.
Exclusion criteria	MS-relapse or change in disease modifying drug use within the previous 12 weeks; change in medication to manage MS symptoms; low body weight (BMI <19 kg/m2); severe mental impairment; self-reported adverse reactions to gluten-containing foods; diagnosed conditions including eating disorders, severe psychiatric disorders, celiac disease, kidney stones, heart failure, angina, or liver cirrhosis; and insulin, warfarin, radiation, or chemotherapy use.
Recruitment / selection of participants	Recruitment took place from August 2016 to May 2019. Recruited from within a 500-mile radius of Iowa City, Iowa. The research team worked with local NMSS support groups, regional MS centers, the North American Research Committee on Multiple Sclerosis, the University of Iowa Hospitals & Clinics Department of Neurology, the Iowa City VA Health Care System neurology clinic, the Swank Foundation, terrywahls.com, and other organizations to recruit study participants

Intervention(s)	Modified Palaeolithic elimination diet (Wahls): initial 12-week run-in period for observation of usual diet and stability of pre-intervention outcomes. Randomised to Wahls diet for 24 weeks. First 12 weeks involved 2 in-person and five telephone-based nutrition counselling sessions from an intervention registered dietician. Also received personalised emails with feedback on their dietary checklists every 4 weeks. At week 12, counselling sessions discontinued but participants allowed to contact dietician at any time for support. The Wahls diet recommends 6-9 servings of fruit and vegetables and provides 6-12 ounces meat per day according to gender. It excludes all grain, legumes, eggs, and dairy (except for clarified butter or ghee). Nightshade vegetables were also excluded in the Wahls group during the first 12-week period from baseline and then the intervention RDs provided guidance to reintroduce nightshades during the second 12-week period on the diet. Instructed to follow their assigned diet ad libitum and were given the following daily supplement regimen: 1 teaspoon cod liver oil, 1,000 mg methyl-B12, 1,000 mg methylfolate, a multivitamin without iron, and 5,000 IU vitamin D3, the latter of which was adjusted based on serum levels with a target range of 40 to 80 ng/mL.
Population subgroups	None
Comparator	Low-saturated fat diet (Swank): initial 12-week run-in period for observation of usual diet and stability of pre-intervention outcomes. Randomised to Wahls diet for 24 weeks. First 12 weeks involved 2 in-person and five telephone-based nutrition counselling sessions from an intervention registered dietician. Also received personalised emails with feedback on their dietary checklists every 4 weeks. At week 12, counselling sessions discontinued but participants allowed to contact dietician at any time for support. The Swank diet restricts saturated fat to 15 g per day and provides 20-50 g (4-10 teaspoons) unsaturated fat per day and four servings each of grains, whole preferred, and fruits and vegetables. Instructed to follow their assigned diet ad libitum and were given the following daily supplement regimen: 1 teaspoon cod liver oil, 1,000 mg methyl-B12, 1,000 mg methylfolate, a multivitamin without iron, and 5,000 IU vitamin D3, the latter of which was adjusted based on serum levels with a target range of 40 to 80 ng/mL.
Number of participants	87 randomised, 72 analysed at 24 weeks
Duration of follow-up	Up to 24 weeks - end of intervention
Indirectness	None

Additional comments	Subgroups: Type of MS: relapsing-remitting EDSS score: unclear, likely <6.0 as had to be able to walk unassisted Disease modifying treatment status: majority using some form of disease-modifying treatment in both groups Group vs individual: individual Delivered remotely vs in person: remotely based on nature of intervention (diet)

Study arms

Modified Palaeolithic elimination diet (Wahls) (N = 43)

Low-saturated fat diet (Swank) (N = 44)

Characteristics

Arm-level characteristics

Characteristic	Modified Palaeolithic elimination diet (Wahls) (N = 43)	Low-saturated fat diet (Swank) (N = 44)
% Female Sample size	n = 32 ; % = 82.1	n = 35 ; % = 92.1
Mean age (SD)	46.4 (1.5)	46.9 (1.7)

Characteristic	Modified Palaeolithic elimination diet (Wahls) (N = 43)	Low-saturated fat diet (Swank) (N = 44)
Mean (SE)		
Caucasian Sample size	n = 38 ; % = 97.4	n = 36 ; % = 94.7
Comorbidities Custom value	NR	NR
MS duration (years) Mean (SE)	9.3 (1)	12.1 (1.6)
None Sample size	n = 10 ; % = 25.6	n = 13 ; % = 34.2
Oral Sample size	n = 11 ; % = 28.9	n = 11 ; % = 28.2
Injectable Sample size	n = 12 ; % = 30.8	n = 10 ; % = 26.3
Infused Sample size	n = 6 ; % = 15.4	n = 4 ; % = 10.5
Fatigue Severity Score Mean (SE)	5.2 (0.2)	5.3 (0.2)

Note characteristics are given for n=39 (Wahls) and n=38 (Swank) that completed at least 12 weeks of the intervention

Outcomes

Study timepoints

- Baseline
- 24 week (24 weeks - end of intervention)

Results - raw data

Outcome	Modified Palaeolithic elimination diet (Wahls), Baseline, N = 43	Modified Palaeolithic elimination diet (Wahls), 24 week, N = 35	Low-saturated fat diet (Swank), Baseline, N = 44	Low-saturated fat diet (Swank), 24 week, N = 37
Fatigue Severity Score Scale reported to be 1-9. Mean (SE)	5.19 (0.2)	3.87 (0.27)	5.32 (0.18)	4.32 (0.25)
MFIS - total score Modified Fatigue Impact Scale. Scale 0-84. Mean (SE)	45.6 (1.99)	26.5 (3)	40.7 (2.4)	30.2 (2.63)
MFIS - physical subscore Scale 0-36. Mean (SE)	20.6 (0.98)	11.3 (1.17)	18.9 (1.36)	14.7 (1.4)

Outcome	Modified Palaeolithic elimination diet (Wahls), Baseline, N = 43	Modified Palaeolithic elimination diet (Wahls), 24 week, N = 35	Low-saturated fat diet (Swank), Baseline, N = 44	Low-saturated fat diet (Swank), 24 week, N = 37
MFIS - cognitive subscore Scale 0-40. Mean (SE)	20.4 (1.24)	12.8 (1.73)	17.6 (1.37)	13.5 (1.37)
MFIS - psychosocial subscore Scale 0-8. Mean (SE)	4.59 (0.31)	2.37 (0.35)	4.18 (0.4)	3.03 (0.34)
MSQOL-54 mental composite Scale 0-100. Mean (SE)	62.3 (3.49)	76.3 (3.59)	67.7 (2.9)	73.6 (2.81)
MSQoL-54 physical composite Scale 0-100. Mean (SE)	53.8 (3.05)	71 (3.2)	55.6 (3.01)	64.9 (3.15)
Serious adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Adherence to diet Definition unclear - Adherence to diet specific food components (i.e., grams of gluten for the Wahls group and grams of saturated fat for the Swank group) was monitored using three-day weighed	n = NA ; % = NA	n = 26 ; % = 74.3	n = NA ; % = NA	n = 30 ; % = 81.1

Outcome	Modified Palaeolithic elimination diet (Wahls), Baseline, N = 43	Modified Palaeolithic elimination diet (Wahls), 24 week, N = 35	Low-saturated fat diet (Swank), Baseline, N = 44	Low-saturated fat diet (Swank), 24 week, N = 37
food records collected on three consecutive days including one weekend day in the week prior to each study visit and were analyzed at the University of Minnesota Nutrition Coordinating Center using Nutrition Data System for Research software No of events				

Fatigue Severity Score - Polarity - Lower values are better

MFIS - total score - Polarity - Lower values are better

MFIS - physical subscore - Polarity - Lower values are better

MFIS - cognitive subscore - Polarity - Lower values are better

MFIS - psychosocial subscore - Polarity - Lower values are better

MSQOL-54 mental composite - Polarity - Higher values are better

MSQoL-54 physical composite - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FSS 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS total score 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS physical subscore 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS cognitive subscore 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MFIS psychosocial subscore 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQoL-54 mental composite 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results MSQoL-54 physical composite 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results serious adverse events 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Results adherence to diet 24 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Yazgan, 2019

Bibliographic Reference	**Yazgan, Y. Z.; Tarakci, E.; Tarakci, D.; Ozdincler, A. R.; Kurtuncu, M.; Comparison of the effects of two different exergaming systems on balance, functionality, fatigue, and quality of life in people with multiple sclerosis: A randomized controlled trial; Multiple Sclerosis and Related Disorders; 2019; vol. 39; 101902**

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study location	Istanbul, Turkey
Study setting	MS outpatient clinic of Neurology department
Study dates	NR
Sources of funding	funded by TUBITAK 1002- Short term R and D Funding programme and TUBITAK BIDEB 211- A national scholarship programme for PHD students.

Inclusion criteria	Participants who were ambulatory, were in the stable phase of the disease, without relapses or worsening in the last 3 months, with an EDSS between 2.5 and 6, aged between 25-60 years.
Exclusion criteria	Had a diagnosis of any other disorder affecting the central nervous system, musculoskeletal disorder, pregnancy, blurred vison, psychiatric problems, or severe cognitive impairment.
Recruitment / selection of participants	participants who were diagnosed with MS and followed up regularly at the MS outpatients clinic volunteered to participate.
Intervention(s)	Video game-based balance training: 16 weeks individual physiotherapist supervised sessions (two 60 min sessions per week) for 8 consecutive weeks. Each session started with 010 mins cycling for warm up then the participants performed the games as their specified intervention. group 1 - the Nintendo Wii fit training protocol comprised of games such as Penguin slide, table tilt, heading and balance bubble. game levels and repetition number for each pt were determined by physios to standardise the progression of exercises. group 2 - The Balance trainer group consisted of games including; collect apples, outline, paddle war and evaluation of movement games which were included in the device software and allowed the pts to perform balance in different directions. progression was provided by increasing the repetition number of the games and changing the difficulty rating. The two groups were combined for the purpose of this review into a balance training arm.
Population subgroups	· According to type (relapsing remitting MS, secondary progressive MS, and primary progressive MS) - mixed · According to disability (EDSS <6 and EDSS ≥6) - <6 · Disease modifying treatment status (currently using and not currently using) - NR

	· Group vs individual - individual · Delivered remotely vs in person - in person
Comparator	group 3- participants in the control group were placed on a wait list and invited to start exercising using the Nintendo wii fit or balance trainer at the end of the study period
Number of participants	N=47 randomised, n=42 analysed
Duration of follow-up	post intervention - 8 weeks
Indirectness	marked down for indirectness as FU less than 3 months
Method of analysis	Per protocol - all apart from those with missing data

Study arms

Video-gamed based balance training (N = 32)

Includes two groups that were randomised separately but combined for the purpose of this review as they are both balance training groups (Nintendo Wii Fit and Balance Trainer devices)

Wait list control (N = 15)

Characteristics

Arm-level characteristics

Characteristic	Video-gamed based balance training (N = 32)	Wait list control (N = 15)
% Female Sample size	n = 25 ; % = 78.1	n = 13 ; % = 86.7
Mean age (SD) Mean (SD)	45.2 (9.89)	40.66 (8.82)
Ethnicity Custom value	NR	NR
Comorbidities Custom value	NR	NR
EDSS score Scale 0-10. Higher indicates increased disability. Mean (SD)	4.01 (1.43)	4.06 (1.26)
Years since MS diagnosis Mean (SD)	13.33 (6.7)	11.06 (5.7)
Relapsing-remitting MS Sample size	n = 19 ; % = 70.37	n = 14 ; % = 93.3
Secondary progressive MS Sample size	n = 2 ; % = 7.41	n = 0 ; % = 0

Characteristic	Video-gamed based balance training (N = 32)	Wait list control (N = 15)
Primary progressive MS Sample size	n = 1 ; % = 3.7	n = 0 ; % = 0
Progressive-relapsing MS Sample size	n = 5 ; % = 18.52	n = 1 ; % = 6.7

Note that baseline values are given for the number analysed (n=27 vs. n=15) rather than the number randomised (n=32 vs. n=15).

Outcomes

Study timepoints

- Baseline
- 8 week

Outcomes 8 weeks

Outcome	Video-gamed based balance training, Baseline, N = 32	Video-gamed based balance training, 8 week, N = 27	Wait list control, Baseline, N = 15	Wait list control, 8 week, N = 15
FSS 9-63 Mean (SD)	47.1 (14.06)	35.96 (12.98)	40.86 (17.47)	40.33 (17.71)
MusiQol 0-100	63.71 (13.01)	73.08 (11.63)	63.28 (13.85)	63.08 (13.17)

Outcome	Video-gamed based balance training, Baseline, N = 32	Video-gamed based balance training, 8 week, N = 27	Wait list control, Baseline, N = 15	Wait list control, 8 week, N = 15
Mean (SD)				
Adverse events No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0
Compliance Statement that all in the intervention group completed 16 sessions of exercise with excellent adherence to exergaming systems. Custom value	NA	Statement that all in the intervention group completed 16 sessions of exercise with excellent adhere	NA	NR

FSS - Polarity - Lower values are better

MusiQol - Polarity - Higher values are better

Adverse events - Polarity - Lower values are better

Note that baseline values are given for those that were analysed (n=27 vs. n=15) and not those randomised.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Results FFS 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum three months in protocol)*

Results MUSIQOL 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum three months in protocol)*

Results adverse events 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum three months in protocol)*

Results compliance 8 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirectly applicable *(time-point less than minimum three months in protocol)*

D.2 Studies extracted in previous review version – bold text indicates outcomes relevant to the new protocol that have been added in the updated review

Table 4: Bombardier 2008

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Bombardier et al. The efficacy of telephone counselling for health promotion in people with multiple sclerosis: a randomised controlled trial. Arch	RCT Randomisation computer generated Allocation concealment shown by envelopes Single blind-	N=130 Motivational interviewing N=70 (all analysed) Control N=60 (all analysed)	Community-residing persons with clinically definite MS. Participants were 18 yrs or over and able to walk 90 m without assistance. EDSS 5.5 or less. All types of MS included. Exclusion. Reported significant depressive symptoms or medical conditions contraindicating exercises			Motivational interviewing 60-90 motivational interview and goal setting meeting. 5 follow up telephone counselling sessions	control	12 wks	None reported
				Motivational interviewing N=70	**Control N=60**				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Phys med Rehabil 2008; 89: 1849-1856	assessor blinding.		Age y	47.5	45				
			Women %	75.7	80.0				
			Relapsing-remitting	69.6	75.0				

Results: All are median(IQR) changes from baseline to 12 weeks

	Median (lower quartile, upper quartile)		
	Motivational interviewing N=70	**Control N=60**	P
Health Promotion Lifestyle Profile HPLP total	0.2 (0.0 to 0.3)	0.0 (-0.2 to 0.2)	<.01
MS modified Fatigue Impact Scale (scale 0-84)	-1 (-9.5 to 0.5)	0 (-7 to 5)	0.02
Modified Fatigue Impact Scale – physical subscale (scale 0-36)	**-1 (-4.0 to 1.0)**	**0 (-3.0 to 3.0)**	**0.02**
Modified Fatigue Impact Scale – cognitive subscale (scale 0-40)	**1 (4 to 0)**	**0 (4 to 4)**	**0.11**

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Source of funding
Modified Fatigue Impact Scale – psychosocial subscale (scale 0-36)		**0 (1 to 0)**	**0 (1 to 1)**	**0.31**				
SF-36 mental component (scale 0-100)		3.6 (0.3 to 8.0)	0.7 (-2.7 to 6.3)	0.02				
SF-36 Physical component (scale 0-100)		-0.3 (-3.4 to 2.1)	1.0 (-2.8 to 5.1)	0.11				
TMT-A s		0.0 (-6.0 to 2.0)	-2.0 (-8.5 to 0.5)	0.15				
TMT-B s		-3.5 (-23.0 to 2.0)	-2.0 (-14.5 to 9.0)	0.14				
Bicycle ergometer time s		0 (-45 to 23)	0 (-34 to 31)	0.62				
Self-selected walking speed		-0.4 (-2.0 to 0.5)	0.0 (-1.7 to 1.0)	0.28				
MS Functional Composite		**0.5 (0.0 to 1.2)**	**0.4 (0.3 to 0.7)**	**0.26**				

Table 5: Cakit 2010

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Cakit et al. Cycling progressive resistance training for people with multiple sclerosis – a randomised controlled study. Am J Phys med Rehabil 2010; 89; 446-457	RCT Computerised randomisation. No report of allocation concealment. Assessor blinding clear.	N=45 (randomised), with 15 in each of the 3 groups Supervised resistance training + balance N=14 analysed, with loss of 1 due to acute exacerbation Home-based resistance training + balance N=10 analysed, with loss of 5 due to work related reasons 92), acute exacerbations	Patients with clinically or laboratory definite relapsing-remitting or secondary progressive MS, EDSS less than or equal to 6.0, and the ability to stand independently for > 3 secs and if they had been without steroid and immunosuppressive therapy within the past 4 wks. Exclusions: Severe MS, acute exacerbation of their symptoms either immediately before or during the program, if they were actively involved in physical therapy treatment or participated in a regular exercise program 4 wks before the beginning of exercise program, and if they were unable to cycle on a static bike. Patients with visual involvement or diplopia, high-level spasticity of the lower limbs, and persistent severe fatigue or depression were also excluded.	**Supervised Resistance training and balance** Twice a week over 2 mths Progressive resistance training in a static bicycle ergometer Plus 20-25 mins of balance exercises **Home based resistance training and balance exercise**	Control – no treatment.	8 wks	None reported

	Supervised Resistance + balance	Home based resistance and balance	Control

Reference	Study type	No. pts	Patient characteristics				Intervention	Comparison	Length of follow-up	Source of funding
		(2) and unknown(1). Control N=9 analysed, with loss of 6 due to acute exacerbation 93) and unknown(3). Thus high risk of attrition bias.	M:F	9/5	8/2	6/3	Lower limb muscle strength and balance Same training as above without bicycle training			
			Age y	36.4	43.0	35.5				
			Assitance device	4	2	3				
			No. exacerbations	3.9	3.2	4.2				
			Fall freq last yr	2.0	2.8	2.4				
			Physical activity tolerance m	395.4	404.0	473.3				

Results [mean (sd) – all change from baseline to 8 weeks].

	Resistance + balance	Home based resistance and balance	Control	
10-m walking test s mean (SD) – change from baseline to 8 weeks	-1.9 (1.2)	-0.08 (0.7)	0.1 (0.8)	
Duration of exercise mins	8.4 (3.8)	1.8 (0.5)	3.3 (5.3)	

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Tolerated maximum work load on bicycle– change from baseline to 8 weeks		123.6 (18.0)	36.0 (8.2)	22.0 (13.03)					
Timed up and go test score secs– change from baseline to 8 weeks		-1.3 (1.2)	0.2 (0.5)	-0.2 (0.8)					
Dynamic Gait Index– change from baseline to 8 weeks		2.7 (0.5)	0.2 (0.4)	0.4 (0.4)					
Functional reach (cm) – change from baseline to 8 weeks		7.3 (2.4)	0.2 (1.8)	-1.0 (2.04)					
Fatigue Severity Score– change from baseline to 8 weeks (scale 9-63?)		-9.5 (2.8)	-0.4 (2.1)	-5.2 (5.3))					
Falls Efficacy Scale– change from baseline to 8 weeks		-11.3 (7.8)	-2.1 (1.3)	-2.6 (3.1)					
Beck Depression Index– change from baseline to 8 weeks (scale 0-63?)		-5.5 (5.3)	1.6 (3.6)	-1.6 (6.0)					

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Source of funding
SF 36– change from baseline to 8 weeks (scale 0-100)								
Physical functioning		21.2 (14.4)	12.1 (6.0)	7.7 (7.4)				
Role-physical functioning		34.0 (30.1)	-5.0 (20.9)	5.0 (44.7)				
Bodily pain		8.8 (5.8)	2.0 (2.1)	4.0 (4.0)				
General health		4.3 (8.4)	2.4 (11.5)	3.2 (11.7)				
Mental component		9.0 (19.3)	12.0 (22.5)	11.0 (20.4)				
Social functioning		3.4 (23.1)	10.0 (13.6)	5.0 (16.7)				
Role-emotional functioning		24.2 (49.6)	-6.7 (27.8)	19.9 (50.5)				
Mental health		7.2 (13.4)	3.0 (6.7)	7.0 (6.7)				
Results [number of events up to 8 weeks]. Number analysed in each group given as denominator.								
Adverse events (acute exacerbations leading to withdrawal)		**1/15 (6.7%)**	**2/12 (16.7%)**	**3/12 (25.0%)**				
Adherence to training protocol		**209/224 prescribed sessions were completed –**	**136/224 prescribed sessions were completed –**	**Not applicable.**				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		average adherence rate of 93%.	**average adherence rate of 60%**				

Table 6: Carter 2014

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Carter et al. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes	RCT Good quality study – allocation concealment likely, assessor blinding, no likely attrition bias, adequate	120 randomised. At 3 month follow up, loss of data for 7 from usual care and 6 from intervention. Reasons for loss were very similar across groups, so attrition bias	Inclusion: McDonald criteria; EDSS 1-6.5; ambulant over 10m; aged 18-65; clinical stability for 4 weeks prior to commencing study; able to do exercise 3x per week; if on DMDs had to have been stable on this for at least 3 months Exclusion: Comorbidity preventing exercise; already on exercise programme, living within 20 miles of training centre.	Intervention: 2x 1 hour supervised sessions/week in weeks 1-6. In weeks 7-12 only 1 supervised session but expected to continue at home. Aerobic exercise in repeated	Usual care: 3 supervised exercise sessions + individual exercise advice for home	3 months (end of treatment) and 9 months)	MS Society. No conflicts of interest.

	Intervention	**Usual care**

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
in people with multiple sclerosis: a randomised controlled trial. Multiple Sclerosis Journal 2014 DOI: 10.1177/1352458513519354 [EQ5D data taken from HE paper: Tosh et al. 2014]	sample size (n=120). But possible performance bias from differing levels of attention and time given to each group.	very unlikely. At 9 month follow up, 3 more lost from usual care and 5 more from the intervention group, but the reasons for loss were similar, and there was <10% differential attrition.	Age	45.7(9.1)	46(8.4)	short bouts (ie 5x3 mins) at 50-69% MHR or 12-14 on Borg scale. Also resistance training for various muscle groups (1-3 sets x 5-20 reps). Exercise sessions incorporated CBT techniques			
			%female	71.7	71.7				
			Mean EDSS	3.8(1.5)	3.891.5)				
			Type						
			RR	78%	85%				
			SP	18%	12%				
			PP	3%	3%				
			$MFIS_{total}$	45(17)	42.8(15.7)				

Results					
	Intervention	**Control**			
Total MFIS 3 months [lower better]	35.8(18.2)	43.2(17.3)			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Total MFIS 9 months [lower better]		39.6(16.6)	41.3(18.8)				
Physical MFIS 3 months [lower better]		17.9(8.3)	21.2(8.9)				
Physical MFIS 9 months [lower better]		20.1(7.8)	20.7(8.5)				
Cognitive MFIS 3 months [lower better]		14.9(9.6)	17.7(8.2)				
Cognitive MFIS 9 months [lower better]		16(8.8)	16.7(9.6)				
Psychosocial MFIS 3 months [lower better]		2.9(2.2)	4.2(2.1)				
Psychosocial MFIS 9 months [lower better]		3.5(1.9)	4(2.4)				
MSQoL-54 3 months [higher better]		68.1(20.3)	60.6(19.2)				
MSQoL-54 9 months [higher better]		65.9(20.1)	60.4(21.1)				
EQ5D 3 months [higher better]		0.744(0.204)	0.684(0.263)				
EQ5D 9 months [higher better]		0.739(0.249)	0.734(0.252)				
PASAT 3 months [higher better]		**41.9(15.0)**	**46.0(13.7)**				
PASAT 9 months [higher better]		**47.4(9.9)**	**46.9(13.9)**				
EDSS 3 months [lower better]		**3.5(1.3)**	**3.7(1.5)**				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
EDSS 9 months [lower better]		3.7(1.5)	3.9(1.7)				
Adverse events (relapse), no/no. analysed, 9 months – number randomised used for analysis as number with data for this outcome unclear		9/60 (15.0%)	14/60 (23.3%)				
Adverse events leading to withdrawal (all MS relapse), no/no. analysed, 3 months		1/55 (1.8%)	1/54 (1.9%)				
Adverse events leading to withdrawal (all MS relapse), no/no. analysed, 9 months		2/51 (3/9%)	1/51 (2.0%)				
Adherence to intervention		Participants attended an average of 16.2 of 18 supervised sessions (90%, range 7-18 sessions) and completed an average of 14.6 of 18 home exercise	Not reported				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		sessions (81%, range 2-18 sessions).					

Table 7: Dalgas 2010A

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Dalgas et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Multiple Sclerosis	RCT. 'concealed randomisation' but no details given of sequence generation or the form of allocation concealment.	39 randomsied (19 each group). In PRT group there were 3 drop outs from treatment (LBP, travel to visit sick relative, personal problems) and 1 from control (personal	Inclusion: RR MS, diagnosed by McDonald criteria; EDSS between 3-5.5; pyramid function score ≥ 2, ability to walk ≥100m, age >18. Exclusion: dementia; alcoholism; pacemaker; serious medical co-morbidities; MS attack within the past 8 weeks; pregnancy; PRT in last 3 months. During study participants excluded if they had an attack influencing pyramidal functions, or if they attended <80% sessions.	Progressive resistance training (PRT) for 12 weeks 2x per week. 5 min warm up on bike, followed by leg press, knee extension, hip flexion, hamstring curl and hip extension. In weeks 1-2, 3	Control – continuation of previous daily activity level.	12 weeks (end of treatment) and 24 weeks	Some commercial sponsorship, but unclear if there was a relationship between their merchandise and

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
2010; 16: 480-490	Stratified for gender.	problems). Hence there were 16 and 18 attending at 12 weeks. There was a further loss of 1 from exercise at 22 weeks (lack of time) and 2 from control (broken arm and psoriasis). Only the LBP loss of data in one exercise participant appeared related to treatment. This small difference is unlikely to have introduced attrition bias. Per protocol approach.		**Exercise**	**Control**	sets of 10resp at 15RM, weeks 3-4 3x12 reps at 12RM, weeks 7-8 4x10 reps at 10RM, weeks 9-10 4x8reps at 8RM, weeks 11-12 3x8 reps at 8RM. 2-3 mins rest between sets. All training supervised, and done in groups of 2-4 subjects. No home exercise program reported.			exercise therapy machines. Overall a conflict of interest appears unlikely
			Age	47.7(10.4)	49.1(8.4)				
			EDSS	3.7(0.9)	3.9(0.9)				
			Years since diagnosis	6.6(5.9)	8.1(6)				
			Immunomodulatory treatment	7/15	11/16				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Results, mean (95% CI)							
Outcome		**Exercise**		**Control**			
FSS 24 weeks (lower better) (scale 1-7?)		**4.9 (4.3-5.5)**		**5.1 (4.2-6.0)**			
MFI-20 Gen fatigue 24 weeks (lower better) (scale 4-20?)		**12.7 (10.1-14.0)**		**11.8 (9.4-14.0)**			
MFI-20 Phys fatigue 24 weeks (lower better) (scale 4-20?)		**11.0 (8.6-13.4)**		**12.6 (10.6-14.6)**			
MFI-20 Reduced activity 24 weeks (lower better) (scale 4-20?)		**10.3 (8.0-12.5)**		**10.9 (8.7-13.1)**			
MFI-20 Reduced motivation 24 weeks (lower better) (scale 4-20?)		**6.2 (5.3-7.0)**		**6.7 (5.1-7.0)**			
MFI-20 Mental fatigue 24 weeks (lower better) (scale 4-20?)		**10.6 (7.8-13.3)**		**10.6 (7.6-13.6)**			
Major Depression Inventory 24 weeks		**8.7 (4.7-12.8)**		**8.9 (6.5-11.2)**			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
(lower better) (scale unclear)							
SF-36 PCS 24 weeks (higher better) (scale 0-100)		45.3 (41.5-49.2)		41.5 (38.2-44.8)			
SF-36 MCS 24 weeks (higher better) (scale 0-100)		55.4 (49.1-61.7)		57.8 (53.8-61.8)			
Functional capacity score (baseline set as 100% so could compare post-test values directly) 24 weeks (higher better)		121.0 (115.6-126.3)		108.9 (102.5-115.3)			
Adherence		Completed a total of 23.9 (95% CI 23.7-24.0) out of 24 planned sessions.		Not reported.			

Table 8: Dettmers 2009

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr><td>Dettmers et al. Endurance exercise improves walking distance in MS patients with fatigue. Acta Neurologica Scandinavica 2009; 120: 251-257</td><td>RCT. Sequence generation method not reported. Some evidence of allocation concealment as ‘the [randomly ordered] list was only available to the therapist who was not involved in patient selection’. No assessor blinding.</td><td>30 randomised. One dropped out from the exrcise group (too demanding) and this person was replaced by a new participant (thus introducing a non-random element). Thus potential for attrition bias as a result of losing a ‘poor responder’. 30 analysed for ambulation distance, but loss of data for the MFIS and HAQUAMS data – 6 lost in exercise group</td><td>Inclusion: Mild-moderate MS with EDSS <4.5; maximal walking distance reduced due to fatigue (by exclusion of other causes).

Exclusion: permanent, serious leg weakness, ataxia or spasticity; relapses/corticosteroids in past 3 months; severe cognitive deficits, major depression and insufficient motivation.

Patients allowed to continue symptomatic medical treatment of DMDs.

<table><tr><th></th><th>Exercise (n=15)</th><th>Control (n=15)</th></tr><tr><td>Age</td><td>45.8(7.9</td><td>39.7(9.1)</td></tr><tr><td>female</td><td>10/15</td><td>11/15</td></tr><tr><td>RR
SP
PP</td><td>13/15
2/15
0/15</td><td>10/15
2/15
3/15</td></tr><tr><td>EDSS</td><td>2.6(1.2)</td><td>2.8(0.7)</td></tr><tr><td>Duration since diagnosis</td><td>8(5.9)</td><td>6.1(4.3)</td></tr><tr><td>Retired</td><td>2/15</td><td>3/15</td></tr><tr><td>MFIS</td><td>36.8(17.4)</td><td>41.8(20.3)</td></tr></table></td><td>Endurance exercise 45 mins 3xper week for 3 weeks. Comprised warm-up, ‘mild’ strength training, repetitive endurance exercise, and relaxation and feedback. Some of the training activities were disguised as games – ie getting the participants to collect cards from different parts of the room. Groups were kept to 5 or under and completion was not encouraged. The most</td><td>45 mins 3xper week for 3 weeks. Warm up, sensory training, stretching, balance co-ordination training and periods of relaxation.</td><td>3 weeks</td><td>Non-commercial</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
		and 5 in control group. No reasons given for this loss. Hence further possibility of attrition	MFIS motor	17.4(8.3)	22(7.3)	demanding tasks were placed at the beginning.			
			Maximum walking distance (m)	1693(978)	1260(794)				
			Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS)	114(15.3)	113.9(10.5)				

Results

Outcome	Exercise	Control	
Increase in walking distance from baseline (m)	650(474)	97(70)	
Increase in walking time from baseline (min)	11.3(6)	1.3(1)	
Improvement in MFIS from baseline	6/9	9/10	
Improvement in MFIS (motor) from baseline	8/9	9/10	
Improvement in HAQUAMS (motor) from baseline	5/9	7/10	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Improvement in BDI from baseline		**6/9**	**9/10**				
Acceptance		**Acceptance stated to be high, with one participant dropping out as they found it too demanding.**	**Not reported, though no drop-outs in this group.**				

Table 9: Dodd 2011

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Dodd et al. Progressive resistance training did not improve walking but can improve muscle performanc	RCT. Stratified by Ambulation Index (AI) level. Random number tables used for	76 randomised (39 to PRT, 37 to control). At week 10, 3 lost from FRT group due to drop-out from	Inclusion: Aged 18 or more; confirmed diagnosis of RR MS; AI score of 2-4; medical clearance to participate. Exclusion: acute exacerbation of MS within 2 months of starting the program; benign or progressive/relapsing types of MS; serious and unstable medical condition; participation in PRT within previous 6 months.	10 weeks of twice weekly progressive resistance training (PRT) in a community gymnasium, supervised by PTs and registered	Usual care, provided it did not include PRT. This included an 'attention and social' programme for 1 hour	10 weeks (end of treatment) and 22 weeks	Non-commercial funding

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
e, quality of life and fatigue in adults with multiple sclerosis: a randomised controlled trial. Multiple Sclerosis Journal 2011; 17: 1362-1374	sequence generation in each block. Allocation concealment fairly likely as opaque sealed sequentially numbered envelopes prepared by research co-ordinator but unclear if he/she was not involved in recruitment or decisions on who would	treatment and subsequent loss to follow up, and 2 lost from control group due to drop-out from treatment and subsequent loss to follow up. At week 22, none *further* lost from FRT group, and 4 *further* lost from control group due to experiencing a relapse and not attending (n=3) and not attending with no reason given (n=1). ITT		**PRT**	**Usual care**	sports trainers). 2 sets of 10-12 reps at intensity of 10-12RM. Leg press, knee extension, calf raise, leg curl and reverse leg press were used on weight machines	each week for 10 weeks to help avoid confounding from more attention and social interaction from the exercise intervention. This included therapies such as 'Bobath' to maximise adherence and to help achieve a comparable placebo effect to the intervention group.		
			Age	47.7(10.8)	50.4(9.6)				
			AI 2	17/36	19/35				
			AI3	14/36	9/35				
			AI4	5/36	7/35				
			Use of gait aids?	12/36	13/35				
			MFIS>38	22/36	19/35				
			Female	26/36	26/35				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
	participate.	with ACA applied.					

Results [mean(sd)] – all changes from baseline as there were some potentially confounding baseline differences for some outcomes

Outcome	FRT	Usual care		
Fast walking speed (m/s) change from baseline to 10 weeks (higher better)	0.05(0.17)	0.01(0.19)		
2 minute walk distance (m) change from baseline to 10 weeks (higher better)	2.8(14.4)	0.7(13.4)		
MFIS total change from baseline to 10 weeks (lower better)	-10.2(11.2)	-3(14.1)		
MFIS physical change from baseline to 10 weeks (lower better)	-5.9(5.9	-1.8(6.8)		
MFIS cognitive change from baseline to 10 weeks (lower better)	-3.2(5.9)	-1.7(6.9)		
MFIS psychosocial change from baseline to 10 weeks (lower better)	-1.1(1.6)	-0.4(2.4)		
WHOQOL-BREF overall QoL change from baseline to 10 weeks (higher better)	0.4(0.9)	0.1(0.8		
WHOQOL-BREF overall health change from baseline to 10 weeks (higher better)	0.3(1.2)	-0.1(1.0)		
WHOQOL-BREF overall physical health change from baseline to 10 weeks (higher better)	1.8(3.4)	0.3(2.8)		
AEs – stiffness MSIS-88 change from baseline to 10 weeks (lower better)	-3.6(7.6)	-0.5(6)		
AEs – muscle spasm MSIS-88 change from baseline to 10 weeks (lower better)	-2(6.2)	0.5(6)		
Fast walking speed (m/s) change from baseline to 22 weeks (higher better)	-0.02(0.19)	0.01(0.18)		
2 minute walk distance (m) change from baseline to 22 weeks (higher better)	-1.6(15.6)	1.6(9)		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
MFIS total change from baseline to 22 weeks (lower better)				-2.9(12.8)	-4.8(12.4)		
MFIS physical change from baseline to 22 weeks (lower better)				-2.6(6.8)	-2.1(5.4)		
MFIS cognitive change from baseline to 22 weeks (lower better)				-0.2(7)	-2.1(6.3)		
MFIS psychosocial change from baseline to 22 weeks (lower better)				-0.1(2)	-0.5(2.2)		
WHOQOL-BREF overall QoL change from baseline to 22 weeks (higher better)				-0.1(1.1)	0.1(0.8)		
WHOQOL-BREF overall health change from baseline to 22 weeks (higher better)				0.1(1.1)	0.1(1)		
WHOQOL-BREF overall physical health change from baseline to 22 weeks (higher better)				0.3(3.3)	0.9(3.2)		
AEs – stiffness MSIS-88 change from baseline to 22 weeks (lower better)				-0.5(7)	-0.7(7.7)		
AEs – muscle spasm MSIS-88 change from baseline to 22 weeks (lower better)				1.1(8.2)	-1.1(7.5)		
Adherence – mean (SD) number of scheduled sessions (out of 20 in intervention group and 10 in control group) attended				**18.4 (2.9), range 6-20**	**6.2 (3.1), range 0-10**		

Table 10: Finlayson 2011

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Finlayson et al. Randomised trial of a teleconference-delivered fatigue management program for people with multiple sclerosis. Multiple Sclerosis 2011; 17: 1130-1140	RCT. Randomisation technique not reported, but opaque serially numbered envelopes prepared by statistician (not the person who recruited the participant). No mention of them being sealed.	190 randomised. 181 analysed. The missing data were due to no baseline data (preventing imputation) – 5 in intervention and 4 in control, so group differential for missing data <10%. An ITT approach meant that those not following protocol were kept in randomised groups for analysis.	Inclusion: self-reported diagnosis of MS; age≥18; FSS≥4; weighted score of at least 12 on short version of the Blessed Orientation Memory Concentration test. Baseline comparison not available. Overall, mean age 55(9); FSS score 5(1), 20(11) since symptoms started; 15(9) years since diagnosis; 79% women; 52% RR, 22% SP, 9% PP; 49% education beyond 15 years; 21% full time employment, 16% part-time employment; 17% retired and 47% unemployed.	6 week group based intervention involving weekly 70 minute teleconference calls facilitated by a licensed OT, who had received training from the principal investigator. Over the course of the 6 sessions, the following topics were covered: impact of fatigue, fatigue cycle, major fatigue management principles, how and when to communicate with others about fatigue, body mechanics, using tools and technology, activity analysis, evaluating priorities and making active decision, living a balanced life, taking control and analysing and modifying a day, goal setting. Homework tasks were also given. Group size was kept small (5-7 participants). All equipment needed was provided to participants'	Wait list control group – no intervention. These were given the intervention after 8 weeks, but the outcomes from that phase not included in this review. Only results at 6 weeks included.	6 weeks	Non-commercial funding.

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
				homes, with assistive manual.			
Results. No separate group data available – only the <u>mean group difference (int-control) in terms of the changes from baseline to 6 weeks</u>.							

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Outcome	**mean group difference (int-control) in terms of the changes from baseline to 6 weeks and SE of the MD (use GIV in rev man)**						
FIS cognitive (lower [more –ve] better)	-3.12(0.954)						
FIS physical (lower [more –ve] better)	-2.53(1.024)						
FIS psychosocial (lower [more –ve] better)	-6.01(1.926)						
FSS (lower [more –ve] better)	-0.18(0.153)						
SF36 vitality (higher [more +ve better)	6.68(4.47)						
SF36 role emotion (higher [more +ve better)	8.69(6.31)						
SF36 mental health (higher [more +ve better)	5.32(2.10)						
SF36 social function (higher [more +ve better)	7.54(3.97)						

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
SF36 general health (higher [more +ve better)		3.37(2.34)					
SF36 role physical (higher [more +ve better)		18.06(4.76)					
SF36 physical function (higher [more +ve better)		1.2(1.95)					
SF36 bodily pain (higher [more +ve better)		5.02(3.08)					
SF36 self efficacy (higher [more +ve better)		0.14(0.25)					
		Number of events per group at 6 weeks, no./no. analysed (%)					
Outcome		Intervention	Control				
Adverse events		**0/89 (0.0%)**	**0/92 (0.0%)**				

Table 11: Garcia 2013

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Garcia Jalon et al. Energy conservation for fatigue management in multiple sclerosis: a pilot randomised controlled trial. Clinical rehabilitation 2013; 27: 63-74</td>
<td>RCT. Computer generated random sequence. Allocation concealment highly likely as an independent person involved in drawing up the random sequence and sealed opaque envelopes were opened after baseline assessment (though</td>
<td>23 randomised. All analysed. One discontinued energy conservation intervention as emotionally draining (1) and 2 missed > 2 sessions. 2 lost at follow up as emotionally draining (1) and time commitments (1). All analysed through imputation from last observation carried forward. Blinding of assessors. Patient and</td>
<td>Inclusion: confirmed diagnosis of MS; age 18-65; community-dwelling; independent for most ADL; EDSS 6 or less; Rivermead 6 or more; FSS 4 or more.

Exclusion: mental score test <6 in Hodgkinson mental test; serious comorbidity; severe depression; changes in therapy, medication or relapses within 2 months of trial; pregnancy; previous experience of an energy conservation programme.
<table>
<tr><th></th><th>Energy conservation</th><th>Control</th></tr>
<tr><td>female</td><td>10/13</td><td>6/10</td></tr>
<tr><td>age</td><td>45.9(9.9)</td><td>52(7)</td></tr>
<tr><td>employed</td><td>6/13</td><td>3/10</td></tr>
<tr><td>RR</td><td>2/13</td><td>3/10</td></tr>
<tr><td>PP</td><td>2/13</td><td>1/10</td></tr>
<tr><td>SP</td><td>8/13</td><td>5/10</td></tr>
<tr><td>Duration of MS - yrs</td><td>11(7)</td><td>14.2(11.9)</td></tr>
<tr><td>RMI</td><td>12.8(2.1)</td><td>13.1(1.4)</td></tr>
</table>
</td>
<td>Energy conservation programme. Group format with 2 hour session once per week for 5 weeks. The programme was as follows:

Wk1: introduction to MS and fatigue. Energy conservation and activity analysis. Communication

Wk2: Biomechanics and ergonomics

Wk3: Goal setting,</td>
<td>Peer support group. Group format with 2 hour session once per week for 5 weeks.

Education and discussion of common topics as recommended by MS charities. Short lectures and discussions</td>
<td>5 weeks (end of treatment), 11 weeks and 4.25 months</td>
<td>Non commercial</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
	no mention of sequential numbering).	HCP blinding not possible.	FSS	5.9(0.6)	5.9(0.9)	prioritising and setting standards. Communication; role play Wk4: resting, pacing, scheduling and planning ahead Wk5: Review of the programme. Activity analysis – a problem solving process.			
			On interferon	8/13	5/10				
			On antidepressants	4/13	1/10				
			On steroids	1/13	0/10				
			On fatigue medications	2/13	3/10				
			FIS cog	20.46(5)	17.1(6.7)				
			FIS phys	24.6(5.8)	25.7(4.9)				
			FIS social	38.2(12.5)	38.1(12)				
			FIS total	83.3(16.3)	80.9(21.7)				

Results: Only post test results were compared. In the paper non-parametric analyses were used. However means and sds are reported. There were baseline differences for some variables (see above) so change values would have been better for group comparison, but this was not possible as 1) no sd given for change values, 2) the p values could not be used to derive change value sds as the p values were based on non-parametric tests of changes [Friedmann], 3) imputation of the sds using an assumed r of 0.5 is not preferred NCGC methodology. Likely effects of baseline inequivalence are noted below, and it should be noted that only FIS physical results are invalidated by them.

Outcome	Energy conservation	Control	Likely bias from baseline inequivalence	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
FIS cog 5 weeks		15(6)	16.2(9)	Would favour control, so any follow-up result in favour of intervention is valid			
FIS physical 5 weeks		16.6(6.2)	19.2(6.8)	Would favour intervention – hence caution required if follow-up result in favour of intervention			
FIS social 5 weeks		28(12.4)	28.2(11.6)	No baseline inequivalence so unlikely to be bias			
FIS total 5 weeks		59.6(23.1)	63.3(26)	Would favour control, so result is conservative			
FSS 5 weeks		4.96(1.4)	4.88(0.98)	No baseline inequivalence so unlikely to be bias			
MSIS total 5 weeks		32.22(16.1)	38.9(12.1)	No baseline inequivalence so unlikely to be bias			
FIS cog 4.25 months (scale 0-40)		14.6(6.4)	21.1(6.8)	Would favour control, so any follow-up result in favour of intervention is valid			
FIS physical 4.25 months (scale 0-40)		20.2(7.8)	23.6(7.7)	Would favour intervention – hence caution required if follow-up result in favour of intervention			
FIS social 4.25 months (scale 0-80)		28(13.5)	34.7(11.3)	No baseline inequivalence so unlikely to be bias			
FIS total 4.25 months (scale 0-160)		58.7(30.3)	79.4(24.5)	Would favour control, so result is conservative			
FSS 4.25 months (scale 1-7)		5.21(1.3)	4.9(1.3)	No baseline inequivalence so unlikely to be bias			
MSIS total 4.25 months (scale 0-100)		38.05(19.6)	42.7(12.9)	No baseline inequivalence so unlikely to be bias			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
MSIS physical 4.25 months (scale 0-100)		38.46(21.06)	45.12(14.51)	Would favour control, so result is conservative			
MSIS psychological 4.25 months (scale 0-100)		36.32(23.55)	37.49(14.88)	Would favour intervention – hence caution required if follow-up result in favour of intervention			
BDI Fast Screen 4.25 months (scale 0-21)		2.31(2.86)	2.20(2.34)	No baseline inequivalence so unlikely to be bias			

Table 12: Garrett 2013A and 2013

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Garrett 2013A and 2013 (latter paper is of the same study, but contains results at 24 weeks, and no control data) Garrett M, Hogan N, Larkin A, Saunders J, Jakeman P, Coote S. Exercise in the community for people with minimal gait impairment due to MS: an assessor-blind randomized controlled trial. Multiple Sclerosis. 2013; 19(6):782-789

Garrett M, Hogan N, Larkin A, Saunders J, Jakeman P,</td>
<td>RCT. Sequence generation and allocation concealment unclear. Assessor blinding clear.</td>
<td>N=314 randomised

Control

N=71 randomised

N=49 analysed at 12 weeks

Mixed aerobic/resistance given by PT N=80 randomised

N=63 analysed at 12 weeks and 41 at 24 weeks

Yoga

N=77 randomised

N=63 analysed at 12 weeks and 38 at 24 weeks</td>
<td>Participants aged 18 yrs or over and had a diagnosis of MS confirmed by a consultant physician or neurologist. Patients were excluded if they had a previous relapse or began steroid therapy in the 12 weeks prior to participating in the first assessment, were pregnant, or had a comorbidity that severely impacted their ability to safely participant in exercise.

Participants used a most unilateral support to walk outdoors i.e. they scores 0,1 or 2 on the Mobility subscale of the Guys Neurological Disability Rating Scale
<table>
<tr><th></th><th>Control</th><th>Mixed aerobic/resistance given by PT</th><th>Yoga</th><th>Mixed aerobic and resistance given by fitness instructor</th></tr>
<tr><td>Age</td><td>48.8</td><td>51.7</td><td>49.6</td><td>50.3</td></tr>
<tr><td>Guys NDRS
0
1
2</td><td>
43%
28%
33%</td><td>
30%
33%
33%</td><td>
41%
22%
34%</td><td>
22%
42%
34%</td></tr>
<tr><td>RR</td><td>55%</td><td>55%</td><td>60%</td><td>49%</td></tr>
</table>
</td>
<td>Delivered in gps of 8, for an hour per week for 10 weeks. Delivered in local community centres

Physiotherapist-led class (mixed aerobic/resistance)

Circuit-style class of exercises that were either resisted by body weight or by the addition of free weights

In addition to the once-weekly class, participants were advised to exercise</td>
<td>Control gp

Asked not to change their exercise habits</td>
<td>12 weeks and 24 weeks</td>
<td>Non commercial.</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics					Intervention	Comparison	Length of follow-up	Source of funding
Coote S. Exercise in the community for people with multiple sclerosis--a follow-up of people with minimal gait impairment. Multiple Sclerosis. 2013; 19(6):790-798		**Mixed aerobic and resistance given by fitness instructor** N=86 randomised N=67 analysed at 12 weeks and 42 at 24 weeks	SP PP Benign Unknown	20% 6% 2% 16%	14% 7% 0% 22%	11% 13% 2% 1%	19% 13% 5% 13%	aerobically in the mode of their choice with the aim of exercising for 30 minutes, twice a week **Fitness-led classes were not pre-defined (mixed aerobic/resistance).** The majority of interventions were a combined exercise intervention (aerobic and progressive resistance exercise) **Yoga** intervention was not predefined			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Results: Change from baseline for 12 week results. Sds of change from baseline calculated from 95% CIs. Given that there were two mixed aerobic/resistance groups in this study, only the results of one have been included in the review. The PT-led group results have been used on the basis that this is more relevant to current clinical practice, and also because the PT-led exercise was reported more fully and more standardised. The follow up results are just the raw values at 24 weeks.							
	Control N=49	**Mixed resistance/aerobic provided by PT N=63**	**Yoga N=63**	**mixed aerobic/resistance provided by fitness instructor N=67**			
MSIS-29 v 2 (physical component) (12 WEEKS) Change from baseline (95%CI)	0.3 (-4.0 to 4.6)	-6.9 (-10.8 to -2.9)	-4.0 (-7.5to -0.5)	-5.7 (-9.1 to -2.4)			
MSIS-29 v2 (psycholo component) (12 WEEKS) Median difference (semi interquartile range)	0 (16.7)	-11.1 (25.9)	-3.7 (22.2)	-3.7 (22.2)			
MFIS (total score) (12 WEEKS) Mean difference (95%CI)	-1.1 (-4.5 to 2.3) Sd=11.83	-7.5 (-11.1 to -3.9) Sd= 14.29	-5.8 (-9.2 to -2.4) Sd=23.02	-6.7 (-9.8 to -3.6) Sd=12.71			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
MFIS (physical subscale) (12 WEEKS) Mean difference (95%CI)	0.4 (1.4 to -1.3) Sd=4.7		-3.9 (-2.2 to -5.6) Sd=6.75	-2.1 (-0.5 to -3.7) Sd=6.35	-3.1 (-1.7 to -4.6) Sd=5.94		
MFIS (cognitive subscale) (12 WEEKS) Mean difference (95%CI)	-0.51 (0.7 to -1.7) Sd=4.18		-2.1 (-1.0 to -3.1) Sd=4.17	-0.96 (-0.1 to 1.7) Sd=3.57	-0.94 (-0.9 to -1.8) Sd=1.844		
6-min walking test Median difference (semi interquartile range) (12 WEEKS)	-10 (91)		10 (52)	0 (82)	20 (61)		
Adherence – mean (95% CI) classes attended (out of possible 10 classes)	**Not applicable**		**8.1 (7.5-8.5)**	**7.8 (7.2-8.3)**	**7.3 (6.7-7.9)**		
			Physiotherapy N=41 unless stated	**Yoga** **N=37 unless stated**	**Fitness instructor N=41 unless stated**		
MSIS-29 v 2 (physical			27.7(16.2)	34(21.8)	37(21.4)		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
component) (24 WEEKS) 24 week data only Mean (sd)							
MSIS-29 v2 (psycho component) (24 WEEKS) 24 week data only Mean (sd)			23.4914.8)	30.1920.9)	28.5922.7)		
MFIS (total score) (24 WEEKS) 24 week data only Mean (sd)			32.9(14.6)	33.9(19.20) (n=36)	36.8917.2) (n=42)		
6-min walking test 24 week data only Mean (sd)			313.9(104.9) (n=34)	281.7(112.5)	340.7(88.9)		
Results: event rate, no./no. analysed							
Adverse events leading to withdrawal at 12 weeks (including relapse and injuries)	**8/57 (14.0%) – relapse (n=6), sprained ankle (n=1) or fall (n=1)**		**3/66 (4.5%) – relapse (n=2) or metatarsal fracture (n=1)**	**2/65 (3.1%) – relapse (n=2)**	**4/72 (5.6%) – relapse (n=3) or severe low back pain (n=1)**		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Adverse events leading to withdrawal at 24 weeks (including relapse and injuries)	**Not reported**	**8/49 (16.3%) – relapse or steroids commenced (n=7) or metatarsal fracture (n=1)**	**3/41 (7.3%) – relapse or steroids commenced (n=3)**	**5/48 (10.4%) – relapse or steroids commenced (n=4) or severe low back pain (n=1)**			

Table 13: Geddes 2009

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Geddes et al. The effects of a twelve week home walking program on cardiovascular parameters and fatigue perception of	RCT. Randomisation by toss of a coin. No evidence of allocation concealment. No reports of	15 randomised, but 3 excluded from analysis (2 control and 1 experimental) due to poor compliance and failure to attend follow up. 8 subjects in exercise	Inclusion: age 18-65; diagnosis of MS >1 year; no relapses within 6 months previously; no regular participation in an aerobic exercise programme in past 6 months; ability to walk 100m with or without resting, with or without walking aids; EDSS<7. Exclusion: CV, pulmonary or orthopaedic co-morbidities.			Home walking programme for 3 times a week for 12 weeks, individualised based on pre-test 6MWT results. HR monitors were worn and subjects were required to stay within a	This group 'were asked to refrain from any regular exercise during the 12 week period'. Hence huge potential for confoundin	12 weeks	Non commercial
				Home walking	**Control**				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
individuals with multiple sclerosis: a pilot study. Cardiopulmonary Physical therapy Journal 2009; 20: 5-12	assessor blinding.	group and 4 in control group were analysed	Female	6/8	3/4	prescribed target HR (THR) range. First 2 weeks: subjects walked 5 minutes below their THR, 15 minutes within their THR range and then a 5 min cool-down below their THR. In weeks 3-12, time at THR was increased to 20-30 minutes. An exercise dairy was completed and biweekly telephone calls were made to the participant for monitoring and compliance purposes.	g due to non-exercise factors, such as attention.		
			Age (mean,range)	51.4, 40-64	34.8,22-50				
			EDSS (mean)	4.7	4.7				
			Assistive device for walking	2/8	1/4				
			%6MWT for age/gender matched healthy norm (mean)	50.4%	55%				
Results. Mean (sd) change from baseline values given									

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Outcome	**Walking**	**Control**					
FSS change from baseline to 12 weeks	-0.24(0.72)	-0.17(0.49)					
6MWT change from baseline to 12 weeks	65.69(24.36)	46.75(37.25)					
Adherence to programme	**75%**	**Not reported**					
Results number of events, no./no. analysed (%)							
Outcome	**Walking**	**Control**					
Adverse events related to intervention	**0/8 (0.0%)**	**0/4 (0.0%)**					

Table 14: Gervasoni 2014

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Gervasoni et al. Effect of treadmill	RCT. Sequence generatio	30. No loss of data and all	12/30 women.	12 sessions over 2 weeks of:	12 sessions over 2 weeks of:	2 weeks	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
training on fatigue in multiple sclerosis: a pilot study. International Journal of Rehabilitation Research 2014; 37: 54-60	n and allocation concealment not described.	completed interventions	Inclusion: ability to stand upright independently for 30 s; ability to walk for 6m with/without aids. Exclusion: History of CV, pulmonary, metabolic or other medical conditions	30 minutes of conventional therapy (aimed at increasing joint ROM, muscle strength, balance, gait and UL function according to the treatment plan) PLUs 15 minutes of treadmill training. Intensity was set at 11-12 RPE. Slope and speed of the treadmill were varied between sessions	45 minutes of conventional therapy (aimed at increasing joint ROM, muscle strength, balance, gait and UL function according to the treatment plan)		

	Treadmill training	Control
Age	49.6(9.4)	45.7(8.9)
Time since onset	14.5(9.7)	15.5(10.3)
EDSS (median,range)	5(3-6.5)	5.5(3.5-6)
RR PP SP	37% 25% 37.5%	54.6% 18.2% 27.3%
FSS (median and range)	5.4(1.8-7)	5.4(2.3-6.6)
Dynamic gait index	15.38(4.48)	16(5.07)

Results

	Treadmill training (n=15)	Control (n=15)					
FSS (median and range) at 2 weeks	5.5(2.4-7)	5.3(1.6-7)					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Dynamic gait index at 2 weeks		17.54(3.95)	18.07(5.15)				
Dynamic gait index at 2 weeks (change from baseline – useful as DGI not the same at baseline)		2.16 (2.175)	2.07 (2.175)	P=0.51. sds for change not given, but estimate from the p value 9assuming same sds in each group)			

Table 15: Grossman 2010

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr><td>Grossman et al. MS quality of life, depression, and fatigue improve after mindfulness training – a randomised trial.Neurology 2010; 75: 1141-1149</td><td>RCT. Sequence generation with computer after pre-test. Allocation concealment uncertain as the sequence sent to the ‘co-ordinator’ who then informed patients of their assignment. Unclear if the co-ordinator was aware of pre-test results,</td><td>150 randomised. All received interventions. 5 lost to FU in intervention group and 7 in control group. Reasons not given. However all included in analysis via linear multiple regression-related imputations. Hence risk of attrition bias is low.</td><td>Inclusion criteria: RR (but not > 2 relapses in past year) or secondary progressive MS; EDSS <7, with <2 step increase in past year.

Exclusion; serious psychological disorders other than anxiety/depression; dementia; co-morbidities; current relapses; changes in symptomatic medication in last 3 months; pregnancy.

<table><tr><th></th><th>MBI</th><th>UC</th></tr><tr><td>age</td><td>45.9(10)</td><td>48.7(10.6)</td></tr><tr><td>%female</td><td>78</td><td>81</td></tr><tr><td>Time since diagnosis (yrs)</td><td>7.7(0.9)</td><td>9.7(0.9)</td></tr><tr><td>%RR</td><td>79</td><td>85</td></tr><tr><td>EDSS</td><td>3.03(1.12)</td><td>2.98(0.77)</td></tr><tr><td>LL mobility (from HAQUAMS)</td><td>2.03(0.95)</td><td>1.85(0.76)</td></tr><tr><td>UL mobility (from HAQUAMS)</td><td>1.63(0.73)</td><td>1.62(0.59)</td></tr><tr><td>On MS DMDs%</td><td>56</td><td>66</td></tr></table></td><td>Mindfulness-based Intervention (MBI). This is based upon concepts of mental training that propose that non-judgemental awareness of moment-to-moment experience (mindfulness) may positively affect accuracy of perception, acceptance of health-related changes, realistic sense of control and appreciation of available life experiences. It comprised: 1) personal interview to</td><td>Usual care.</td><td>8 weeks and 6 months</td><td>Some commercial funding reported but unclear if related to this study.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
	and, if so, there was scope for alteration of the allocation.		On psychotropic drugs%	20	20	define goals; 2)8 weekly 2.5 hour classes in mindfulness practices, with 10-15 in each group; 3)One Saturday 7 hour session at week 6; 4) Homework assignments; 5) post-intervention interview. The classes conducted by 2 experienced teachers, each with >9 years of teaching experience.			
			MFIS	35.15(16.7)	30.28(14.9)				
			HAQUAMS	2.22(0.7)	2.13(0.6)				

Results. Changes from baseline given.

	MBI		UC		
	mean	**sd**	**mean**	**sd**	
MFIS change from baseline to 8 weeks (adjusted for baseline	-6.19	9.725383	-0.36	9.726247	

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
differences)[lower better]									
MFIS change from baseline to 6 months (adjusted for baseline differences) [lower better] (scale 0-84)		-5.94	12.83575	+0.09	12.4496				
HAQUAMS change from baseline to 8 weeks[lower better]		-0.18	0.394272	+0.09	0.432278				
HAQUAMS change from baseline to 6 months[lower better] (scale 1-5)		-0.13	0.525696	+0.05	0.518733				
CES-D – depression change from baseline to 6 months [lower better] (scale 0-60)		**-4.63**	**-9.42945**	**-0.86**	**8.44871**				
STAI – anxiety change from baseline to 6 months [lower better] (scale 20-80)		**-3.68**	**8.18406**	**-0.13**	**7.68065**				
Adherence – average adherence rate		**92% of all sessions.**		**Not reported/applicable**					

Table 16: Hayes 2011A

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr><td>Hayes et al. Effects of high-intensity resistance training on strength, mobility, balance, and fatigue in individuals with multiple sclerosis: a randomised controlled trial. JNPT 2011; 35: 2-10</td><td>RCT. No details of sequence generation or allocation concealment. No reports of assessor blinding.</td><td>N=22 randomised

Resistance N=10 analysed

Exercise N=9 analysed</td><td>Definite MS with no exacerbations in the past three months, between ages 18 and 65 yrs, ambulatory with or without assistance device or braces, have impaired giat pattern and have no lower extremity joint problems. They must have not have been put in a regular strength training exercise program.

<table><tr><th></th><th>Res + std ex</th><th>Std ex</th></tr><tr><td>Age</td><td>49.7</td><td>48</td></tr><tr><td>Females</td><td>6/10</td><td>5/9</td></tr><tr><td>EDSS</td><td>5.15</td><td>5.33</td></tr><tr><td>Duration disease</td><td>142 mo</td><td>150 mo</td></tr><tr><td>FSS</td><td>6.1</td><td>5.8</td></tr></table></td><td>Resistance

Standard exercises 3 times per week for 45 to 60 minutes per session for 12 weeks. Standard exercises included aerobic training, lower extremity stretching, upper extremity strength training and balance exercises

Plus lower extremity eccentric ergometric resistance exercise.</td><td>Standard exercise only</td><td>12 wks</td><td>None reported</td></tr>
<tr><td colspan="8">Results. Change values used as potentially confounding baseline differences. Means (sd) given: sd derived from 95% CIs given for the pre-post change in each group.</td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		Resistance + standard exercise	**Standard exercise**				
Timed Up and Go s		0.2(2.68)	0.69(5.78)				
TMWSS 10-min walk self-selected pace m/s		0.03(0.168)	0.04(0.133)				
6-Minute Walk Test m		37(49.42)	32(99.95)				
FSS Fatigue Severity Scale /10 max – change from baseline mean(sd)		-0.94 (1.129)	-1.38 (0.957)				
Participation - % only		**Average of 30/36 days of exercise (82% participation)**	**Average of 30/36 days of exercise (82% participation)**				
Results, number of events, no./no. analysed (%)							
Adverse events		**0/10 (0.0%)**	**1/9 (11.1%)**				

Table 17: Hebert 2011

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Hebert JR et al. Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control. Physical therapy 2011; 91: 1166-1183	3 arm single blinded stratified blocked RCT. Stratified into those with/without brain stem or cerebellar involvement. Method of randomisation not reported but clear allocation concealment. One PT performed all	38 (12 in vestibular rehab group and 13 each in other 2 control groups). No loss to follow up or loss from treatment, apart from one patient in wait list group due to dissatisfaction with group assignment. But ITT approach used.	Inclusion: 18-65; clinically definite MS; able to walk 100m with/without a single-sided device; score of ≥ 45 on modified fatigue impact scale questionnaire; composite score ,72 on computerised sensory organisation test. Exclusion; unable to walk; use of medication to control fatigue or that which caused fatigue; change in MS specific disease modification treatment within past 3 months; documented MS relapse within 6 months of the study; other causes of fatigue such as sleep disorders or depression; impaired postural control; participation in a vestibular/endurance training programme within 8 weeks of the study. Baseline characteristics: the vestibular rehab group appeared to have better ambulatory capacity.	**Standardised vestibular rehabilitation programme 2x per week for 6 weeks** consisting of upright postural control and eye movement exercises. Each item was performed for 1-2 minutes, for a total of 55 minutes. Specific items were selected for a daily independent home exercise programme (HEP), assigned throughout the intervention and follow up phases. Non HEP done in a human performance laboratory under supervision. Plus 5 minute fatigue management education, including discussion of daily rest intervals, self-	Two comparison groups: **1. Exercise control group 2x per week for 6 weeks,** including endurance and stretching exercises: stationary cycling for 40 mins @ 65% to 75% HR max in central 30 mins with pedal rate of 50 rpm. Stretches were of major lower limb muscle groups, held for 30 seconds each. HEP comprised stretches and stationary cycling/walking. Non HEP done in a human performance laboratory under supervision	6 weeks (EOT) and 10 weeks	Non commercial.

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr><td></td><td>outcome assessments and was blinded to group.</td><td></td><td><table>
<tr><th></th><th>Vestibular</th><th>Exercise</th><th>Wait list</th></tr>
<tr><td>age</td><td>47(11)</td><td>43910)</td><td>50(9)</td></tr>
<tr><td>%female</td><td>75</td><td>85</td><td>85</td></tr>
<tr><td>MS duration</td><td>6.5(5.6)</td><td>5.1(3.2)</td><td>9.197.3)</td></tr>
</table></td><td>monitoring of exertion, work station ergonomics and heat tolerance education.</td><td>Plus 5 minute fatigue management education, including discussion of daily rest intervals, self-monitoring of exertion, work station ergonomics and heat tolerance education.

1. Wait-listed control – no intervention given at all.</td><td></td><td></td></tr>
</table>

Reference	Study type	No. pts	Patient characteristics				Intervention	Comparison	Length of follow-up	Source of funding
			%RR %SP	92 8	85 15	92 8				
			%brain stem/cerebellar	33	31	31				
			MFIS	51(6.8)	51(8.6)	55.9(11.6)				
			6MWT (ft)	1336(320)	1066(336)	1049(329)				
			BDI-II	16.5(9.1)	17.3(8.6)	8.5(6.4)				

Results

	Vestibular	exercise	Wait list	
MFIS 6 weeks	29.5(15.8)	44.3(16.4)	52.1(17.1)	
MFIS 10 weeks	30.3(20.8)	44.7(16.3)	52.6(17.4)	
6MWT 6 weeks	1420.7(283.6)	1112.1(391.3)	1071.6(375)	
6MWT 10 weeks	1396.1(330.5)	1053.9(448.7)	1110.5(284)	
BDI-II (depression) 10 weeks	**11.6(12.3)**	**12.9(8.0)**	**16.6(9.6)**	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Adverse events at 6 weeks, no./no. analysed (%)		**0/12 (0.0%)**	**1/13 (7.7%)**	**0/12 (0.0%)**			

Table 18: Hugos 2010

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Hugos et al. Clinical trial of a formal group fatigue program in multiple sclerosis 2010; 16: 724-732	RCT. No details of randomisation strategy. Study statistician created the randomised sequence	41 randomised (21 intervention and 20 control). Analysed 30 (15 each group). Missing data was due to those not receiving	Inclusion: definite MS by McDonald criteria; self-assessed EDSS ≤6; no initiation of DMT within 6 months of study start; no relapses within30 days. BDI II score <18. **Intervention** / **Control** Female % 87 / 73	'Fatigue: take Control' program, a fatigue management education program. 6x2 hour group sessions over 6 weeks. Involved DVD viewing on the causes of MS fatigue and the best ways to combat it, topic focussed group discussion, individual goal setting and homework assignments.	Waiting list control group. These were given the intervention after 8 weeks, but the outcomes from that phase not	6 weeks	Non-commercial funding

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
	and provided these in sealed envelopes. No report of these envelopes being serially numbered or opaque. Subject and HCP blinding not possible. Assessor blinding not reported.	intervention/control being excluded by researchers. In intervention group, time (4), distance (1) and illness(1) were reasons for non-attendance; in control group time (3), distance (1) and other study (1) were reasons for non-attendance. It appears as though these failures to attend occurred before the inception of intervention, so unlikely to be related to	Unemployed %	47	52	All received program workbooks including all the information presented, opportunities for responses to thought provoking questions related to the material and homework assignments.	included in this review. Only results at 6 weeks included.		
			DMTs%	87	60				
			Antidepressants %	40	47				
			Stimulants%	33	40				
			age	55.4(9)	58.4(8)				
			Time from diagnosis	14.2(7)	15.5(6.5)				
			EDSS	4.9(1.2)	5.5(0.8)				
			MFIS (total)	44(10.7)	45.9(10.3)				
			MFIS (physical)	21.4(5.3)	22.3(5.1)				
			MFIS (cog)	19.3(7.9)	19.1(6.1)				
			MFIS (psychosocial)	4.2(2)	4.4(1.7)				
			FSS	52.5(6.8)	51.5(8.4)				
			MSSE	1362.7(184)	1268.7(296.9)				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
		efficacy/AEs of treatments. Thus probably minimal risk of bias.	Exercise (mins)	188.6(195)	149.9(208.9)				

Results [mean(se)]				
	Intervention	**Control**		
FSS at 6 weeks (end of treatment)	**48.60(1.50)**	**45.82(1.54)**		
MFIS at 6 weeks (end of treatment)	**39.07(1.10)**	**44.46(1.14)**		
MFIS physical at 6 weeks (end of treatment)	**19.83(0.55)**	**21.69(0.56)**		
MFIS cognitive at 6 weeks (end of treatment)	**16.01(0.60)**	**18.85(0.61)**		
MFIS psychosocial at 6 weeks (end of treatment)	**3.50(0.15)**	**4.11(0.16)**		
MSSE at 6 weeks (end of treatment)	1332.92(32.89)	1427.44(31.77)		

Table 19: Kargarfard 2012

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Kargarfard et al. Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. ArchPhys Med Rahabil 2012; 93: 1701-1708</td>
<td>RCT. Randomisation achieved without computer/ random number table by shuffling sealed envelopes with group allocations inside. No mention of opaque envelopes.</td>
<td>32 randomised (16 each group). 6 excluded due to medical or non-medical reasons in exercise group, with 10 analysed. 5 dropped out of the control group, with 11 analysed. Per-protocol analysis used. Reasons for loss per group not clear, so not possible to conclude that the groups were comparable for lost data.</td>
<td>Women with RRMS; EDSS ≤3.5.

Inclusion: Clinically or laboratory supported MS; minimum of 2 years since diagnosis; no relapses within past 4 weeks; ability to do exercise.

Exclusion; relapse during intervention period; disease preventing participation.

All participants asked to refrain from medication (except routine treatments), supplements, caffeine, smoking and any rigorous exercise within 48 hours of the baseline tests

Groups similar at baseline
<table>
<tr><th></th><th>Exercise (n=10)</th><th>Control (n=11)</th></tr>
<tr><td>Age</td><td>33.7(8.6)</td><td>31.6(7.7)</td></tr>
<tr><td>BMI</td><td>23.9(4)</td><td>24(3)</td></tr>
<tr><td>Disease duration</td><td>4.9(2.3)</td><td>4.6(1.9)</td></tr>
<tr><td>EDSS</td><td>2.9(0.9)</td><td>3.0(0.7)</td></tr>
<tr><td>MFIS overall</td><td>42.1(14.1)</td><td>45.6(8.9)</td></tr>
<tr><td>MSQOL-54 physical</td><td>43.9(6.8)</td><td>43.5(5.8)</td></tr>
</table>
</td>
<td>Aquatic exercise training. 3 sessions per week for 8 weeks. Each session lasted 60 minutes, including 10 mins warm up, 40 mins of exercise and 10 mins of cool-down. Led by a certified aquatic exercise trainer. Intensity was 50%-75% of maximal HR.

The core aquatic exercises focussed on joint mobility, flexor and extensor muscle strength, balance, posture,</td>
<td>Maintenance of current treatment and behaviour throughout the 8 weeks. ‘Treated similarly’ except for the aquatic exercise.</td>
<td>4 weeks and 8 weeks</td>
<td>Academic funding only; no commercial conflicts of interest.</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
			MSQOL-54-mental	44.4(9.3)	42.5(10.5)	functional activities and intermittent walking.			

Results [mean(sd) unless stated]				
	Exercise (n=10)	**Control (n=11)**		
MFIS overall 8 weeks (lower better)	32.3(6.4)	60.8(9)		
MFIS-physical 8 weeks(lower better)	14(3.3)	29.5(5.8)		
MFIS-psychosocial 8 weeks(lower better) – reported as cognitive but must be an error as scale is 0-8 for this usually. Assumed cognitive and psychosocial domain results have been mixed up.	3.9(1.7)	6.7(1.5)		
MFIS-cognitive 8 weeks(lower better) reported as psychosocial but must be an error as scale is	14.4(3)	24.5(5.7)		

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
0-8 for the psychosocial domain but values given are >8 in both groups for that domain. Assumed cognitive and psychosocial domain results have been mixed up.									
MSQOL-54-physical 8 weeks (higher better)		65.4(6.6)	44.2(4.4)						
MSQOL-54-mental 8 weeks(higher better)		70.2(5.7)	43.6(8.9)						
MFIS overall change from baseline to 8 weeks(lower better)		-9.8(10.1)	15.3(8.0)						
MFIS-physical change from baseline to 8 weeks(lower better)		-5.2(5.4)	8.8(4.6)						
MFIS-psychosocial change from baseline to 8 weeks(lower better)		-2.7(7.0)	5.9(8.3)						

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
MFIS-cognitive change from baseline to 8 weeks(lower better)		-1.9(1.9)	0.5(2.0)				
MSQOL-54-physical change from baseline to 8 weeks(higher better)		21.5 (5.4)	0.7(3.3)6				
MSQOL-54-mental change from baseline to 8 weeks(higher better)		25.8(9.8)	1.1(5.3)				

Table 20: Kos 2007

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Kos et al. Multidisciplinary fatigue management programme in multiple sclerosis: a randomised clinical trial. Multiple Sclerosis 2007; 13: 996-1003</td>
<td>Parallel group RCT. This had the appearance of a cross-over study, but there was no symmetry across randomised groups in terms of the comparator used (intervention followed by control for one randomised group but placebo followed by intervention for the other randomised group). Furthermore no paired analysis was</td>
<td>51 randomised (28 to MFMP) and 23 to control. All analysed with ITT analysis, despite 2 in MFMP and 2 in control not attending for follow up (assumedly via imputation by last measure forward)but results relevant to this study were all per-protocol.</td>
<td>Inclusion: Diagnosis of MS; score of 3 or more on the fatigue sub-scale of The Guys Neurological Disability Scale; community-dwelling; able to walk >100m without assistance or a walking aid; no rehab programmes in past 2 years; no energy management programme in past; not under meds for depression.

Baseline comparison (mean[sd] unless stated; *=median[iqr])
<table>
<tr><th></th><th>MDMP</th><th>Control</th></tr>
<tr><td>Age</td><td>42.9(9.1)</td><td>44.5(9.9)</td></tr>
<tr><td>Female</td><td>71.4%</td><td>65.2%</td></tr>
<tr><td>Years since diagnosis</td><td>6.1(4.9)</td><td>8.2(9.0)</td></tr>
<tr><td>RR
PP
CP</td><td>72%
7%
7%</td><td>61%
13%
17%</td></tr>
<tr><td>MSFC score</td><td>0.13(0.6)</td><td>-0.16(0.7)</td></tr>
<tr><td>VAS for fatigue impact *</td><td>6(5-8)</td><td>5.5(5-7)</td></tr>
<tr><td>MFIS total*</td><td>46(38-54)</td><td>46(42-54)</td></tr>
</table>
</td>
<td>Multidisciplinary fatigue management programme (MFMP) – 4 sessions of 2 hours, spread over 4 weeks. Each session started with information provided by the instructor, followed by an interactive part, where participants discussed the strategies they used and planned in the near future. Information was provided concerning possible strategies to manage fatigue</td>
<td>Similar to the MFMP, except topics did not concern themes directly related to fatigue(car adaptations, lift techniques etc).</td>
<td>4 weeks</td>
<td>Non commercial</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
	presented. Hence only results from the first phase have been reported here. Randomisation stratified by matched pairs for MFIS score (each matched pair put into one envelope). Independent research assistant separated each pair and divided to the two groups by 'random draw' though details are not described. As this happened AFTER the baseline tests and an independent person was	Only 24 in MFMP group analysed and 16 in control. The 4 lost in MFMP were because of withdrawal from treatment before commencement (1), only doing ¾ of the treatment 91), and not attending FU (2). The 7 lost in the control group were due to withdrawing from treatment before	MFIS physical*	22(17-26)	22.5919-26)	and reduced energy levels, such as drug treatment, diet, informing and involving the social environment, regular sleep, exercise, relaxation, cooling, assistive devices, adaptation of home or work environment and energy saving methods.			
			MFIS cognitive*	21(16-26)	20.5(16-25)				
			MFIS psychosocial*	4(3-6)	5(4-6)				
			MS self-efficacy scale – function*	760(655-810)	670(530-800)				
			MS self-efficacy scale – control*	540(390-660)	510(400-590)				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
	used, it is unlikely that selection bias could have occurred. Not reported if there was assessor blinding, though clearly patient blinding and HCP blinding were impossible. Blinding carried out for analysis only.	commencement due to lack of interest 94), not attending ¾ of the intervention (2) and not attending FU (1). Thus potential attrition bias for the per protocol analysis.					

Results.

	MFMP	Control		
Proportion of participants with clinically relevant changes of MFIS scores (improvement of 10 or more)	4/24	7/16		

Table 21: Learmouth 2012

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Learmonth et al. The effects of a 12 week leisure centre-based, group exercise intervention for people moderately affected with multiple sclerosis: a randomised controlled pilot study. Clinical rehabilitation 2012; 26: 579-593</td>
<td>RCT. Computer randomisation, but no reporting of allocation concealment. Clear assessor blinding.</td>
<td>Randomised N=32

Exercise N=20 randomised N=15 measurements taken. 5 losses due to family commitments, participating in another study, unable to attend FU, suspected trigeminal neuralgia and flu like symptoms

Control N=12 randomised N=10 measurements. 2 losses due to time</td>
<td>Patients had a confirmed diagnosis of MS, EDSS score of 5 to 6.5, stable rehabilitation and drug therapy for 30 days before entry into the study. Score of over 24 on the MMSE

Exclusion: Exacerbation in MS three mths prior to the study. Medical conditions precluding participation
<table>
<tr><th></th><th>Intervention</th><th>Control</th></tr>
<tr><td>M:F</td><td>5:15</td><td>4:8</td></tr>
<tr><td>Age</td><td>51.4</td><td>51.8</td></tr>
<tr><td>EDSS</td><td>6.14</td><td>5.82</td></tr>
<tr><td>Yrs since onset</td><td>13.4</td><td>12.6</td></tr>
</table>
</td>
<td>Exercise

Leisure centre-based exercise class, twice weekly for 12 weeks. Led by a physiotherapist and fitness instructor. 10 min aerobic and stretching, 30-40 min circuit exercises</td>
<td>Control

Continue usual routine and to avoid beginning any new exercise</td>
<td>12 wks</td>
<td>NHS Ayrshire and Arran, Bevan Endowment Fund, MS Society</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
		commitment and weather conditions. Attrition bias likely.							

Results – all post-test values [mean(sd)] at 12 weeks

	Exercise	Control		
Timed 25 Foot Walk Test s	14.9 (13.6)	13.1 (8.6)		
6 Minute Walk Test m	262.2 (127.4)	215.8 (175.7)		
Berg Balance Scale higher better	46.7 (10.6)	40.9 (15.2)		
Timed Up and Go s	18.4 (14.95)	16.22 (11)		
PhoneFITT higher better	78.2 (35.5)	54.6 (16.7)		
Activities Balance Confidence higher better	79.8 (28.3)	60.9 (35.6)		
Fatigue Severity Scale at 12 weeks lower score better	5 (1.8)	6.2 (0.7)		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Hospital Anxiety and Disability Scale at 12 weeks Lower better		**11.7 (5.9)**	**13.8 (6.6)**				
Leeds MS Quality of Life at 12 weeks Lower better		10.9 (3.9)	12.4 (3.1)				
Adherence		**Adherence at classes was 69%**	**Not reported/not applicable**				

Table 22: Mathiowetz 2005

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Mathiowetz et al. Randomised controlled trial of an energy conservation course for persons with multiple sclerosis. Multiple Sclerosis 2005; 11: 592-601	**Cross-over RCT**. Sequence generation in advance by coin-flipping; no reports of allocation concealment. However, as a cross-over study any selection bias will only affect bias arising from order effects, and so this is not a serious risk of bias. No patient or HCP blinding. Assessor blinding unclear, though it was stated that the outcome assessment was administered by 'neutral' research assistants which were 'unlikely to influence participants' completion of their self-assessments'.	169 randomised. 16 did not receive allocated intervention in group having EC first and 22 in group having control first. ITT using imputation via maximum likelihood method enabled all 169 to be included in analysis.	Inclusion: MS diagnosis; 18 or older; FSS of 4 or more; independent community dweller Exclusion: failure in >1 cognitive tests (from PASAT, Selective Reminding test, Word list generation). 82.8% female; 61.55 RR, 18.9% SP, 5.9% PP, 1.8% PR; employed full time 28.4%, part time 20.7%, retired 8.9%, unemployed 3.6%, disability benefit 33.1%; other factors affecting fatigue 24.3%.	Energy conservation course. A 6 week community based EC course. 6 weeks of highly structured 2 hour classes. Each course had 7-10 participants/group and taught in community settings. The sessions were taught in a variety of ways, from lectures to practice activities and homework tasks. The sessions addressed the importance of rest, positive and effective	Control – no treatment for 6 weeks. Cross over to intervention after post-test assessment	6 weeks	Non-commercial funding

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
	Analysis was unclear. Not fully clear that a paired analysis between TREATMENTS (within subject) was carried out.			communication, body mechanics, ergonomic principles, modifications of the environment, changing standards, setting priorities, activity analysis and modification and living a balanced lifestyle. Instructors were fully trained. Cross over to comparator after post-test assessment.			

Results (using ITT with likelihood imputation)			
Outcome	**Difference between intervention and control group (95% CIs n=169**	**SE (derived from upper CI/1.97*)** ***95% CI on t distribution for 167df**	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
FIS cognitive (more –ve indicates benefit for intervention relative to control)	-2.55 (-4.88, -0.21)			1.188			
FIS physical (more –ve indicates benefit for intervention relative to control)	-3.71(-6.06, -1.37)			1.188			
FIS social (more –ve indicates benefit for intervention relative to control)	-6.10(-10.24, -1.95)			2.107			
SF36 (physical) (more +ve indicates benefit for intervention relative to control)	1.75(-4.36, 7.87)			3.107			
SF36 (role physical) (more +ve indicates benefit for intervention relative to control)	15.18(0.78, 29.57)			7.304			
SF36 (bodily pain) (more +ve indicates benefit for intervention relative to control)	2.69(-6.33, 11.71)			4.579			
SF36 (general health) (more +ve indicates benefit for	0.81(-5.4, 7.02)			3.152			

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
intervention relative to control)							
SF36 (vitality) (more +ve indicates benefit for intervention relative to control)			11.64(5.48, 17.79)		3.122		
SF36 (social function) (more +ve indicates benefit for intervention relative to control)			6.06(-2.49, 14.6)		4.335		
SF36 (role emotional) (more +ve indicates benefit for intervention relative to control)			13.23(-6.77, 33.24)		10.157		
SF36 (mental health) (more +ve indicates benefit for intervention relative to control)			6.12(0.01, 12.24)		3.107		

Table 23: McCullagh 2008

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
McCullagh et al. Long term benefits of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: a pilot study. Clinical rehabilitation 2008; 22: 206-214	RCT. Randomisation by picking lots blindly from a box [2 slips of paper in box (one intervention and one control)]. The researcher then made the allocation. This was after verbal consent to participate, so it is unlikely that the researcher could refuse to admit the participant if the allocation drawn did not tally with any researcher bias. However there were clearly no checks to ensure the researcher did	30 'randomised'. 17 exercise group and 13 control group. Only 12 analysed in each group at the 3 and 6 month follow ups. 5 did not complete exercise treatment (relapses (2), inconvenient time of classes 91), pregnancy (1), personal reasons(1) and were not analysed. As it was reported that there were none lost to follow up, it	Inclusion: definite diagnosis of MS; independently mobile without use of aids; able to attend 2x classes per week and independent at home. Exclusion; relapses or progression over past 3 months; cardiac, cognitive or psychological conditions.	Exercise classes 2x per week for 12 weeks. 5 min warm up and warm down with 40 mins of exercise. There were 4 stations each lasting 10 minutes, with a 5 minute rest in between. The stations varied between treadmill walking/running, cycling, Stairmaster training, arm strengthening, volleyball and outdoor walking over varied terrains. Home exercise (1x per week) for 40-60 mins also prescribed.	Usual activity levels. Monthly visits to physiotherapist to "discuss any issues".	3 and 6 months	Biogen pharmaceuticals.

	Exercise	Control
female	14/17	10/13
age	40.5912.7)	33.6(6.1)
Disease duration	5.4(4.4)	5(3.5)
RR	9/17	8/13
SP	3/17	4/13
FAMs	169(150-200)	191(170.5-208)
MSIS-29	43(40-61)	44.5(38.5-57)
MFIS	26(17-40.5)	26.5(21.5-33.5)

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
	not 'amend' the allocation. Also, "when the exercise group had 17 allocations it was decided to assign the remaining persons to the control group to maintain a balanced number of participants in both groups". This means that the study was not truly random, and it is possible that participants with specific prognostic characteristics were targetted for the final places earmarked for the control group. Hence	appears this was a per-protocol analysis, as those not completing treatment were not allowed to continue. In control group, one did not complete treatment due to moving house and was not included in the analysis. Very high risk of attrition bias.					

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
	this study must be regarded as at very serious risk of bias.						

Results: Non parametric analyses, and results correctly reported as medians (IQR) in the paper. The change from baseline values were compared between groups. Median (IQR) below.

Outcome	Exercise	Control	p
MFIS change from baseline to 3 months (lower better)	-13 (-20.5, -3)	1(-4, +4.5)	0.02
MSIS-29 change from baseline to 3 months (lower better)	-6.5(-10, +1)	-1(-4.5, +4.5)	0.13
FAMS change from baseline to 3 months (higher better)	23(+9.5, +42.5)	-3.5(-16, +5)	0.006
MFIS change from baseline to 6 months (lower better)	-8.5(-19.5, -1)	0.5(-2.5, +6.5)	0.02
MSIS-29 change from baseline to 6 months (lower better)	-6(-9, +0.5)	0(-1, +1)	0.10

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
FAMS change from baseline to 6 months (higher better)	19(+14, +31)	-4.5(-25, +8)	0.002				
Results – number of events, no./no. analysed (%)							
Outcome	**Exercise**	**Control**					
Adverse events (relapse leading to withdrawal) at 6 months	**2/14 (14.3%)**	**0/12 (0.0%)**					
Adherence	**All completed at least 20/24 hospital-based classes (only 2 completed all 24) but none completed >50% of prescribed home sessions.**	**Not reported/not applicable.**					

Table 24: Moss-Morris 2012

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Moss-Morris et al. A pilot randomised controlled trial of an internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. Behaviour research and Therapy 2012; 50: 415-421</td>
<td>RCT. Randomisation done by automated simple randomisation system, which probably avoids allocation concealment. No reports of assessor blinding.</td>
<td>45 randomised (23 to CBT and 22 to control). 5 controls were withdrawn as they effectively ‘swapped’, accessing the Invigor8 site. Hence this was a per-protocol analysis (though because it was the control subjects who swapped it would not make sense to downgrade for this, as it does not relate to how the intervention worked; in actual fact keeping the</td>
<td>Inclusion: definite MS; FS >4; ambulatory with/without a stick for at least 100m; willingness to abstain from other fatigue treatments.
<table>
<tr><th></th><th>CBT</th><th>Control</th></tr>
<tr><td>age</td><td>40.0(17.8)</td><td>41.8(11.4)</td></tr>
<tr><td>Yrs since diagnosis</td><td>21(9)</td><td>16(8)</td></tr>
<tr><td>% female</td><td>69.6</td><td>94.1</td></tr>
<tr><td>Able to walk ≥100m without aid or rest</td><td>13/23</td><td>12/17</td></tr>
<tr><td>RR
SP
PP</td><td>10/23
7/23
2/23</td><td>12/17
2/17
0/17</td></tr>
<tr><td>Unemployed</td><td>7/23</td><td>4/17</td></tr>
<tr><td>Fatigue scale</td><td>21.39(4.3)</td><td>21.53(3.6)</td></tr>
<tr><td>MFIS</td><td>13.17(3.8)</td><td>12.69(3.89)</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
</td>
<td>MS Invigor8: breaking the cycle of fatigue. This was an online CBT programme for fatigue. Comprised 8 weekly sessions as follows:

Understanding MS fatigue; fatigue diary; rest and activity patterns; improving sleep; understanding MS symptoms; recording thoughts; managing stress; emotions, support and the future. Followed the CBT approach.</td>
<td>Standard care – no details given.</td>
<td>10 weeks</td>
<td>Non-commercial</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		swappers in would probably have created much more bias). Despite this all other data were analysed regardless of non-attendance at 10 week follow up (3 no follow up in CBT group and 1 no follow up in control) using last score carried forward.		Also received 3 telephone support sessions of between 30-50 minutes, provided by trained psychologist			

Results. Post test results only compared as very good baseline equivalence.

Outcome	CBT	Control		
FS at 10 weeks	12.39(6.84)	19.57(5.20)		
MFIS at 10 weeks	9.00(3.75)	12.88(3.89)		
HADS – anxiety at 10 weeks	**6.44(3.91)**	**11.65(5.26)**		

Reference	Study type	No. pts	Patient characteristics		Intervention	Comparison	Length of follow-up	Source of funding
HADS – depression at 10 weeks		5.18(3.38)	8.73(3.62)					
Adherence at 10 weeks		Mean (SD) sessions completed: 4.91 (2.10) of 8 sessions. Only one finished all 8 sessions. 60.8% finished >5 sessions.	Not reported/not applicable.					

Table 25: Mostert 2002

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Mostert et al. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler 2002; 8: 161-168	RCT. No details of sequence generation or allocation concealment. No reports of assessor blinding.	N=37 (20 exercise, 17 control) Exercise N=13 analysed. 6 lost due to ST segment changes (2), unknown (3) and elevated spasticity (2) Control N=13 analysed. 5 lost due to motivation (3) and symptom exacerbation (2). Note that numbers don't add up! Likely attrition bias.	Inpatient rehabilitation program. Confirmed clinical diagnosis and able to pedal on a free-standing bicycle ergometer and had no medical conditions precluding participation. No exacerbations during at least two previous months.			**Exercise** 5 training sessions over 3-4 wks. Each session consisted of a 30-min bicycle exercise training	**Control** Normal physical therapy of rehabilitation program but agreed not to increase their physical activity level	4 wks	Klein-Vogelbach-Stiftung, Zurich
				Exercise	**Control**				
			Age y	45.23	43.9				
			Relapsing – remitting %	30.8	38.5				
			Chronic-progressive	23/1	30.8				
			Relapsing-progressive	46.2	23.1				
			EDSS range	2.5 to 6.5	1 to 6.5				
Results: all mean(sd) at 4 weeks									

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		Exercise	Control				
Work mean SD		2.6 (0.6)	2.7 (0.9)				
Sport		2.0 (0.4)	1.7 (0.4)				
Leisure		2.5 (0.8)	2.4 (0.8)				
Fatigue Severity Scale		4.4 (1.9)	5.0 (1.9)				

Table 26: Negahban 2013

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Negahban H et al. Massage therapy and exercise therapy in patients with multiple	RCT. Random number tables used for stratified (for age and sex) allocation	48 randomised. No loss to follow up and all received randomised treatment.	Inclusion: Clinically or laboratory confirmed RR or SP MS, EDSS 2-6; ability to stand for at least 60 seconds (with aids if needed) and ability to walk 10m safely with/without an assistive device. Exclusion: severe relapse one month before the study; involvement in any physical therapy programme prior to the study, unstable CV	30 minutes sessions of supervised intervention 3x per week for 5 weeks as: Massage therapy, using a	Usual care. Asked to avoid any exercise programme or change their usual activities over the 5	5 weeks	Academic grant only

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>sclerosis: a randomised controlled pilot study. Clin Rehabil 2013: 27: 1126-1136</td>
<td>to the 4 groups. No allocation concealment reported. Assessor blinding only.</td>
<td></td>
<td>condition; diabetes; neurological or MSK conditions except MS.
<table>
<tr><th></th><th>mass</th><th>Ex</th><th>Mass/ex</th><th>Usual care</th></tr>
<tr><td>Age</td><td>36.3(7.6)</td><td>36.7(6.7)</td><td>36.7(7.6)</td><td>36.8(8.7)</td></tr>
<tr><td>EDSS</td><td>3.8(1.4)</td><td>3.5(1.1)</td><td>3.8(1.4)</td><td>3.8(1.4)</td></tr>
<tr><td>Time since diagnosis</td><td>149(97)</td><td>102(81)</td><td>115(78)</td><td>87(34)</td></tr>
</table>
</td>
<td>Swedish technique, of the lower limb muscles, involving petrissage , effleurage and friction
OR
Exercise, using strength, strengthening, endurance and balance exercises (ie straight leg raises, forward lunges, treadmill walking, balance board training)
OR
Combined exercise and massage (15 minutes of each</td>
<td>weeks of the study.</td>
<td></td>
<td></td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
				per 30 minute session)			

Results. Change from baseline given [mean(sd)].

	Mass	Ex	Mass/ex	Usual care			
Pain VAS (lower better)	-3.16(2.12)	-0.41(0.79)	-2.08(1.16)	0.58(1.88)			
FSS(lower better)	-8.08(7.58)	-10.75(7.27)	-9.41910.63)	3(4.11)			
MAS(lower better)	-0.54(0.55)	-0.47(0.66)	-0.14(0.77)	0.33(0.46)			
TUG(lower better)	-4.68(5.94)	-0.99(1.03)	-4.41(8.22)	0.95(1.26)			
2MinWalk [m](higher better)	25.29(23.44)	21.28(19.79)	15.31(9.27)	-2.58(8.02)			

Table 27: Rampello 2007

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>Rampello et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomised crossover controlled study. Physical therapy 2007; 87: 545-555.</td>
<td>Randomised crossover trial

Computerised randomisation. No report of allocation concealment. Assessor blinding evident.</td>
<td>19 randomised and 11 analysed in both phases.

Aerobic training
<u>Phase 1</u>

n=8 randomised and analysed

<u>Phase 2</u>

N=9 randomised; N=6 analysed.

Neurological rehabilitation
<u>Phase 1</u>

n=11 randomised and analysed

<u>Phase 2</u></td>
<td>Diagnosis of MS according to the criteria of Poser et al, score of 6 or less on the EDSS and aged between 20 and 55 yrs.

Subjects were excluded if they had a relapse 4 weeks before the study, had a medical history precluding participation, were currently receiving steroids or had been treated with steroids within 2 mths prior to the study
<table>
<tr><th></th><th>Completers N=11</th></tr>
<tr><td>Age yrs</td><td>44</td></tr>
<tr><td>Female/ male</td><td>8/3</td></tr>
<tr><td>Disease duration yrs</td><td>6</td></tr>
<tr><td>EDSS score</td><td>3.5 (range 1 to 4)</td></tr>
</table>
</td>
<td>Aerobic training

3 training sessions per wk in a leg cycle ergometer for 8 wks</td>
<td>Neurorehabilitation

3 sessions per wk for 8 wks. Exercises aimed at improving respiratory-postural and respiratory-motor synergies and of stretching exercises</td>
<td>8 wks</td>
<td>None reported</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		n=6 randomised; N=5 analysed					

Results: post test at 8 week given.

	Aerobic training N=11	Neurological rehab N=11	p
Walking distance m mean SD	332 (108)	308 (110)	
Walking speed m/min mean SD	55 (18)	51 (18)	
MFIS total median range	29 (4-56)	26 (3-67)	0.86
MFIS physical median range	14 (4-23)	13 (3-26)	0.89
MFIS cognitive median range	8 (0-36)	10 (0-40)	0.71
MFIS psychosocial median range	3 (0-7)	2 (0-6)	0.92
MSQOL-54 Overall quality of life median range	28 (10-82)	736 (20-82)	

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
MSQOL-54 physical median range		59 (44-81)	57 (41-81)						
MSQOL-54 mental health median range		66 (24-90)	66 (32-87)						
Average adherence rate		**87.0 (8.0)%**	**90.0 (6.0)%**						

Table 28: Tarakci 2013

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Tarakci et al. Group exercise training for balance, functional status, spasticity, fatigue and quality of life in multiple sclerosis: a	RCT. Computer-generated sequence generation but no reporting of allocation concealment. No reports of	110 randomised (55 each group). 4 were lost from analysis for exercise group [exacerbation(1), personal problems (1), participation in <80% of training (2)]	Inclusion: Definite MS (McDonald criteria); EDSS 2-6.5; no relapses within 30 days; stability of medication. Exclusion: other CNS disease; pregnancy; conditions/meds preventing exercise; regular training in past 3 months.			Exercise 3 x 60 minute sessions per week for 12 weeks. Focussed on flexibility, range of movement, strengthening with/without therabands for LL, core, balance, co-	Waiting list; no intervention, but advised to continue normal routine.	12 weeks	No funding
				Exercise	**Control**				
			Age	41.5(9.4)	39.7(11.2)				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
randomised controlled trial. Clinical Rehabilitation 2013; doi 10.1177/0269215513481047cre.sagepub.com	allocation concealment. Assessor blinding clear.	and 7 from the control group [participation in exercise programme (1), exacerbation of symptoms (3), not coming to second assessment (3)]. Per-protocol analysis used with clear potential for attrition bias.	Female	34/51	30/48	ordination and function. Intensity was set at a RPE of 13			
			EDSS	4.38(1.4)	4.2(1.4)				
			Disease duration	9(4.7)	8.4(5.4)				
			RR PP SP	32/51 10/51 9/51	33/48 8/48 7/48				
			FSS	39.3(7.2)	39.898.4)				
			10MWT (s)	17.9(2.9)	17.2(3.9)				
			MusiQoL	74.4(9.2)	73.4(9.7)				
			R hip flex modified Ashworth scale (MAS)	1.35(1.33)	1.52(1.03)				
			L hip flex MAS	1.29(1.15)	1.13(1.18)				
			R hams MAS	1.35(1.18)	1.28(0.89)				
			L hams MAS	1.01(1.15)	1.02(0.88)				
			R achilles MAS	0.86(0.87)	0.94(0.61)				
			L achilles MAS	0.58(0.82)	0.81(0.69)				
Results: As there were clear pre-test differences for most outcomes, the post-pre change scores have been used. Sds for the change values were not reported, so the sd for these have been derived from the post-pre group comparison p which was provided. Note that the estimated sds are the same in each group, as these were estimated from the single value of the SE of the difference in means									

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding

Outcome	Exercise (n=51)	Sd exercise	Control (n=48)	Sd control	
FSS	-8.26	16.9239	3.29	16.9239	
10MWT (s)	-4.73	9.055387	1.45	9.055387	
MusiQoL	1.98	5.00333	-0.4	5.00333	
R hip flex modified Ashworth scale (MAS)	-0.67	1.172218	0.13	1.172218	
L hip flex MAS	-0.29	0.943736	0.18	0.943736	
R hams MAS	-0.65	1.230829	0.19	1.230829	
L hams MAS	-0.47	1.040344	0.24	1.040344	
R achilles MAS	-0.18	0.675574	0.16	0.675574	
L achilles MAS	-0.31	0.571456	0.08	0.571456	
Results – number of events, no./no. analysed (%)					
Outcome	**Exercise**		**Control**		
Adverse events (symptom exacerbation leading to withdrawal)	**1/52 (1.9%)**		**3/51 (5.9%)**		

Table 29: Thomas 2013

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Thomas et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. J Neurol	RCT. Computerised sequence generation and allocation concealment ensured by randomisation and allocation being done by a third party statistician off-site. No participant blinding. HCP blinding also not possible.	164 randomised (84 FACETS and 80 CLP). 12 withdrew from FACETS intervention [changed mind(3), operation (1), unwell/relapse (2), work commitments (3), too busy (1), reservations about group format 91), unknown reason (1)] and none withdrew from CLP. 13/84 did not attend first FU in FACETS [non-	Inclusion: Clinically definite MS diagnosis; FSS total score >4; ambulant. Exclusion; Participation in fatigue programme within past year; cognitive impairments; relapse in past 3 months; starting treatment with DMTs or antidepressants within the past 3 months. **FACETs** / **CLP** Age: 48(10.2) / 50.1(9.1) %female: 73 / 73 Benign: 5% / 3% RR: 43% / 51% SP: 20% / 29% PP: 6% / 10% Full time employment: 18% / 14% Part time: 14% / 17% Self-employed	Group based fatigue management programme (FACETS). 6x 90 minute sessions held weekly and facilitated in groups of 6-12 by two health professionals with experience of working with people with MS (minimum Band 7 PTs or OTs). The sessions were highly structured, comprising presentations, discussions, group activities and homework. A participant	Current local practice only	10 weeks (4 weeks after final session) and 5.5 months (4 months after final session)	Non commercial

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Neurosurg Psychiatry 2013; 00: 1-8: doi: 10.1136/jnnp-2012-303816	No assessor blinding reported.	responder (7), dropped out (2), bereavement 92), unwell - relapse (1), unwell food-poisoning (1). 5/80 did not attend first FU in CLP [non-responders (2), personal reasons 91), additional illness (1), too much on 91). At 2nd FU there was 12/84 lost from FACETs and 6/80 lost from CLP. Main analysis was reported as ITT, but the results reported were the per-protocol results. Hence	Not employed	5% 63%	5% 64%	handbook was also used, that mirrored the course content.			
			Years since diagnosis >10 yrs	41%	43%				

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
		high risk of attrition bias.					

Results: Pre and post test results but overall MD results used as there were some baseline differences that could confound in a post-test only analysis.

Outcome	Difference between change from baseline in intervention group and change from baseline in control group (95% CIs n=164	SE (derived from upper CI/1.96*) *conservative estimate of critical t as it is unclear what n was for the analysis of group diffs		
Global Fatigue Severity (-ve indicates benefit to FACETS) at 10 weeks	-0.03(-0.33 to 0.28), mean final value 5.48 in FACETs and 5.55 in control	0.158		
Global Fatigue Severity (-ve indicates benefit to FACETS) at 5.5 months	-0.36(-0.63 to -0.08), mean final value 5.26 in FACETs and 5.66 in control	0.143		
Fatigue self-efficacy scale (+ve indicates benefit to FACETS) at 10 weeks	9(4 to 14), mean final value 57.0 in FACETs and 50.0 in control	2.551		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Fatigue self-efficacy scale (+ve indicates benefit to FACETS) at 5.5 months			6 (0-12), mean final value 56.0 in FACETs and 53.0 in control	3.061			
MSIS-29 (-ve indicates benefit to FACETS) at 10 weeks			1.44(-2.36 to 5.25), mean final value 47.3 in FACETs and 42.2 in control	1.944			
MSIS-29 (-ve indicates benefit to FACETS) at 10 weeks			-1.56 (-6.45 to 3.34), mean final value 44.9 in FACETs and 43.0 in control	2.500			
Results – event number, no./no. analysed (%)							
Outcome			**FACETS**	**CLP**			
Adverse events – withdrawal due to relapse			**2/61 (3.3%)**	**0/72 (0.0%)**			
Adherence – attended at least 4 sessions (out of possible 6)			**72/84 (85.7%)**	**Not reported/not applicable**			
Results – mean (SD)							
Satisfaction – content/format/usefulness/pace /length. Scale 1-5 (5=ideal).			**Content: 4.6 (0.6)** **Format: 4.5 (0.7)** **Usefulness: 4.6 (0.7)** **Pace: 3.1 (0.6)** **Length: 3.1 (0.6)**	**Not reported/not applicable**			

Table 30: Van den Berg 2006

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Van den Berg et al. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. J Neurol Neurosurg Psychiatry 2006; 77: 531-533	RCT crossover. Unfortunately they did not do a paired analysis, so extraction is of the first phase part only. Computer generated sequence generation and very likely allocation concealment. No reports of assessor blinding	N=19 randomised 1st phase Exercise N=8 completed. 2 dropped out (no reasons) Control N=8 completed. 1 dropped out (no reasons). Possible attrition bias.	Confirmed clinical diagnosis of MS. Required to walk 10 m in < 60 sec without hands on support, using an aid if necessary, and to be able to walk on a treadmill with or without hands on support. Excluded if relapse within past 8 weeks or medical precluding participation.	**Exercise** Supervised treadmill training, three session each week, for 4 weeks.	**Control** No training	7 wks (1st phase)	None reported

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Results. Due to poor analysis in study, only first phase results are given at 7 weeks. The scores below are the change from baseline to 7 weeks							
	Exercise	**Control**					
10 metre timed walk s	-3.1 (2.5)	0.6 (1.4)					
2 minute walk m	10.8 (6.7)	5.8 (7.8)					
Fatigue Severity Scale	-4.5 (7.7)	-4.4 (7.8)					
Guy's neurological disability scale	0.75 (1.8)	0.13 (2.0)					

Table 31: van Kessel 2008

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Van Kessel et al. A randomised controlled trial of cognitive behaviour	RCT. Computer block randomisation and very clear allocation	72 randomised (35 intervention and 37 control). All CBT patients	Patients with MS in Auckland, noted to suffer from fatigue and to be ambulatory. Inclusion: McDonald criteria; EDSS≤6, Fatigue Scale score of 4 or greater; abstention from any other psychological or	Cognitive behavioural therapy – seen individually for 8 weekly sessions of up to 50 minutes each by the same therapist. Three were	Relaxation therapy – seen individually for 8 weekly sessions of up to 50 minutes each by the same	8 weeks, 5 months and 8 months	Academic funding only. No commercial conflicts

<table>
<tr><th>Reference</th><th>Study type</th><th>No. pts</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Source of funding</th></tr>
<tr>
<td>therapy for multiple sclerosis fatigue. Psychosomatic medicine 70: 205-213</td>
<td>concealment. Patient and HCP blinding not possible due to nature of study. No reports of assessor blinding. ITT approach, with last measurement carried forward imputation.</td>
<td>received full intervention. 2 control patients did not complete treatment due to ‘no time’ and ‘lack of efficacy’. 1 lost to follow up in CBT group due to ‘no time’.
All analysed using ITT with imputation.</td>
<td>pharmacological treatments during the study.

Patients were allowed to join study if on beta-interferon and/or ant-depressant treatments > 3 months.

Exclusion: serious psychological disorders.

<u>Baseline comparability</u>

Outcomes well matched at baseline. Demographic variables are below:
<table>
<tr><th></th><th>CBT</th><th>Control</th></tr>
<tr><td>Age</td><td>43(9)</td><td>47(9)</td></tr>
<tr><td>Length if illness</td><td>5.5(4.8)</td><td>6.7(6)</td></tr>
<tr><td>% female</td><td>80</td><td>70</td></tr>
<tr><td>%RR
%SP
%PP</td><td>66
31
3</td><td>49
30
21</td></tr>
<tr><td>%European
%Maori</td><td>91
9</td><td>97
3</td></tr>
</table>
</td>
<td>face to face at hospital, and the other 5 were done by telephone. A manual was used that helped as a visual aid during telephone sessions. This included a chapter of information for each week and structured homework sheets. All sessions followed a similar format, which included an agenda, a review and questions from the previous week, a review of homework tasks, followed by an introduction of the new “topic”, setting new practice tasks, a brief summary and questions at the end.

Collaborative in style and therapist used Socratic questioning wherever possible.</td>
<td>therapist. Three were face to face at hospital, and the other 5 were done by telephone. A manual was used that helped as a visual aid during telephone sessions. This included a chapter of information for each week and structured homework sheets. All sessions followed a similar format, which included an agenda, a review and questions from the previous week, a review of homework tasks, followed by an introduction of the new “topic”, setting new</td>
<td></td>
<td>of interest.</td>
</tr>
</table>

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
			% working less	37	35	The main aim was to challenge any behavioural, cognitive, emotional and external factors that may be contributing to MS fatigue. The sessions were tailored to the individual but the sessions followed a broad curriculum including causes of fatigue, rationale of CBT, sleep, symptoms, changing thinking, negative thoughts, managing stress and social support was covered.	practice tasks, a brief summary and questions at the end. Relaxation techniques were taught in the sessions, including daiphragmatic breathing, progressive muscle relaxation, visualisation, cue-controlled relaxation, and rapid relaxation. In order to engage patients the rationale for teaching relaxation was that relaxation may reduce fatigue through reducing muscle tension. The curriculum covered in the		
			% unemployed	26	35				
			% using meds	49	57				
			EDSS	3.04(1.8)	3.86(1.5)				

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
							CBT arm was not covered. Provided by the same single CBT-trained clinical psychologist as for CBT		

Results [mean(sd) given unless stated]. Lower better for all outcomes

	CBT	Control		
Total fatigue (FS) 8 weeks	7.9(4.34)	11.57(5.28)		
Total fatigue (FS) 5 months	8.99(5.31)	11.11(4.57)		
Total fatigue (FS) 8 months	10.37(6.37)	12.49(5.24)		
Fatigue-related impairment (Work and social adjustment scale) 8 weeks	16.13(9.97)	19.71(9.72)		
Fatigue-related impairment (Work and	13.38(8.30)	19.24(9.56)		

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
social adjustment scale) 5 months							
Fatigue-related impairment (Work and social adjustment scale) 8 months		14.97(9.88)	20.16(10.53)				
HADS – depression 5 months		**3.62(2.73)**	**5.13(3.14)**				
HADS – depression 8 months		**3.97(2.76)**	**5.05(3.61)**				
HADS – anxiety 5 months		**5.60(3.27)**	**5.81(3.21)**				
HADS – anxiety 8 months		**6.00(4.08)**	**5.81(3.03)**				
Satisfaction - usefulness end of treatment (scale 0-4, lower better)		**0.76(0.95)**	**0.97(0.85)**				

Table 32: Velikonja 2010

Reference	Study type	No. pts	Patient characteristics			Intervention	Comparison	Length of follow-up	Source of funding
Velikonja O, Curic K, Ozura A, Jazbec SS. Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis. Clinical Neurology and Neurosurgery. 2010; 112(7):597-601	RCT.No reports of sequence generation or allocation concealment. There was assessor blinding.	20 randomised and analysed.	RR, PP or SP; 26-50 years, EDSS <7; EDSSpyr >2 Variable / Climbing / Yoga MFIS total: 40 / 32 MFIS cog: 17 / 12 MFIS ps: 3 / 4 MFISphys: 25 / 17.5 Spasticity MSA: 10 / 9.3 EDSSpyr: 4 / 2.5			Sports climbing sessions once a week for 10 weeks. Climbing wall with inclination of 90degrees and height of 5m adjusted for disabled users by use of larger and more holds. Top rope system used for safety. This has been placed in the category of 'resistance training' in the review as it is primarily a resistance training exercise.	Yoga sessions once a week for 10 weeks. Hatha Yoga technique adjusted for people with disabilities.	10 weeks	None reported

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding

Results: Non parametric analyses, and median (IQR*) baseline and post-test values given below. *unclear if IQR – could have been range.

Overall, climbing appeared to lead to greater improvements in fatigue than yoga, but this may partly be explained by the climbing group starting off at a worse level. EDSS also improved more in the climbing group but again the climbing group were worse at baseline. Neither group seemed to change much in spasticity, though climbing was numerically more improved.

Variable	Climbing (n=10)			Yoga (n=10)			
	baseline	10 weeks	p	baseline	10 weeks	p	
MFIS total	40(36.5-53)	27(21.5-45.5)	0.015	32(22-42)	23(20.5-36)	0.057	
MFIS cog	17(8.5-21.5)	8(6-19.5)	0.024	12(4.5-14.3)	7(3.8-12.5)	0.282	
MFIS ps	3(1.5-6)	3(1-5.5)	0.334	4(1-4.5)	3(0.8-4)	0.234	
MFISphys	25(21.5-28.5)	19(9-26.5)	0.021	17.5(14.3-24.5)	18(9.8-19)	0.064	
Spasticity MSA	10(8.5-18.3)	12.5(10-17.3)	0.574	9.3(3.5-18.4)	8.8(5.5-17.1)	0.673	
EDSSpyr	4(3-4)	3(2.5-4)	0.046	2.5(2-4)	2(2-3.3)	0.317	
CES-D - depression	**10.0 (6.5-19.0)**	**5.0 (3.0-22.5)**	**0.678**	**9.5 (3.8–20.3)**	**3.0 (1.8–13.0)**	**0.212**	
Executive function – NAB (Mazes subtest of Executive module from Neuropsychological assessment battery)	**14.0 (7.5–19.5)**	**16.0 (11.0–20.5)**	**0.341**	**20.5 (12.5–22.5)**	**19.0 (12.8–21.5)**	**0.437**	
Executive function – TOLtnm (Tower of	**34.0 (23.0–48.0)**	**26.0 (12.5–49.0)**	**0.172**	**23.0 (9.5–29.5)**	**33.0 (22.0–44.8)**	**0.059**	

Reference	Study type	No. pts	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
London total number of moves)							
Executive function – TOLtt (Tower of London total time)	333.0 (263.5–435.5)	267.0 (193.5–372.5)	0.515	210.0 (176.0–296.3)	267.5 (148.3–327.8)	0.333	
Attention – d2CP (index of concentration performance)	115.0 (98.3–125.5)	119.5 (91.3–139.0)	1.000	151.0 (94.5–175.5)	176.5 (116.5–191.3)	0.005	

Appendix E – Forest plots

E.1 Aerobic exercise vs. control (no intervention, waitlist control, education only) – up to 6 month outcomes

Figure 2: Fatigue Severity Scale (1-7; lower better)

	Aerobic			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ahmadi 2013	1.9	0.73	10	4.23	1.04	10	25.7%	-2.33 [-3.12, -1.54]	
Geddes 2009	-0.24	0.72	8	-0.17	0.49	4	26.4%	-0.07 [-0.76, 0.62]	
Heine 2017	5.2	0.9	37	5.1	1.1	34	27.9%	0.10 [-0.37, 0.57]	
Mostert 2002	4.4	1.9	13	5	1.9	13	19.9%	-0.60 [-2.06, 0.86]	
Total (95% CI)			**68**			**61**	**100.0%**	**-0.71 [-1.87, 0.45]**	

Heterogeneity: Tau² = 1.20; Chi² = 28.34, df = 3 (P < 0.00001); I² = 89%

Test for overall effect: Z = 1.20 (P = 0.23)

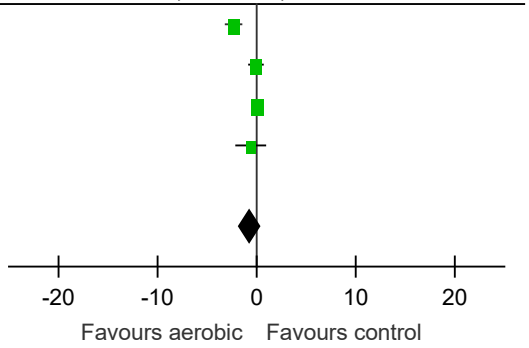
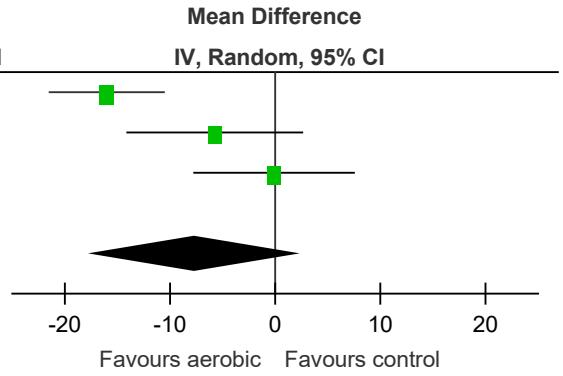


Figure 3: Fatigue Severity Scale (9-63; lower better)

	Aerobic			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Pazokian 2013	31.64	14.13	80	47.65	14.4	40	35.9%	-16.01 [-21.44, -10.58]
Sadeghi Bahmani 2019	39.31	17.23	26	45.05	11.77	21	31.5%	-5.74 [-14.06, 2.58]
Van den Berg 2006	-4.5	7.7	8	-4.4	7.8	8	32.6%	-0.10 [-7.70, 7.50]
Total (95% CI)			**114**			**69**	**100.0%**	**-7.59 [-17.64, 2.47]**

Heterogeneity: Tau² = 65.58; Chi² = 12.19, df = 2 (P = 0.002); I² = 84%

Test for overall effect: Z = 1.48 (P = 0.14)



1

Figure 4: Modified Fatigue Impact Scale – Total (0-84; lower better)

	Aerobic			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Hebert 2011	44.7	16.3	13	52.6	17.4	13	25.6%	-7.90 [-20.86, 5.06]
Heine 2017	38.3	13.7	37	34.7	11.8	34	43.2%	3.60 [-2.33, 9.53]
Schulz 2004	21.5	15	15	30.3	13.3	13	31.2%	-8.80 [-19.28, 1.68]
Total (95% CI)			**65**			**60**	**100.0%**	**-3.21 [-12.34, 5.92]**

Heterogeneity: Tau² = 41.02; Chi² = 5.49, df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 0.69 (P = 0.49)

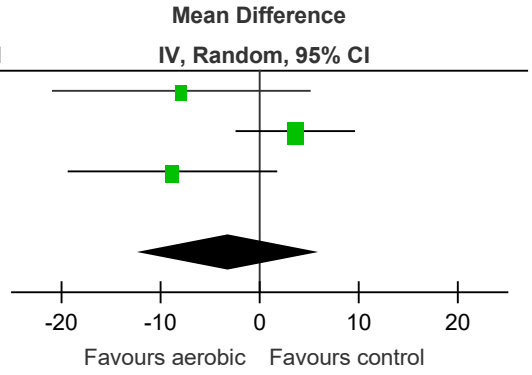


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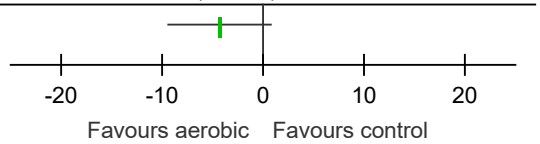
Figure 5: Modified Fatigue Impact Scale – Physical (0-36; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Schulz 2004	9.7	6.8	15	14.5	6.4	13	-4.80 [-9.69, 0.09]	

1

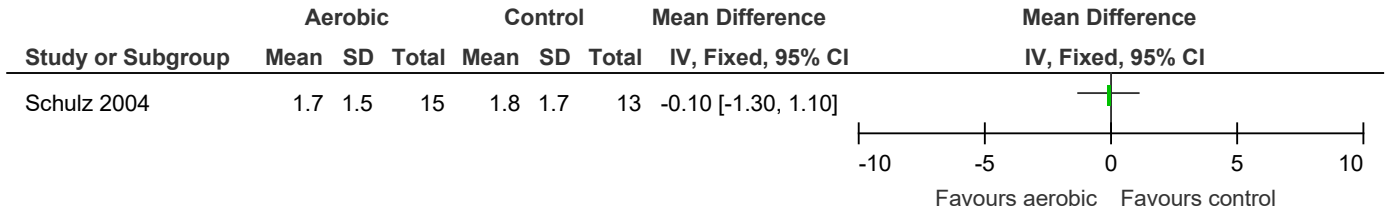
Figure 6: Modified Fatigue Impact Scale – Cognitive (0-40; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Schulz 2004	9.7	7.5	15	14	6.2	13	-4.30 [-9.38, 0.78]	



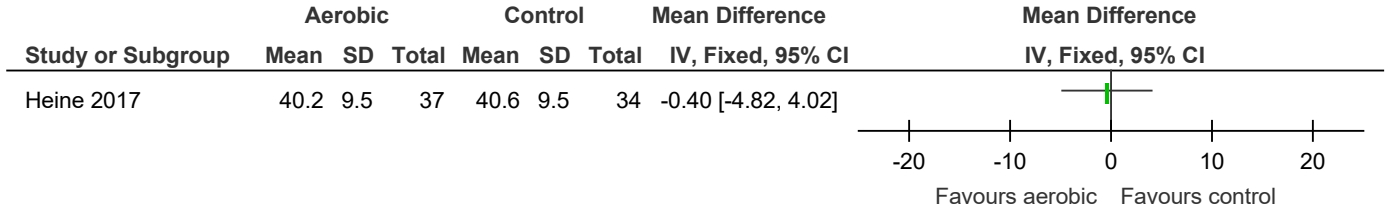
2

Figure 7: Modified Fatigue Impact Scale – Psychosocial (0-8)



1

Figure 8: Checklist Individual Strength (CIS)20r – fatigue subscale (8-56; lower better)



2

Figure 9: Fatigue Scale for Cognitive and Motor Challenge (FSMC) – Physical (10-50; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Feys 2019	26.2	10.2	21	29.6	8.2	21	-3.40 [-9.00, 2.20]	

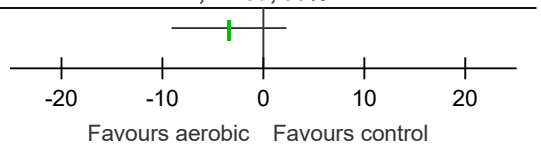


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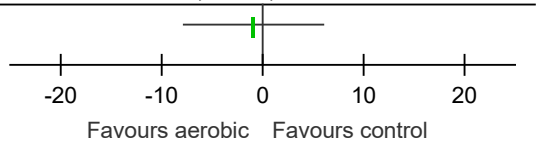
Figure 10: Fatigue Scale for Cognitive and Motor Challenge (FSMC) – Cognitive (10-50; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Feys 2019	28	12.6	21	28.9	10.1	21	-0.90 [-7.81, 6.01]	



2

Figure 11: Rhoten Fatigue Scale (0-10; lower better)

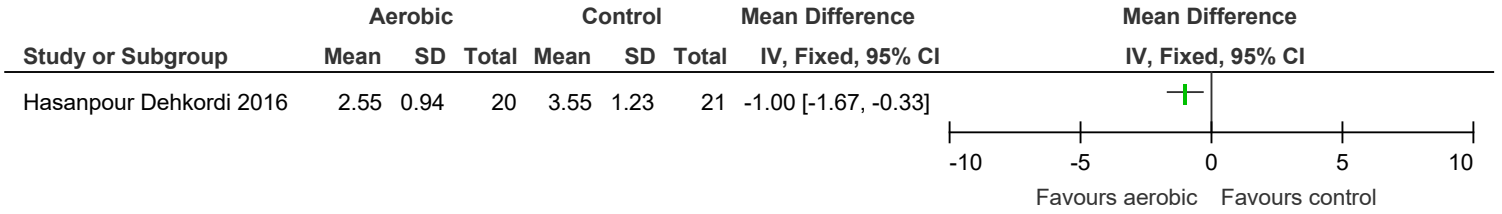


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Figure 12: Fatigue Impact Scale (0-160; lower better)

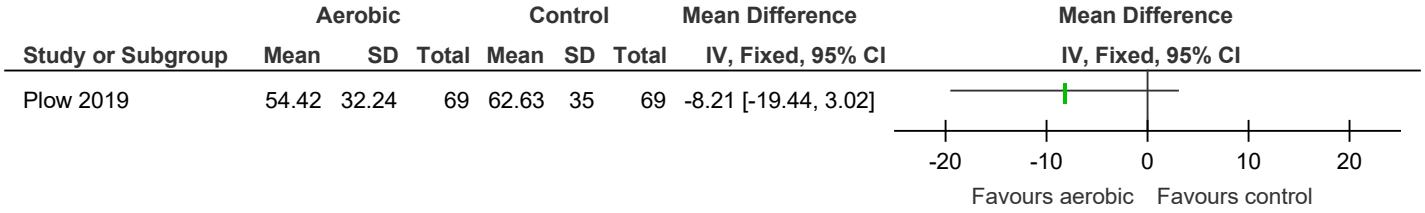

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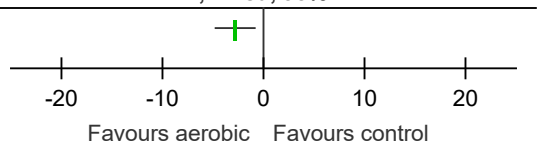
Figure 13: Multidimensional Fatigue Inventory – General Fatigue (4-20; lower better)

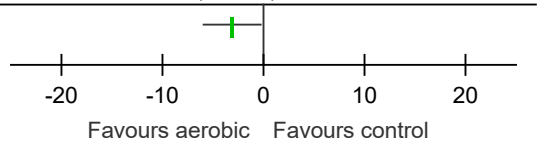
	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	12.1	2.8	15	14.9	3	20	-2.80 [-4.73, -0.87]	



1

Figure 14: Multidimensional Fatigue Inventory – Physical Fatigue (4-20; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	10.8	4	15	13.9	4.5	20	-3.10 [-5.93, -0.27]	



2

Figure 15: Multidimensional Fatigue Inventory – Reduced Activity (4-20; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	9.9	3.9	15	11.5	4.5	20	-1.60 [-4.39, 1.19]	

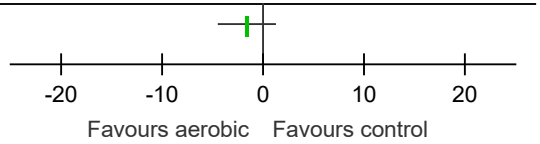


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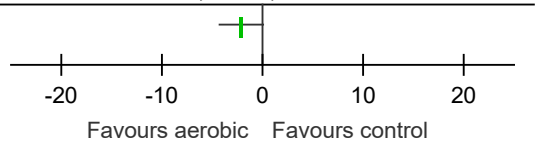
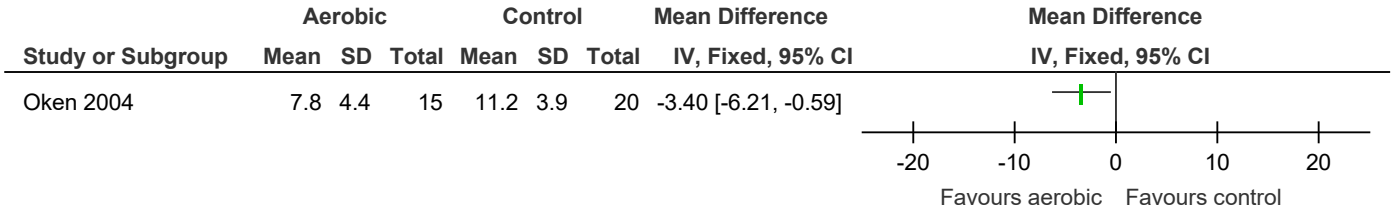
Figure 16: Multidimensional Fatigue Inventory – Reduced Motivation (4-20; lower better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	7.7	3.4	15	9.8	3	20	-2.10 [-4.27, 0.07]	



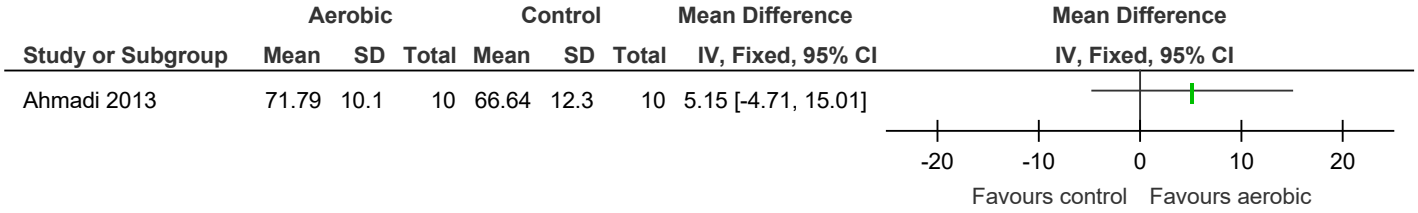
2

Figure 17: Multidimensional Fatigue Inventory – Mental Fatigue (4-20; lower better)



1

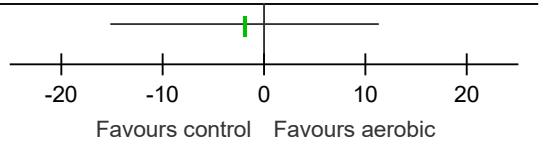
Figure 18: MSQOL-54 – Physical composite (0-100; higher better)



2

Figure 19: MSQOL-54 – Mental composite (0-100; higher better)

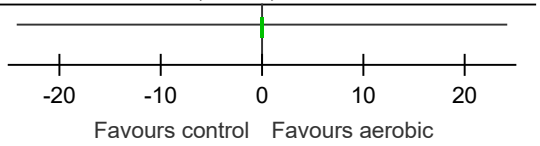
	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ahmadi 2013	64.62	15.12	10	66.54	14.89	10	-1.92 [-15.07, 11.23]	



1

Figure 20: MSQOL-54 – Change in Health domain (0-100; higher better)

	Aerobic			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ahmadi 2013	52.5	27.51	10	52.5	27.51	10	0.00 [-24.11, 24.11]	



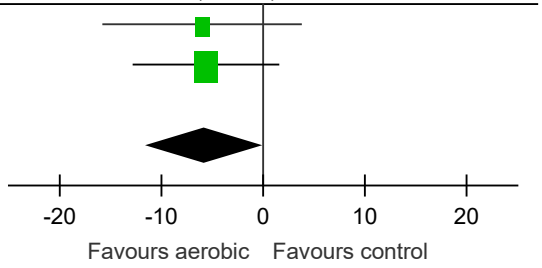
2

Figure 21: MSIS-29 – Physical domain (0-100; lower better)

	Aerobic			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Feys 2019	16.3	12.6	21	22.3	18.9	21	35.0%	-6.00 [-15.72, 3.72]	
Plow 2019	32.19	20.47	69	37.81	22.18	69	65.0%	-5.62 [-12.74, 1.50]	
Total (95% CI)			**90**			**90**	**100.0%**	**-5.75 [-11.50, -0.01]**	

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.96 (P = 0.05)



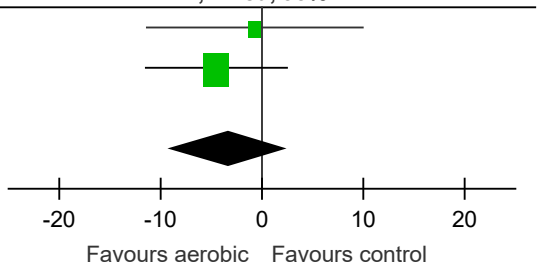
1

Figure 22: MSIS-29 – Psychological domain (0-100; lower better)

	Aerobic			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Feys 2019	23	17.2	21	23.7	18	21	29.9%	-0.70 [-11.35, 9.95]	
Plow 2019	31.08	20.39	69	35.57	21.3	69	70.1%	-4.49 [-11.45, 2.47]	
Total (95% CI)			**90**			**90**	**100.0%**	**-3.36 [-9.18, 2.47]**	

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%

Test for overall effect: Z = 1.13 (P = 0.26)



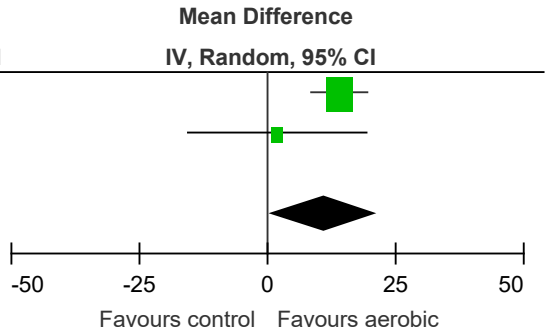
2

Figure 23: SF-36 – physical functioning (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hasanpour Dehkordi 2016	52.12	9.87	20	38.12	7.88	21	74.3%	14.00 [8.52, 19.48]
Oken 2004	60	27.9	15	58.1	23.3	20	25.7%	1.90 [-15.52, 19.32]
Total (95% CI)			**35**			**41**	**100.0%**	**10.89 [0.53, 21.25]**

Heterogeneity: Tau² = 29.77; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%

Test for overall effect: Z = 2.06 (P = 0.04)



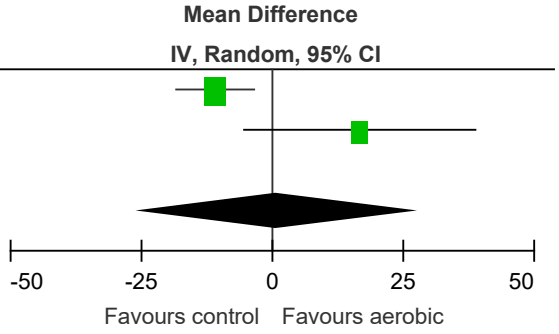
1

Figure 24: SF-36 – emotional limitations (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hasanpour Dehkordi 2016	36.23	12.65	20	47.15	11.65	21	57.4%	-10.92 [-18.37, -3.47]
Oken 2004	88.9	30	15	72.2	36.6	20	42.6%	16.70 [-5.39, 38.79]
Total (95% CI)			**35**			**41**	**100.0%**	**0.85 [-25.92, 27.62]**

Heterogeneity: Tau² = 310.71; Chi² = 5.39, df = 1 (P = 0.02); I² = 81%

Test for overall effect: Z = 0.06 (P = 0.95)



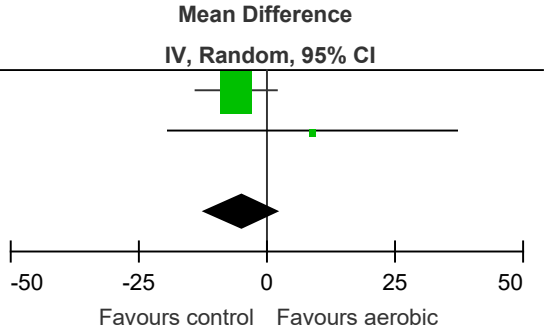
2

Figure 25: SF-36 – physical role limitations (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hasanpour Dehkordi 2016	46.14	13.45	20	52.14	12.4	21	92.7%	-6.00 [-13.93, 1.93]
Oken 2004	61.7	41	15	52.8	43.6	20	7.3%	8.90 [-19.31, 37.11]
Total (95% CI)			**35**			**41**	**100.0%**	**-4.91 [-12.54, 2.72]**

Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 1 (P = 0.32); I² = 0%

Test for overall effect: Z = 1.26 (P = 0.21)



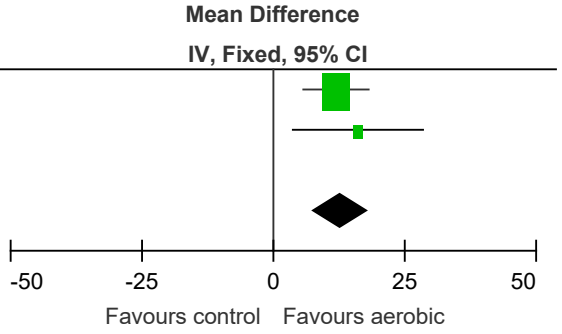
1

Figure 26: SF-36 – energy/vitality (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	55.24	11.54	20	43.32	8.45	21	79.9%	11.92 [5.70, 18.14]
Oken 2004	52.8	18.8	15	36.7	18.1	20	20.1%	16.10 [3.71, 28.49]
Total (95% CI)			**35**			**41**	**100.0%**	**12.76 [7.21, 18.32]**

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%

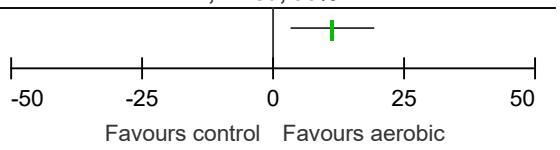
Test for overall effect: Z = 4.50 (P < 0.00001)



2

Figure 27: SF-36 – mental health (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	61.78	10.87	20	50.44	14.45	21	11.34 [3.54, 19.14]



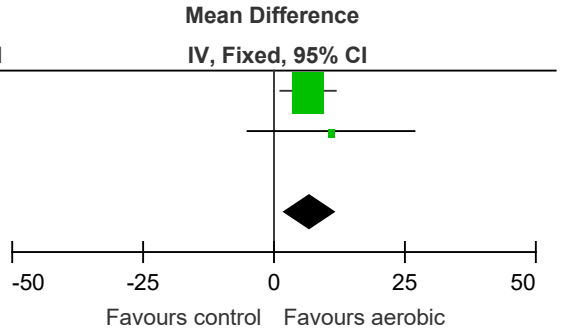
1

Figure 28: SF-36 – social functioning (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	47.22	8.78	20	40.7	8.44	21	90.1%	6.52 [1.24, 11.80]
Oken 2004	81.7	24	15	70.8	23.5	20	9.9%	10.90 [-5.02, 26.82]
Total (95% CI)			**35**			**41**	**100.0%**	**6.95 [1.94, 11.96]**

Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Test for overall effect: Z = 2.72 (P = 0.007)



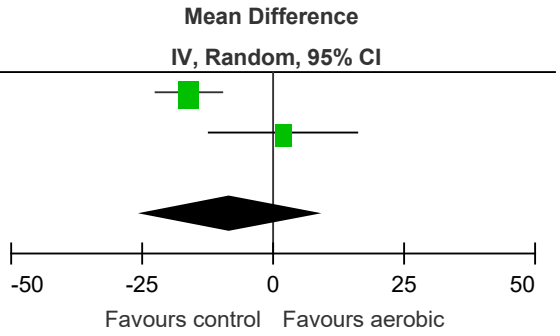
2

Figure 29: SF-36 – body pain (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hasanpour Dehkordi 2016	39.65	11.19	20	55.71	9.47	21	56.5%	-16.06 [-22.42, -9.70]
Oken 2004	70.8	17.4	15	68.9	25.3	20	43.5%	1.90 [-12.26, 16.06]
Total (95% CI)			**35**			**41**	**100.0%**	**-8.24 [-25.69, 9.21]**

Heterogeneity: Tau² = 129.92; Chi² = 5.14, df = 1 (P = 0.02); I² = 81%

Test for overall effect: Z = 0.93 (P = 0.35)



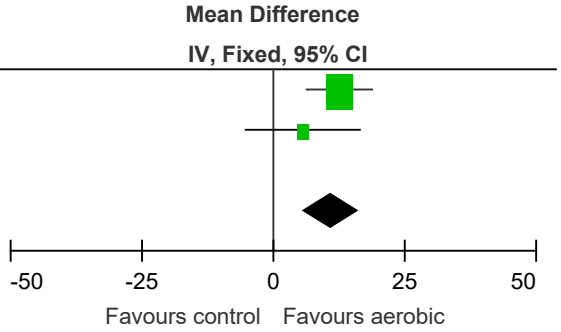
1

Figure 30: SF-36 – general health (0-100; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	55.23	10.96	20	42.65	9.25	21	75.3%	12.58 [6.36, 18.80]
Oken 2004	61	16	15	55.4	16.5	20	24.7%	5.60 [-5.26, 16.46]
Total (95% CI)			**35**			**41**	**100.0%**	**10.85 [5.45, 16.25]**

Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² = 16%

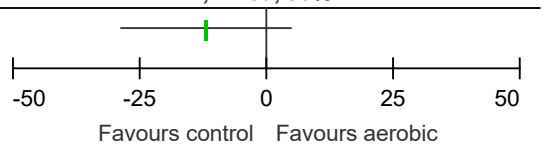
Test for overall effect: Z = 3.94 (P < 0.0001)



2

Figure 31: SF-36 – health transition (0-100; higher better)

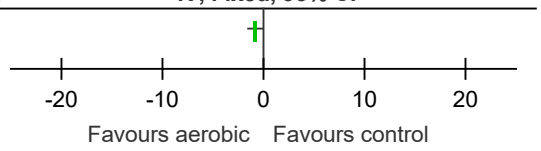
Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Oken 2004	36.7	28.1	15	48.6	20.1	20	-11.90 [-28.63, 4.83]



1

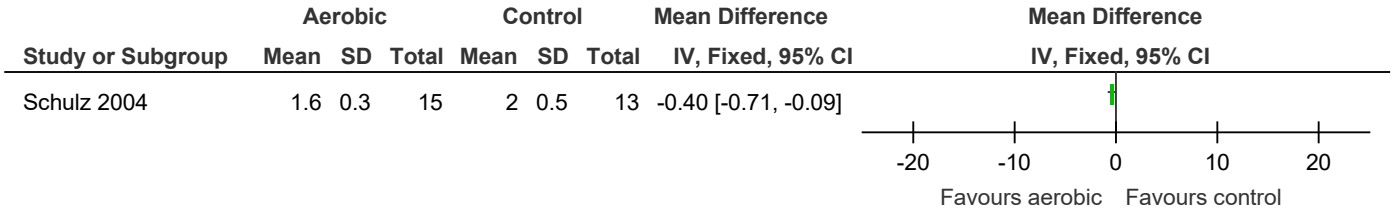
Figure 32: Hamburg Quality of Life in MS Scale (HAQUAMS) – fatigue/thinking (1-5; lower better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Schulz 2004	1.9	0.9	15	2.7	1	13	-0.80 [-1.51, -0.09]



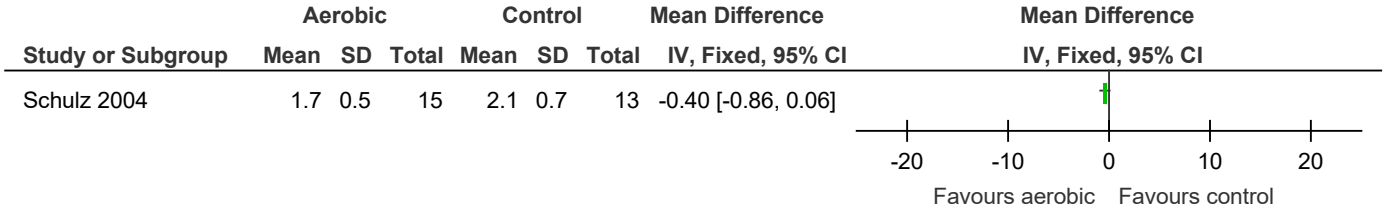
2

Figure 33: Hamburg Quality of Life in MS Scale (HAQUAMS) – total (1-5; lower better)



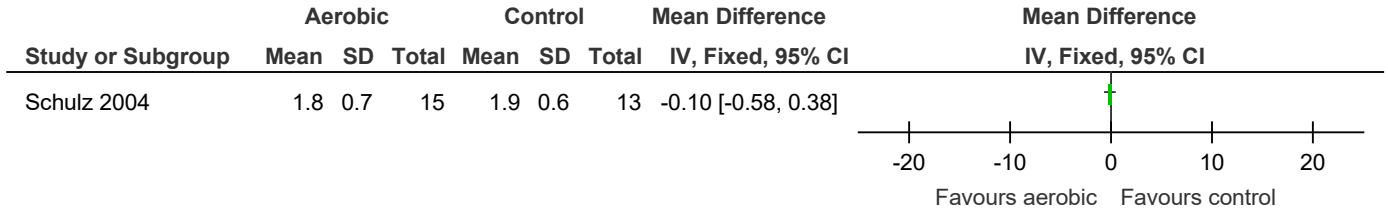
1

Figure 34: Hamburg Quality of Life in MS Scale (HAQUAMS) – mood (1-5; lower better)



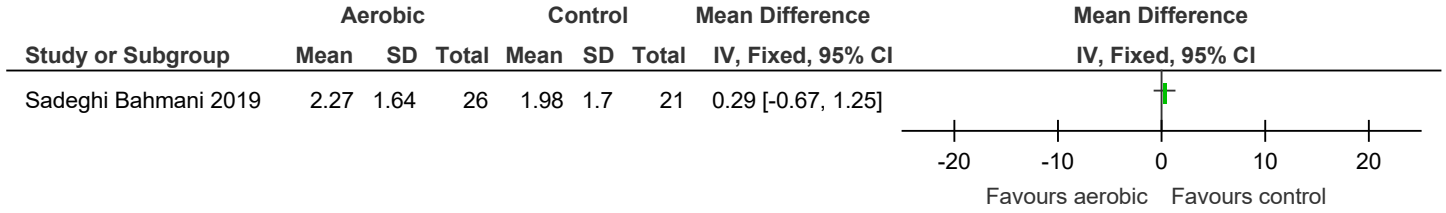
2

Figure 35: Hamburg Quality of Life in MS Scale (HAQUAMS) – social function (1-5; lower better)



1

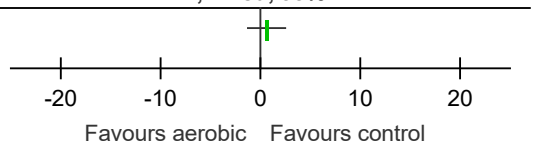
Figure 36: EDSS scale (0-10; lower better)



2

Figure 37: Guy's Neurological Disability scale (0-60; lower better)

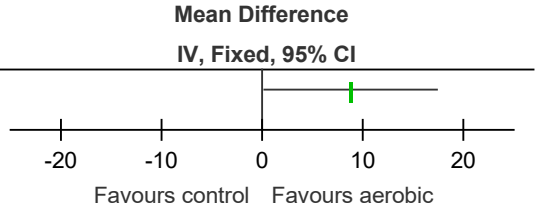
Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Van den Berg 2006	0.75	1.8	8	0.13	2	8	0.62 [-1.24, 2.48]



1

Figure 38: Cognitive – Digital Symbol Substitution Test (higher better)

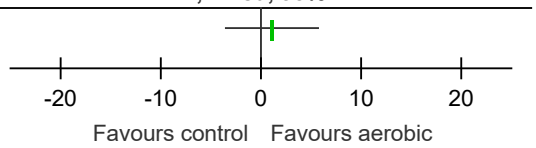
Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Feys 2019	94.3	15.9	21	85.5	12.2	21	8.80 [0.23, 17.37]



2

Figure 39: Cognitive – Word List Generation (higher better)

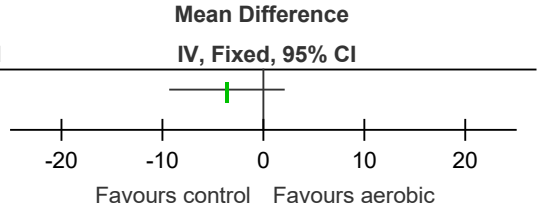
Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Feys 2019	32.5	7.4	21	31.4	7.8	21	1.10 [-3.50, 5.70]



1

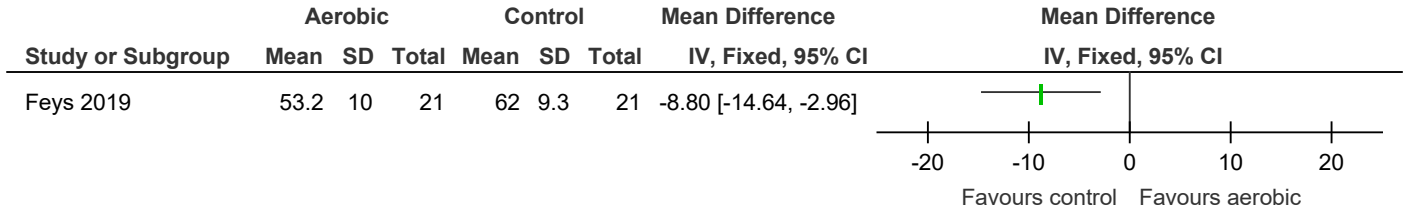
Figure 40: Cognitive – Selective Remining Test (long-term storage; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Feys 2019	47.2	10.6	21	50.8	7.8	21	-3.60 [-9.23, 2.03]



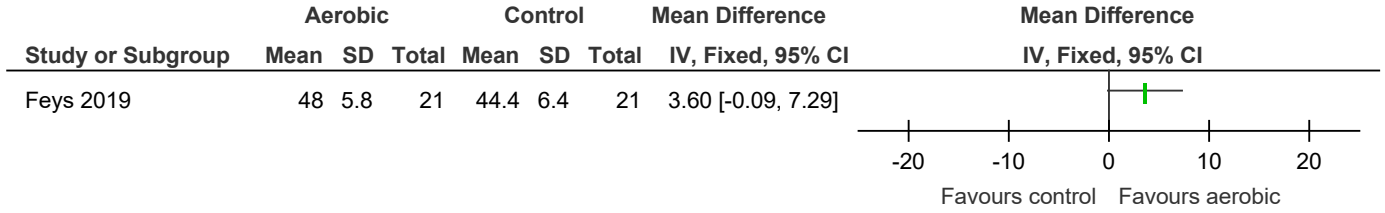
2

Figure 41: Cognitive – Selective Remining Test (consistent long-term retrieval; higher better)



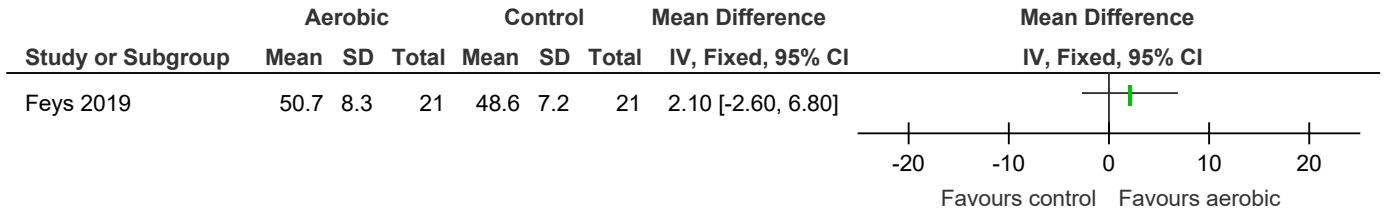
1

Figure 42: Cognitive – Spatial Recall Test (higher better)



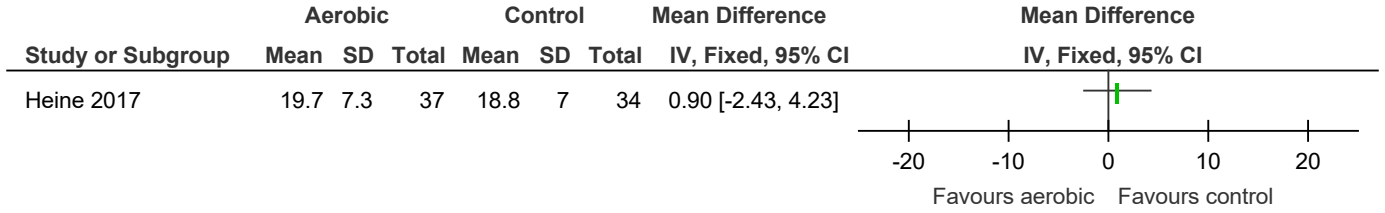
2

Figure 43: Cognitive – PASAT (higher better)



1

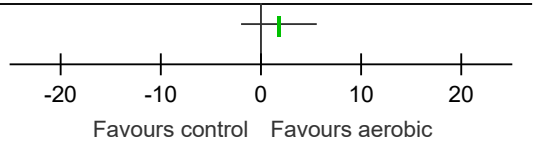
Figure 44: Cognitive – Checklist Individual Strength (CIS)20r – concentration (5-35; lower better)



2

Figure 45: Cognitive – Stroop Colour Word Interference (concentration/attention; higher better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Oken 2004	9.9	6.2	15	8.1	4.4	20	1.80 [-1.88, 5.48]



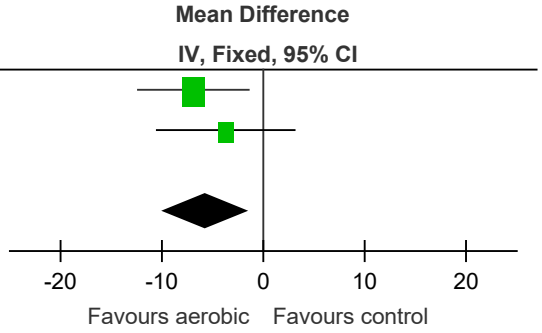
1

Figure 46: Beck Depression Inventory (0-63; lower better)

Study or Subgroup	Aerobic Mean	Aerobic SD	Aerobic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Ahmadi 2013	5.6	3.4	10	12.5	8.12	10	60.8%	-6.90 [-12.36, -1.44]
Hebert 2011	12.9	8	13	16.6	9.6	13	39.2%	-3.70 [-10.49, 3.09]
Total (95% CI)			**23**			**23**	**100.0%**	**-5.65 [-9.90, -1.39]**

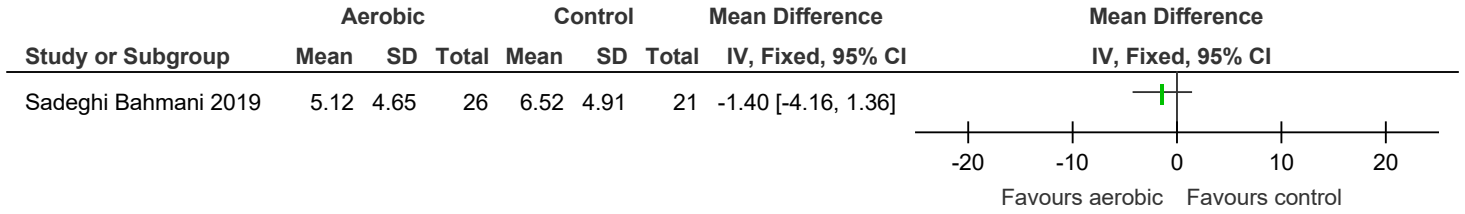
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%

Test for overall effect: Z = 2.60 (P = 0.009)



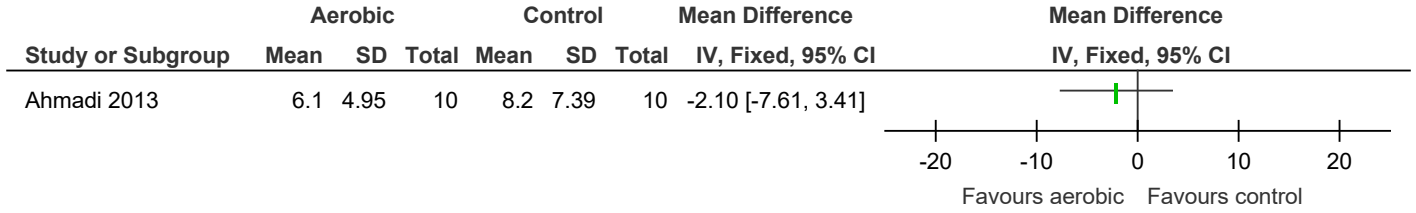
2

Figure 47: Beck Depression Inventory – fast screen (0-21; lower better)



1

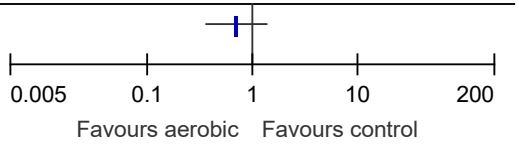
Figure 48: Beck Anxiety Inventory (0-63; lower better)



2

Figure 49: Incidence of adverse events – only MS exacerbations reported

Study or Subgroup	Aerobic Events	Aerobic Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Plow 2019	12	69	17	69	0.71 [0.37, 1.36]



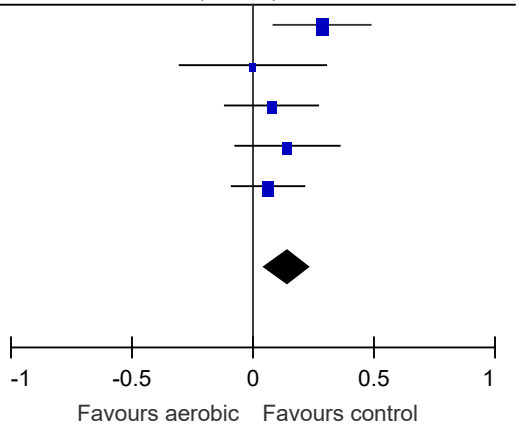
1

Figure 50: Incidence of adverse events – various types included

Study or Subgroup	Aerobic Events	Aerobic Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Feys 2019	6	21	0	21	30.2%	0.29 [0.09, 0.49]
Geddes 2009	0	8	0	4	7.7%	0.00 [-0.30, 0.30]
Hebert 2011	1	13	0	12	18.0%	0.08 [-0.12, 0.27]
McCullagh 2008	2	14	0	12	18.6%	0.14 [-0.07, 0.36]
Oken 2004	1	16	0	20	25.6%	0.06 [-0.09, 0.21]
Total (95% CI)		**72**		**69**	**100.0%**	**0.14 [0.04, 0.24]**
Total events	10		0			

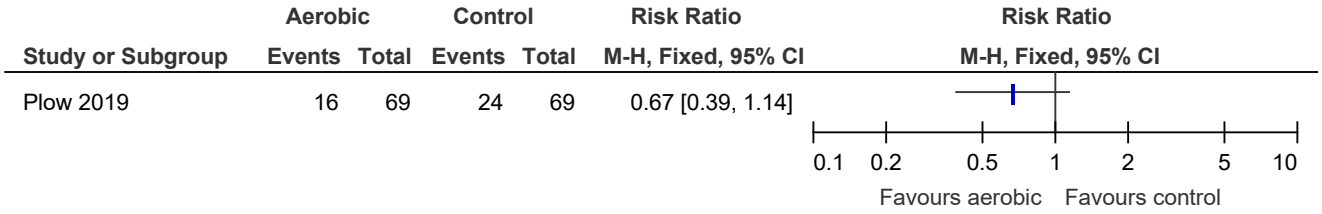
Heterogeneity: Chi² = 4.36, df = 4 (P = 0.36); I² = 8%

Test for overall effect: Z = 2.84 (P = 0.005)



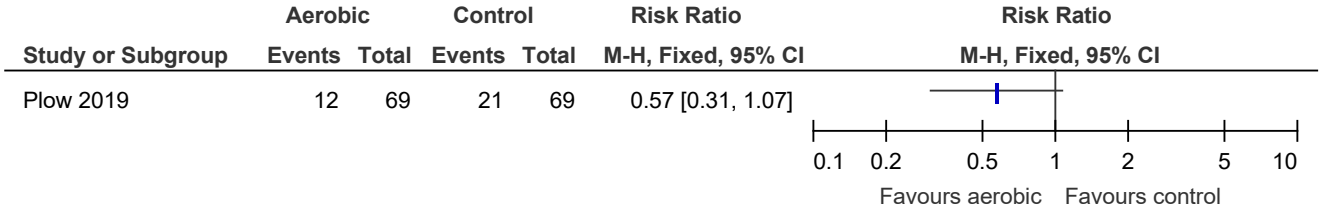
2

Figure 51: Incidence of adverse events – orthopaedic problems



1

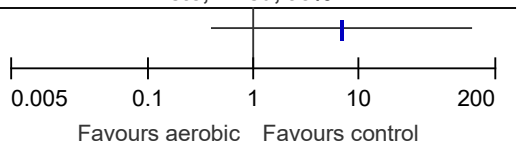
Figure 52: Incidence of adverse events – at least one fall



2

Figure 53: Adverse events leading to withdrawal

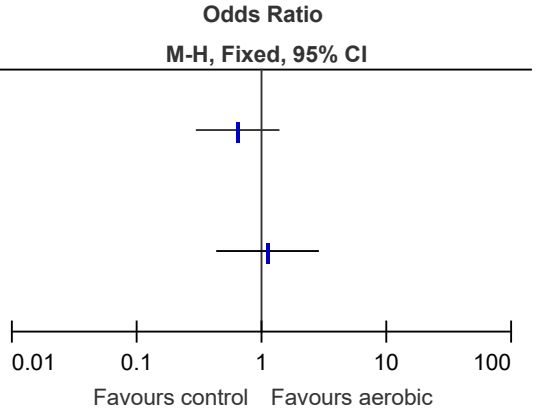
Study or Subgroup	Aerobic Events	Aerobic Total	Control Events	Control Total	Peto Odds Ratio Peto, Fixed, 95% CI
McCullagh 2008	2	14	0	12	6.92 [0.41, 118.14]



1

Figure 54: Acceptability of intervention – proportion completing all individual and group telephone calls

Study or Subgroup	Aerobic Events	Aerobic Total	Control Events	Control Total	Odds Ratio M-H, Fixed, 95% CI
1.53.1 Completed all 1-1 phone calls					
Plow 2019	47	69	53	69	0.64 [0.30, 1.37]
1.53.2 Completed all teleconference calls with or without at least one makeup session					
Plow 2019	59	69	58	69	1.12 [0.44, 2.84]



2

E.2 Aerobic exercise vs. control (no intervention, waitlist control, education only) – >6 month outcomes

Figure 55: Fatigue Severity Scale (1-7; lower better)

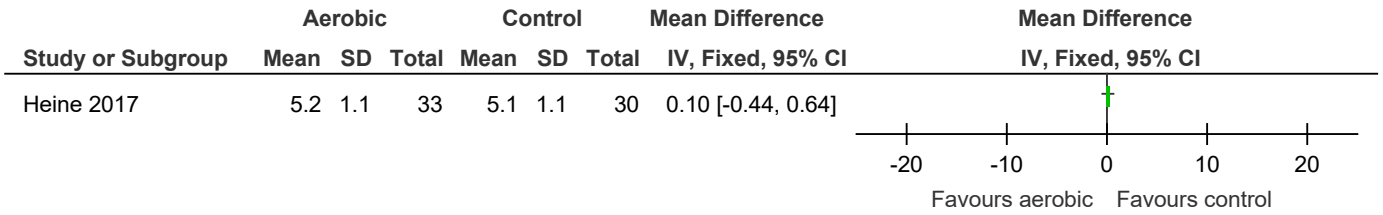


Figure 56: Modified Fatigue Impact Scale – total (0-84; lower better)

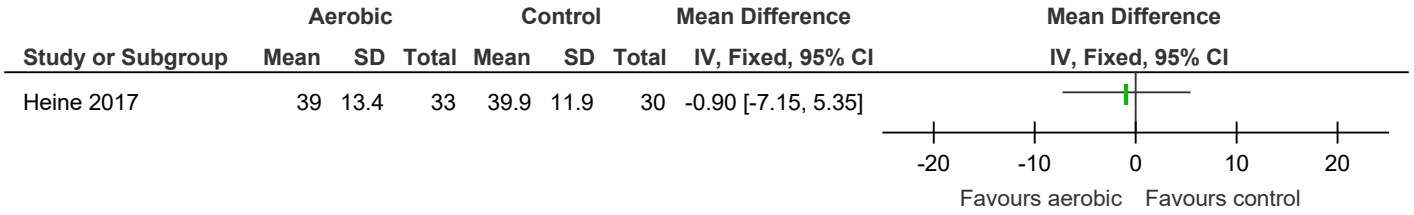


Figure 57: Checklist Individual Strength (CIS)20r – fatigue subscale (8-56; lower better)

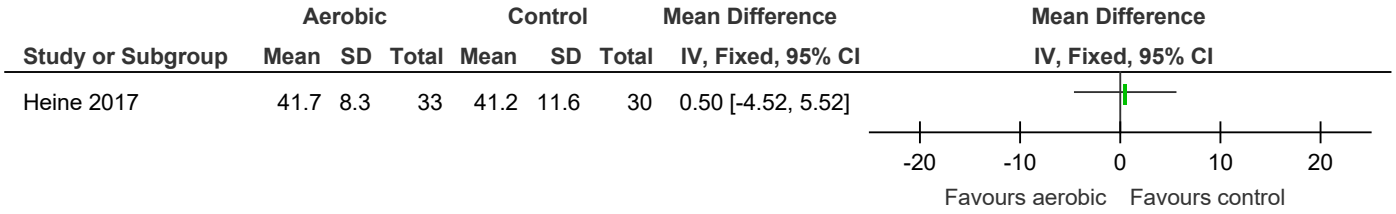


Figure 58: Cognitive – Checklist Individual Strength (CIS)20r – concentration subscale (5-35; lower better)

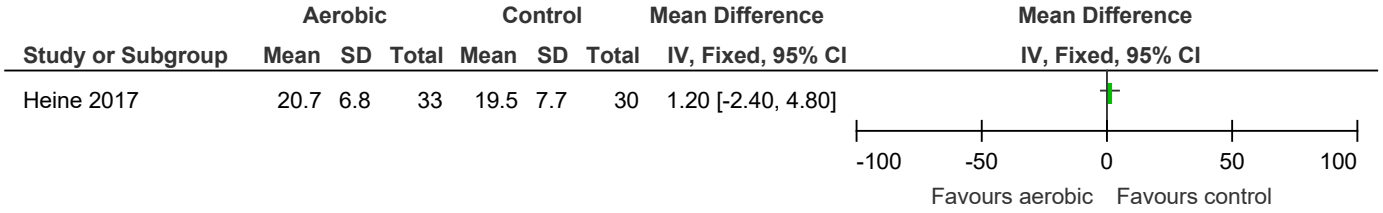
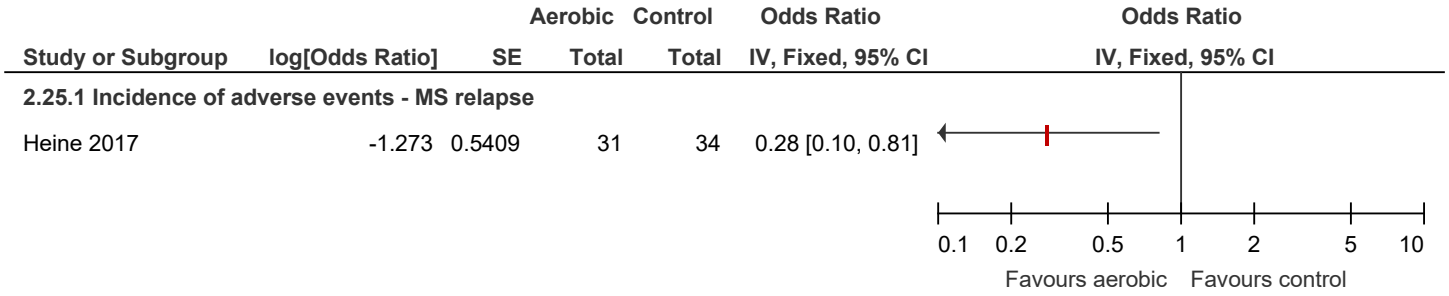
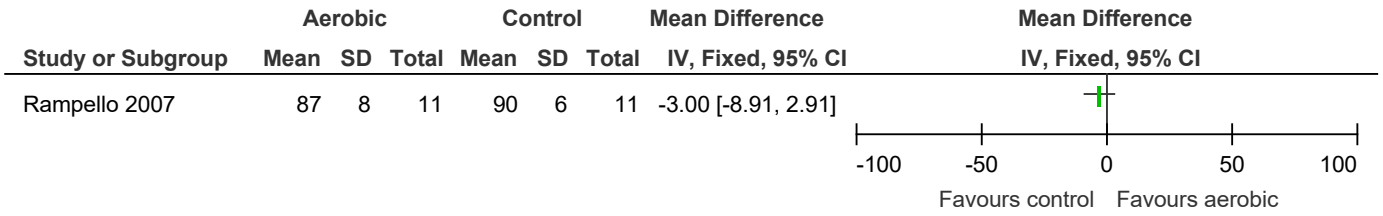


Figure 59: Incidence of adverse events (MS relapse)



E.3 Aerobic exercise vs. neurological rehabilitation (respiratory, postural and stretching) – up to 6 months outcomes

Figure 60: Average adherence rate (higher better)



Note that additional outcomes for this study were only available as median values and have been presented in a table in the summary of effectiveness evidence section.

E.4 Functional electrical stimulation + aerobic exercise vs. control (waitlist) – up to 6 months outcomes

Figure 61: 5-Item Modified Fatigue Impact Scale (0-20; lower better)

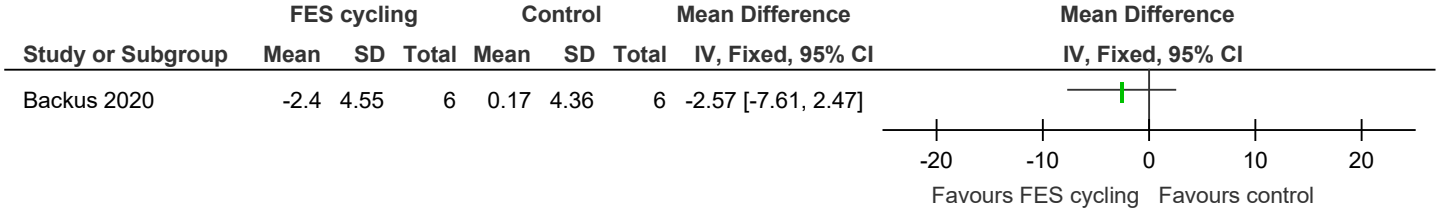


Figure 62: Decrease (any decrease) in score on 5-Item (scale 0-20) Modified Fatigue Impact Scale

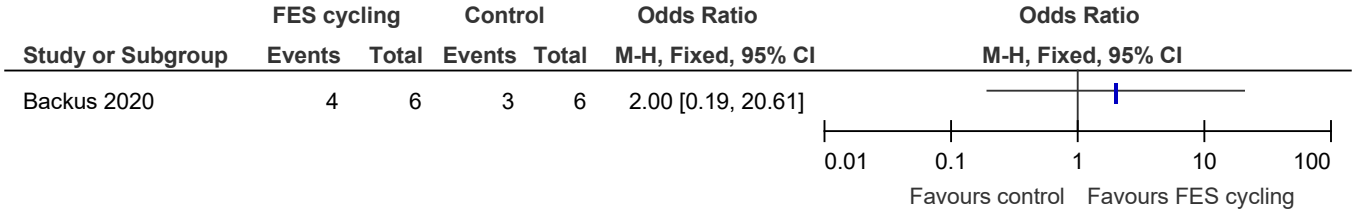


Figure 63: Fatigue Scale of Motor and Cognitive Functions (scales 20-100 or 10-50; lower better)

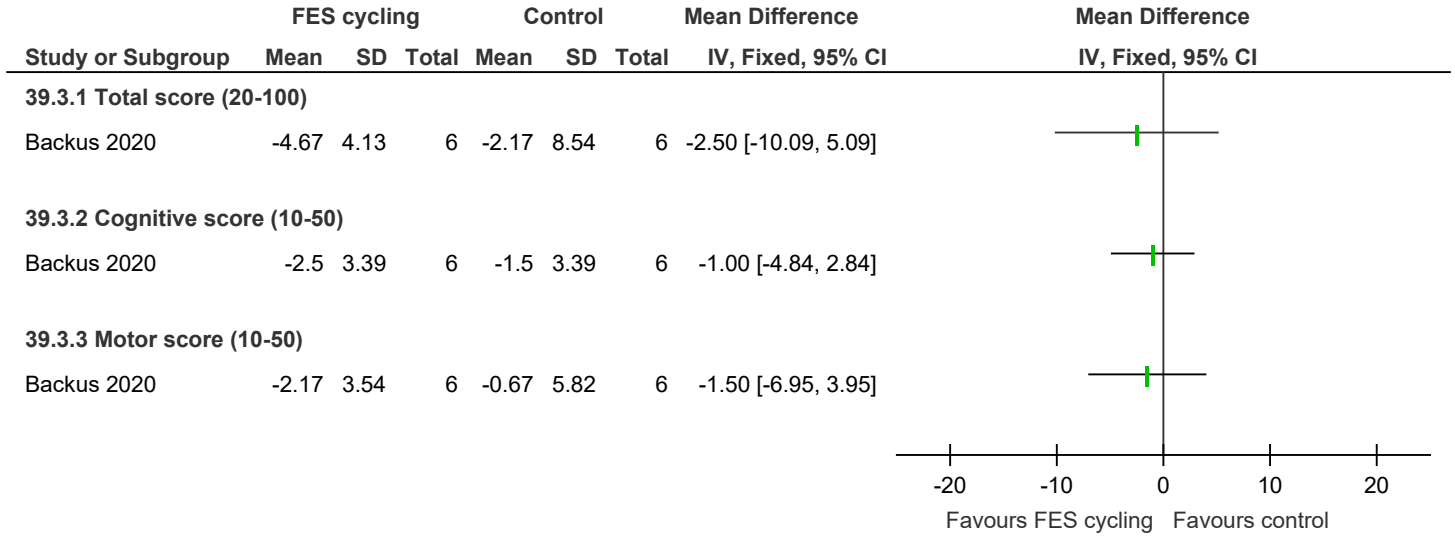


Figure 64: Decrease (any decrease) in Fatigue Scale of Motor and Cognitive Functions – total score

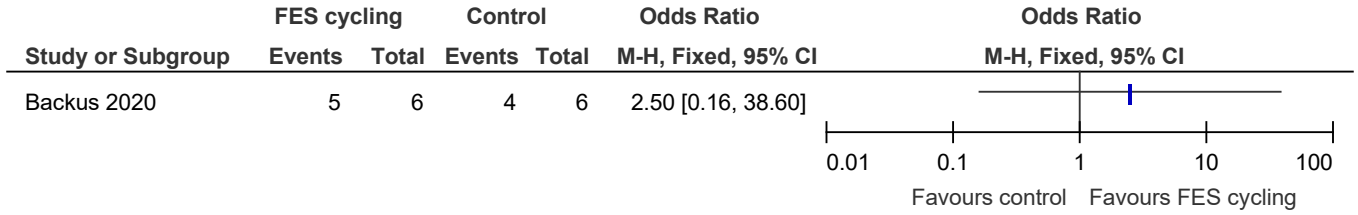


Figure 65: MSQOL-54 (0-100; higher better)

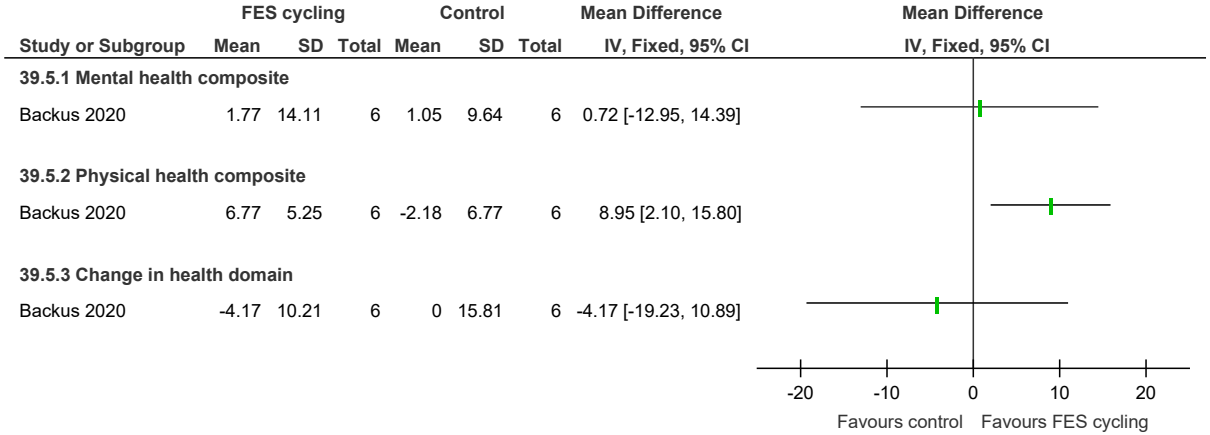


Figure 66: Patient Health Questionnaire-9 (PHQ-9; 0-27; lower better)

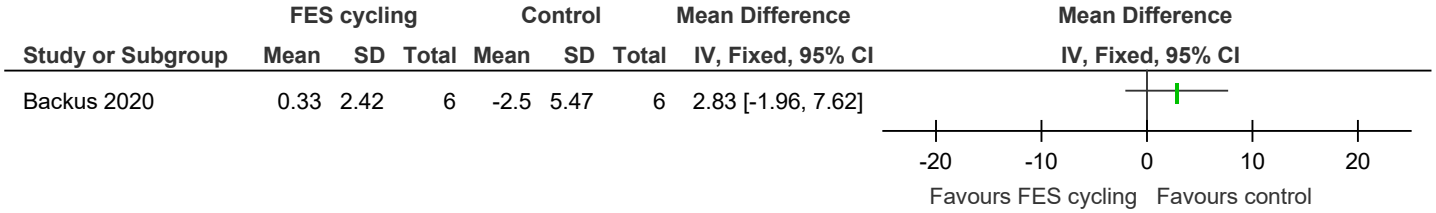
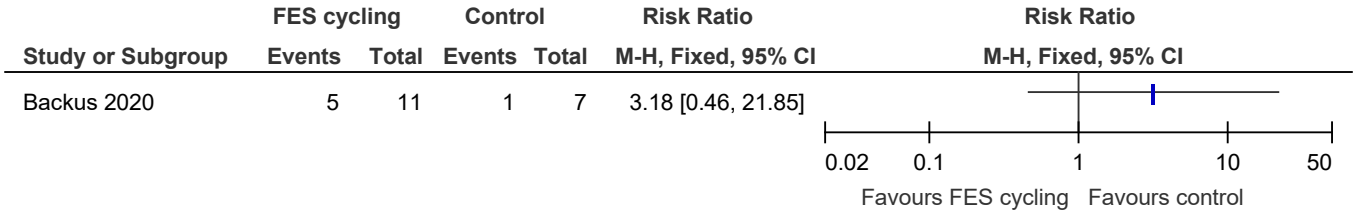


Figure 67: Adverse events leading to withdrawal



E.5 Resistance training vs. control (waitlist control, no intervention, usual care or education only) – up to 6 months outcomes

Figure 68: Modified Fatigue Impact Scale – total (0-84; lower better)

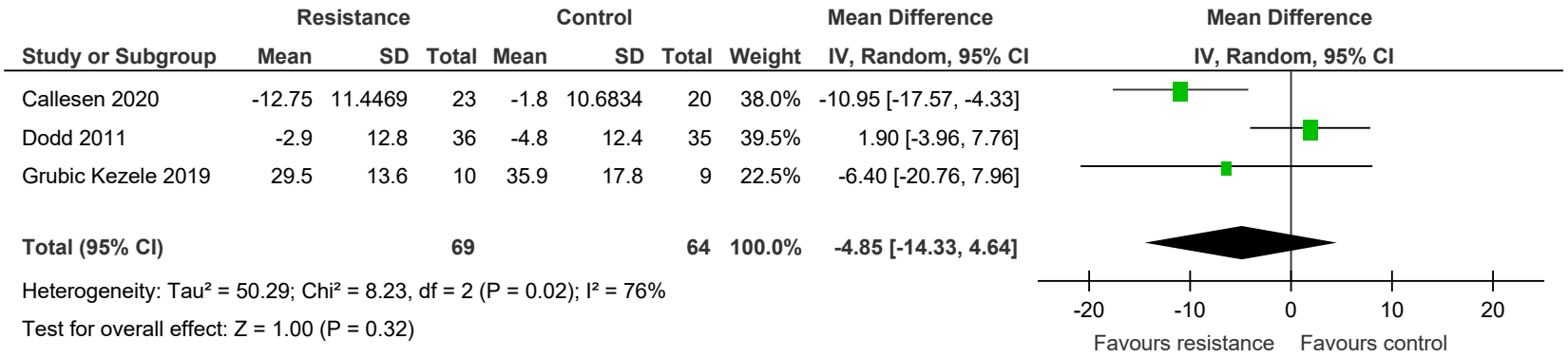


Figure 69: Modified Fatigue Impact Scale – physical (0-36; lower better)

	Resistance			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Dodd 2011	-2.6	6.8	36	-2.1	5.4	35	88.9%	-0.50 [-3.35, 2.35]
Grubic Kezele 2019	16.6	6.2	10	19.9	10.9	9	11.1%	-3.30 [-11.39, 4.79]
Total (95% CI)			**46**			**44**	**100.0%**	**-0.81 [-3.50, 1.88]**

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%

Test for overall effect: Z = 0.59 (P = 0.56)

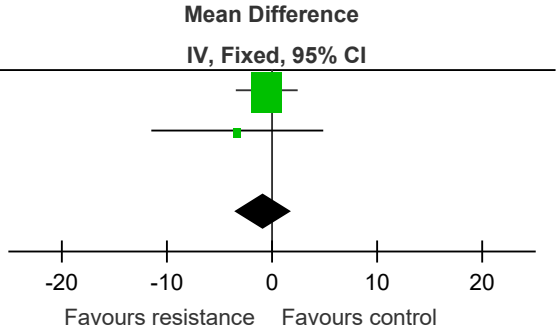


Figure 70: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

	Resistance			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Dodd 2011	-0.2	7	36	-2.1	6.3	35	81.4%	1.90 [-1.20, 5.00]
Grubic Kezele 2019	10.3	6.7	10	11.6	7.6	9	18.6%	-1.30 [-7.77, 5.17]
Total (95% CI)			**46**			**44**	**100.0%**	**1.30 [-1.49, 4.10]**

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 0.92 (P = 0.36)

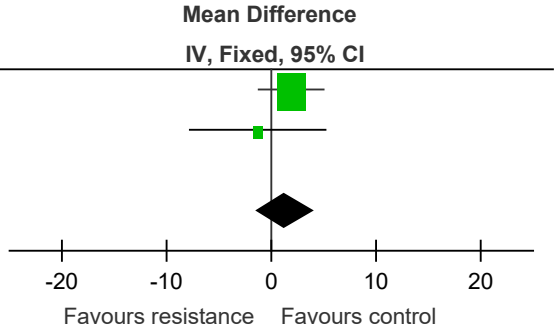


Figure 71: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

Study or Subgroup	Resistance Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dodd 2011	-0.1	2	36	-0.5	2.2	25	59.9%	0.40 [-0.68, 1.48]
Grubic Kezele 2019	2.2	1.9	10	3.6	2.3	9	40.1%	-1.40 [-3.31, 0.51]
Total (95% CI)			**46**			**34**	**100.0%**	**-0.32 [-2.05, 1.41]**

Heterogeneity: Tau² = 0.99; Chi² = 2.58, df = 1 (P = 0.11); I² = 61%

Test for overall effect: Z = 0.36 (P = 0.72)

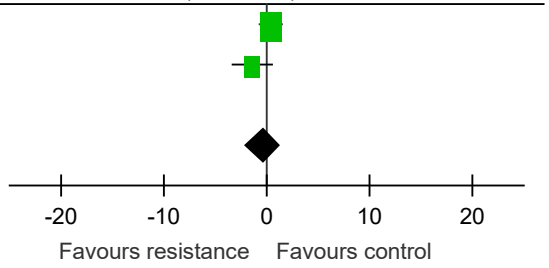


Figure 72: Fatigue Severity Scale (1-7; lower better)

Study or Subgroup	Resistance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Callesen 2020	4.9	1.126	16	5.1	1.8098	18	-0.20 [-1.20, 0.80]

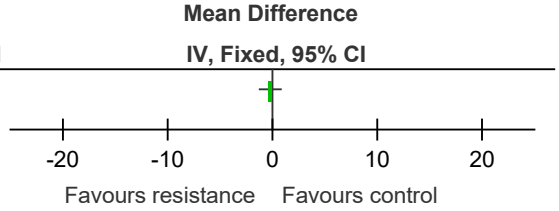


Figure 73: Multidimensional Fatigue Index (4-20 for each domain; lower better)

	Resistance			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
4.6.1 General fatigue								
Dalgas 2010	12.7	4.8793	16	11.8	4.8262	18	0.90 [-2.37, 4.17]	
4.6.2 Physical fatigue								
Dalgas 2010	11	4.504	16	12.6	4.0218	18	-1.60 [-4.48, 1.28]	
4.6.3 Reduced activity								
Dalgas 2010	10.3	4.3163	16	10.9	4.424	18	-0.60 [-3.54, 2.34]	
4.6.4 Reduced motivation								
Dalgas 2010	6.2	1.689	16	6.7	3.2174	18	-0.50 [-2.20, 1.20]	
4.6.5 Mental fatigue								
Dalgas 2010	10.6	5.2546	16	10.6	6.0327	18	0.00 [-3.79, 3.79]	

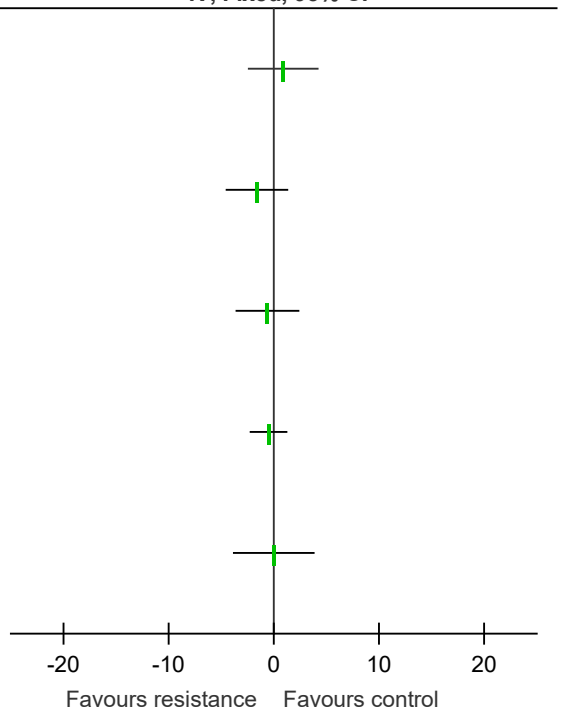


Figure 74: SF-36 quality of life (0-100 for each domain; higher better)

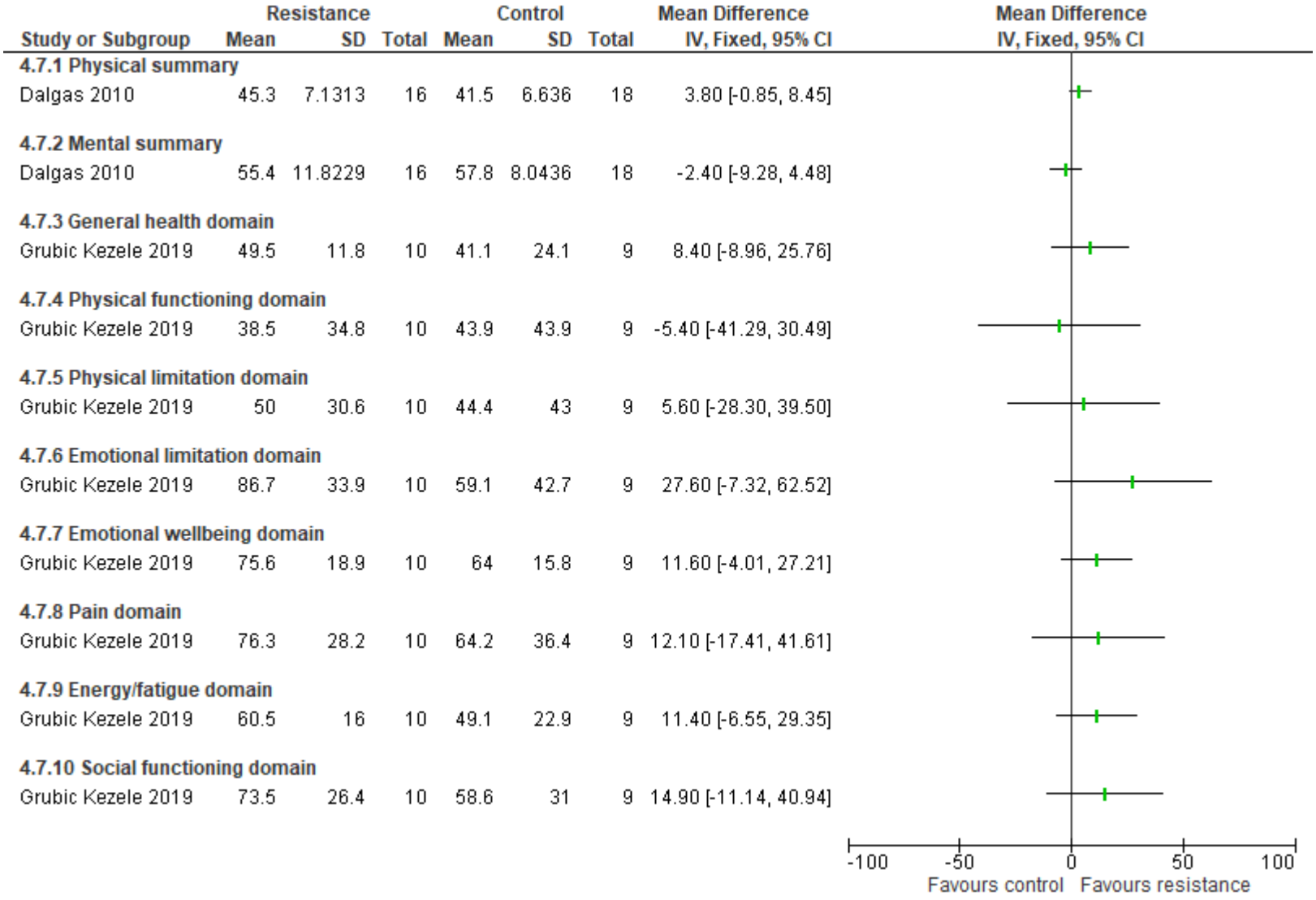


Figure 75: World Health Organisation Quality of Life – BREF (0-100 for each domain; higher better)

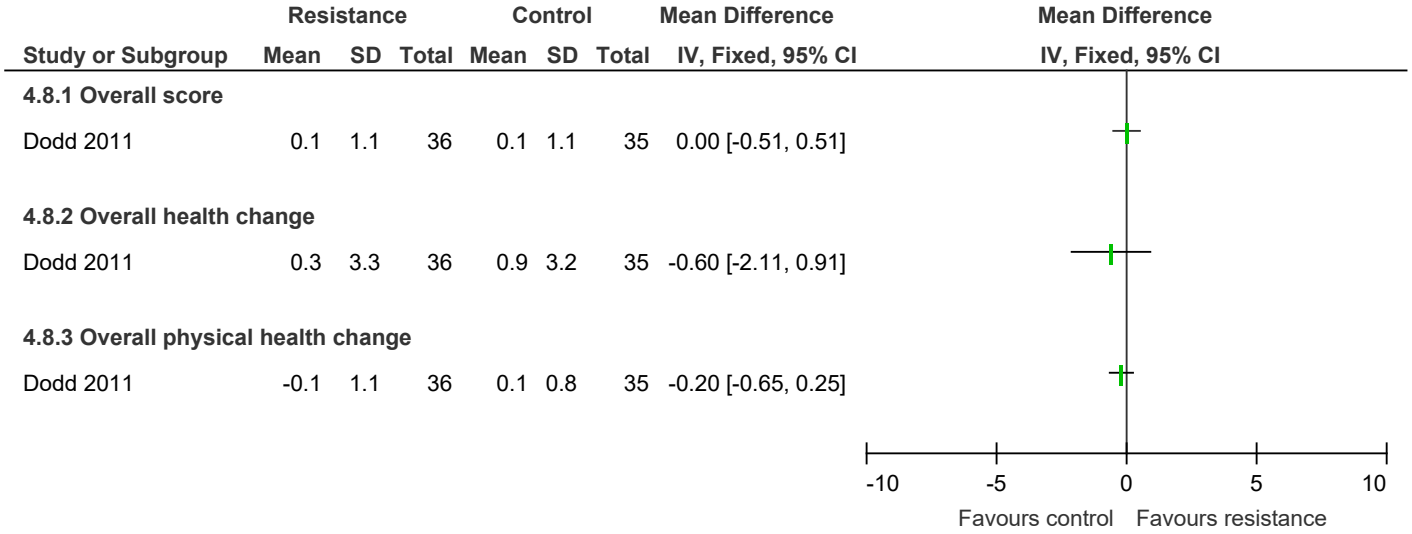


Figure 76: Functional capacity (% of that at baseline; higher better)

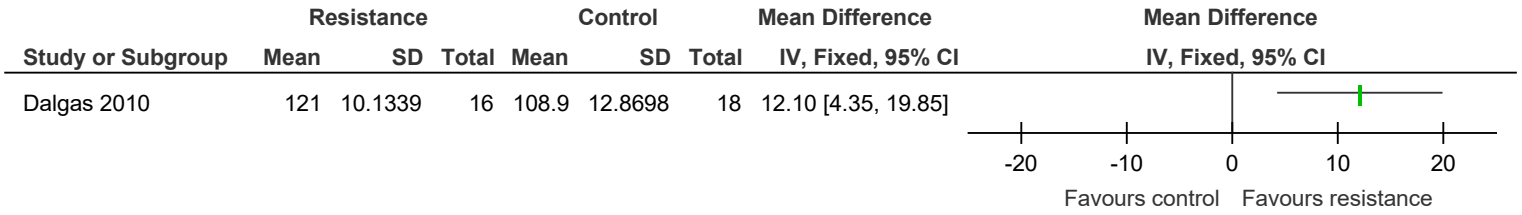


Figure 77: Major Depression Inventory (scale unclear; lower better)

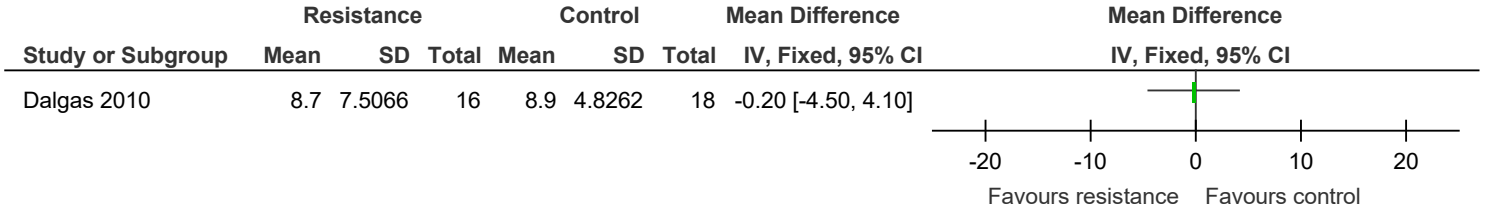


Figure 78: Incidence of adverse events (harm)

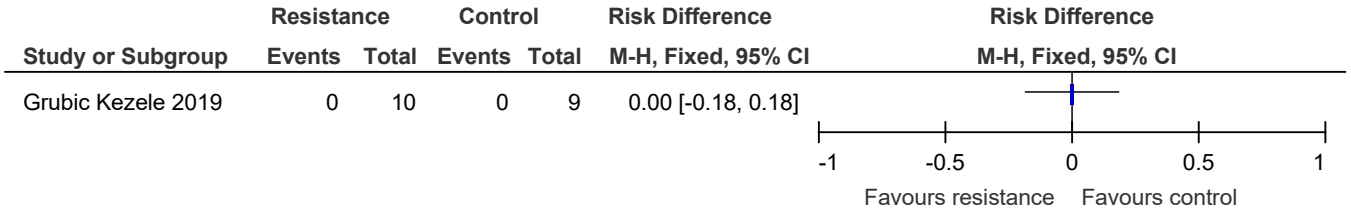
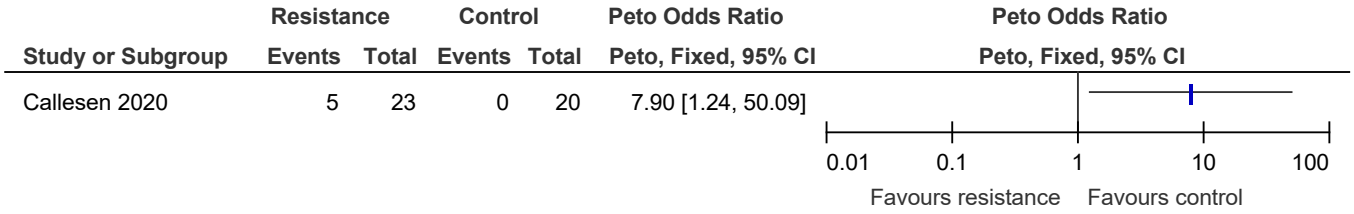


Figure 79: Adverse events leading to withdrawal



E.6 Vestibular/balance training vs. control (waitlist control, routine care, information only) – outcomes up to 6 months

Figure 80: Modified Fatigue Impact Scale – total (0-84; lower better)

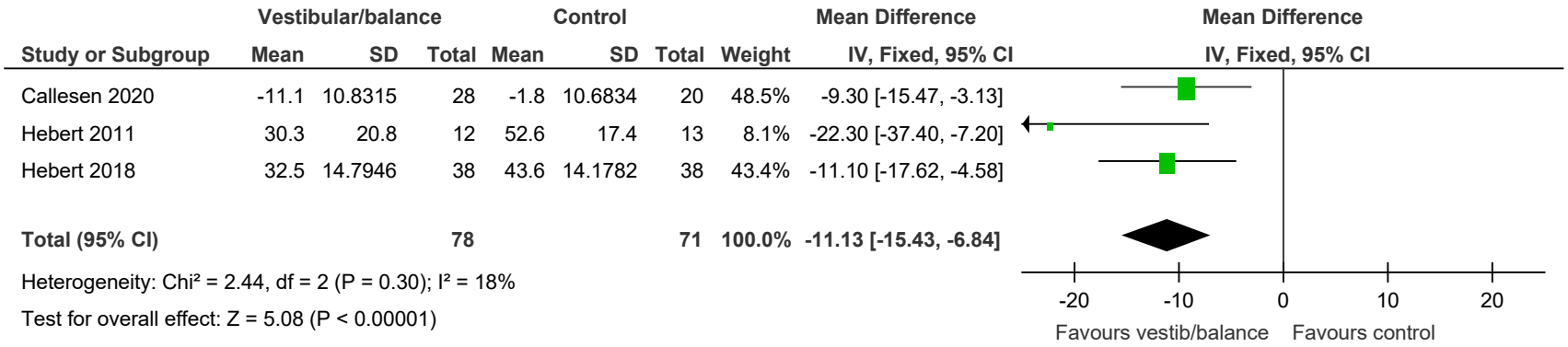


Figure 81: Modified Fatigue Impact Scale – physical (0-36; lower better)

	Vestibular/balance			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hebert 2018	16	7.3973	38	20.7	6.7809	38	-4.70 [-7.89, -1.51]	

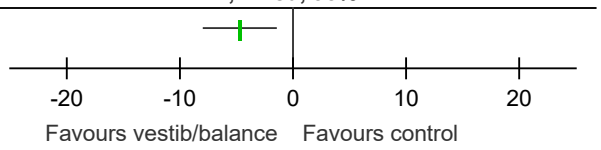


Figure 82: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

	Vestibular/balance			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hebert 2018	14.2	7.3973	38	19.3	7.3973	38	-5.10 [-8.43, -1.77]	

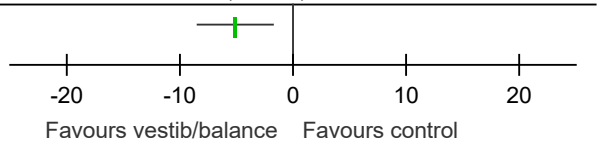


Figure 83: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

	Vestibular/balance			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hebert 2018	2.44	1.911	38	3.61	1.8493	38	-1.17 [-2.02, -0.32]	

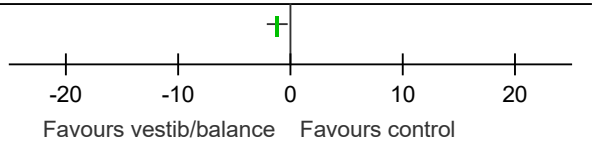


Figure 84: Fatigue Severity Scale (9-63; lower better)

	Vestibular/balance			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sadeghi Bahmani 2019	34.08	15.15	24	45.05	11.77	21	62.7%	-10.97 [-18.85, -3.09]	
Yazgan 2019	35.96	12.98	27	40.33	17.71	15	37.3%	-4.37 [-14.58, 5.84]	
Total (95% CI)			**51**			**36**	**100.0%**	**-8.51 [-14.75, -2.27]**	

Heterogeneity: Chi² = 1.01, df = 1 (P = 0.32); I² = 1%

Test for overall effect: Z = 2.67 (P = 0.008)

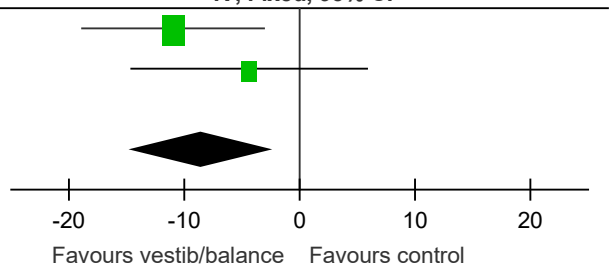


Figure 85: Fatigue Impact Scale (0-160, 0-80 or 0-40; lower better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.6.1 Total score (0-160)							
Karami 2018	70.8	17.2	47	96.5	18	25	-25.70 [-34.30, -17.10]
5.6.2 Physical subscale (0-40)							
Karami 2018	19	6.5	47	28.8	6.4	25	-9.80 [-12.92, -6.68]
5.6.3 Cognitive subscale (0-40)							
Karami 2018	17.1	3.6	47	22	3.6	25	-4.90 [-6.65, -3.15]
5.6.4 Psychosocial subscale (0-80)							
Karami 2018	32.3	10.2	47	45.8	11.5	25	-13.50 [-18.87, -8.13]

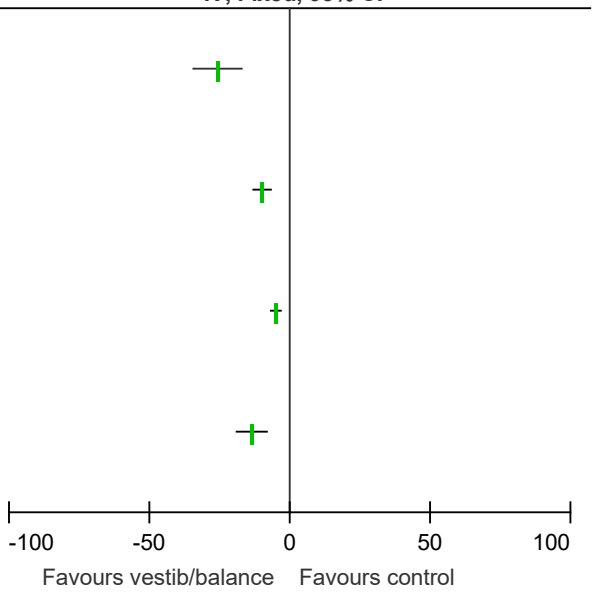


Figure 86: SF-36 physical summary (0-100; higher better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hebert 2018	41	8.6302	38	37.3	8.6302	38	3.70 [-0.18, 7.58]

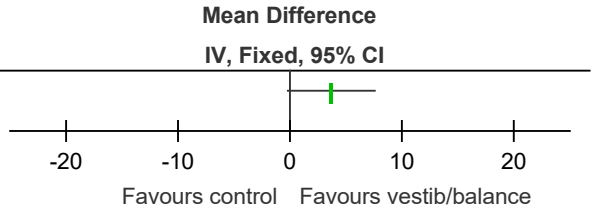


Figure 87: SF-36 mental summary (0-100; higher better)

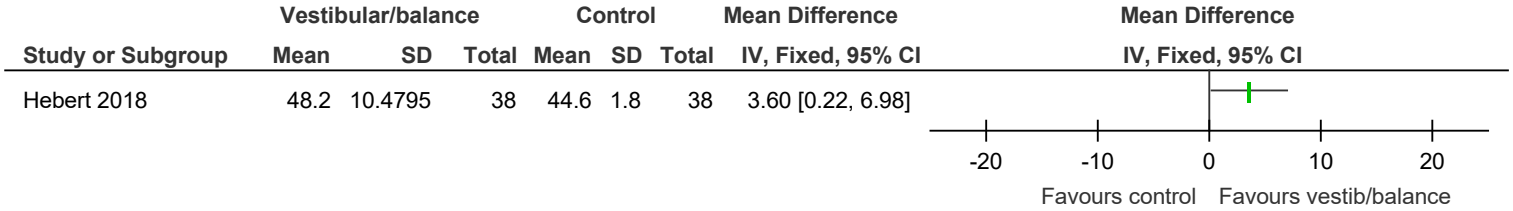


Figure 88: MS International Quality of Life Questionnaire (MusiQoL; 0-100; higher better)

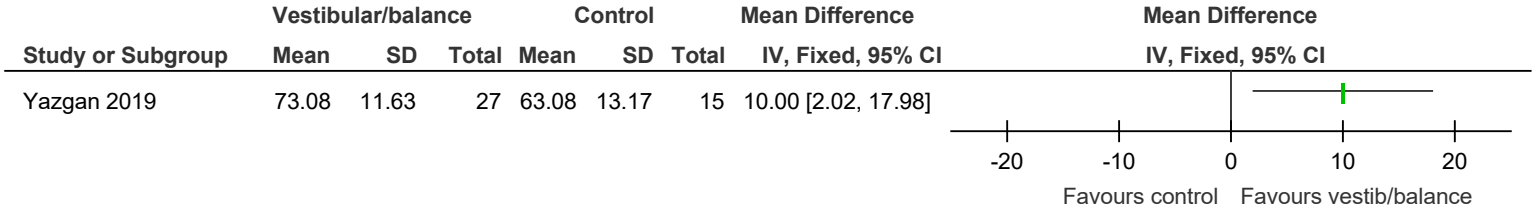


Figure 89: EDSS score (0-10; lower better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sadeghi Bahmani 2019	3.1	1.86	24	1.98	1.7	21	1.12 [0.08, 2.16]

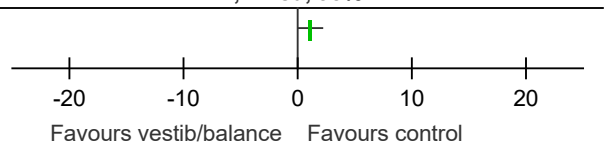


Figure 90: Cognitive – Perceived Deficits Questionnaire (0-80; lower better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hebert 2018	29	14.1782	38	35.3	13.5617	38	-6.30 [-12.54, -0.06]

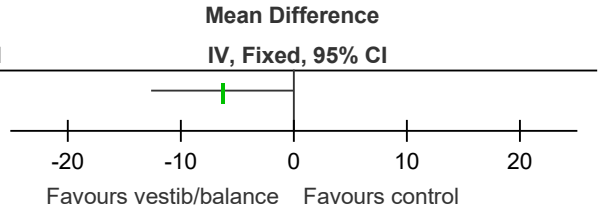


Figure 91: Beck Depression Inventory (0-63; lower better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hebert 2011	11.6	12.3	12	16.6	9.6	13	-5.00 [-13.70, 3.70]

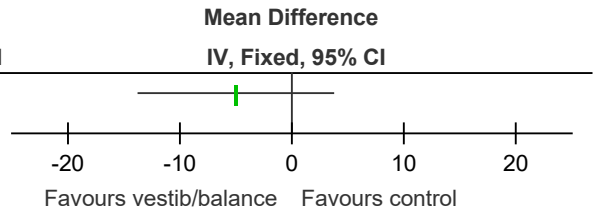


Figure 92: Beck Depression Inventory – fast screen (0-21; lower better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sadeghi Bahmani 2019	5.29	5.75	24	6.52	4.91	21	-1.23 [-4.34, 1.88]

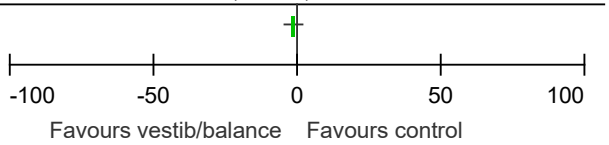


Figure 93: Incidence of adverse events

Study or Subgroup	Vestibular/balance Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Hebert 2011	0	12	0	12	38.4%	0.00 [-0.15, 0.15]
Yazgan 2019	0	27	0	15	61.6%	0.00 [-0.10, 0.10]
Total (95% CI)		**39**		**27**	**100.0%**	**0.00 [-0.09, 0.09]**
Total events	0		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

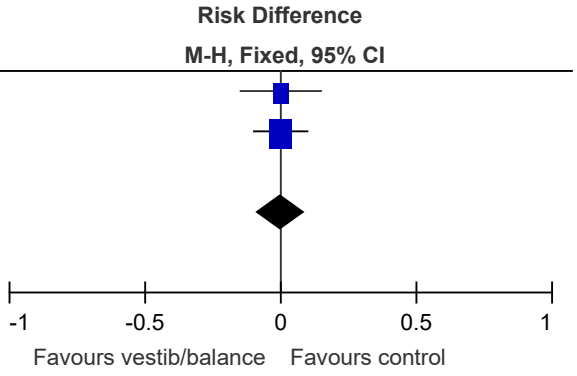
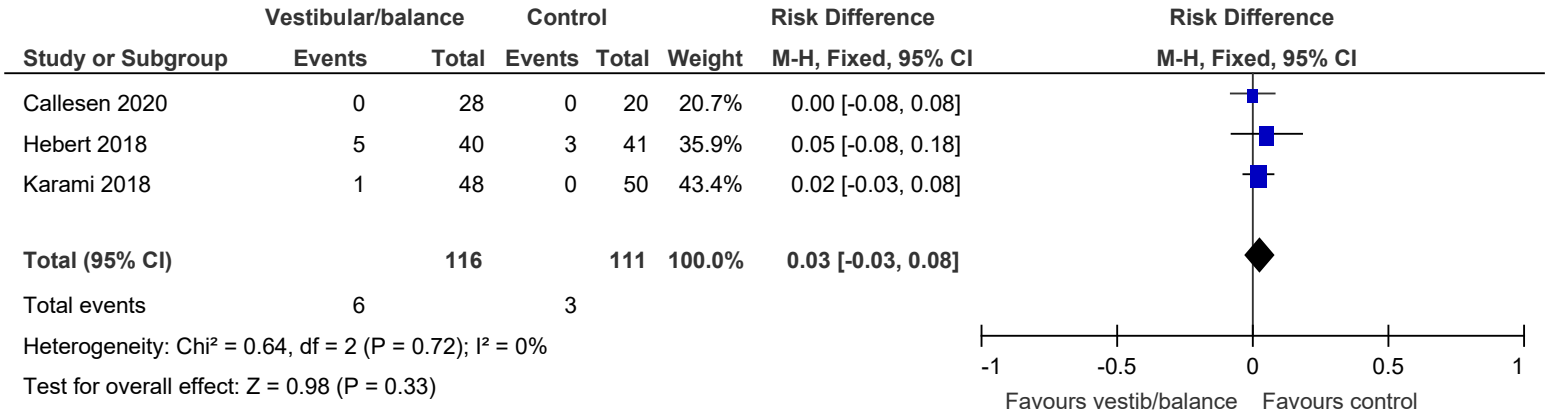


Figure 94: Adverse events leading to withdrawal



E.7 Vestibular/balance training vs. standard neurorehabilitation – outcomes up to 6 months

Figure 95: Fatigue Severity Scale (9-63; lower better)

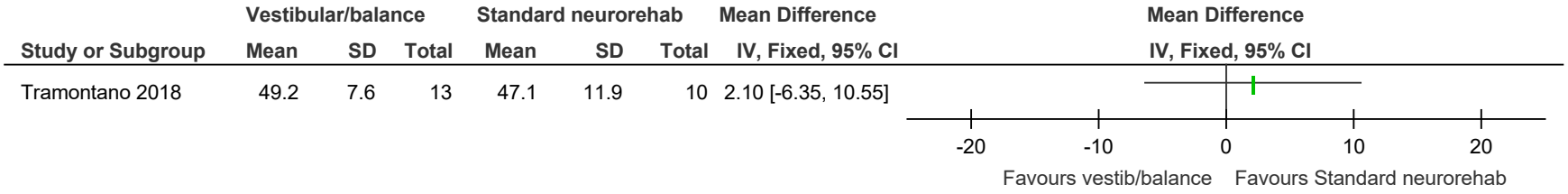
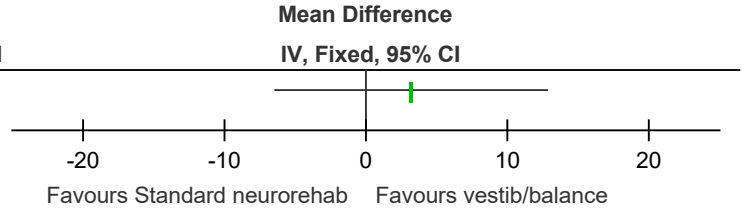


Figure 96: Functional – Barthel Index (0-100; higher better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Standard neurorehab Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Tramontano 2018	84.5	10.3	13	81.3	12.6	10	3.20 [-6.41, 12.81]



E.8 Resistance training vs. aerobic exercise – outcomes up to 6 months

Figure 97: Modified Fatigue Impact Scale – physical (0-36; lower better)

Study or Subgroup	Resistance Mean	SD	Total	Aerobic Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sabapathy 2011	-1.6	3.3	16	-2.7	5.3	16	1.10 [-1.96, 4.16]

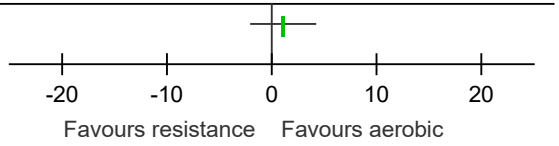


Figure 98: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

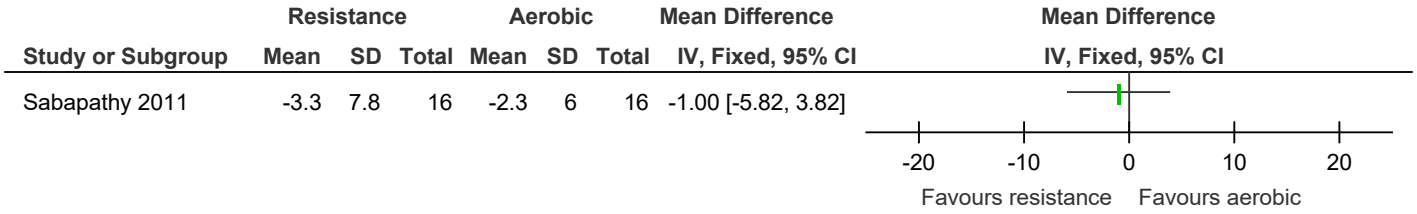


Figure 99: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

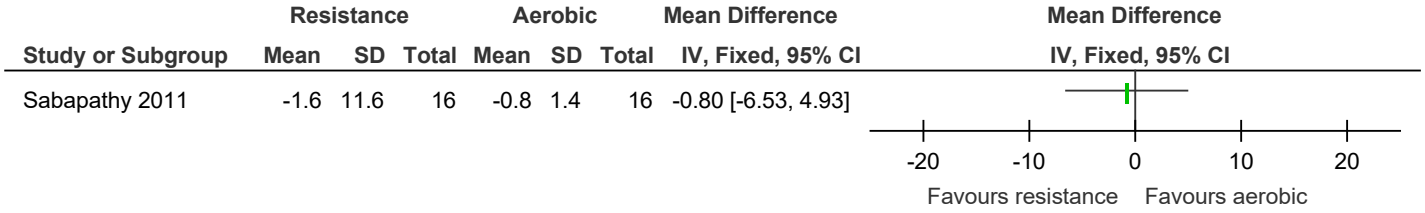


Figure 100: SF-36 physical composite (0-100; higher better)

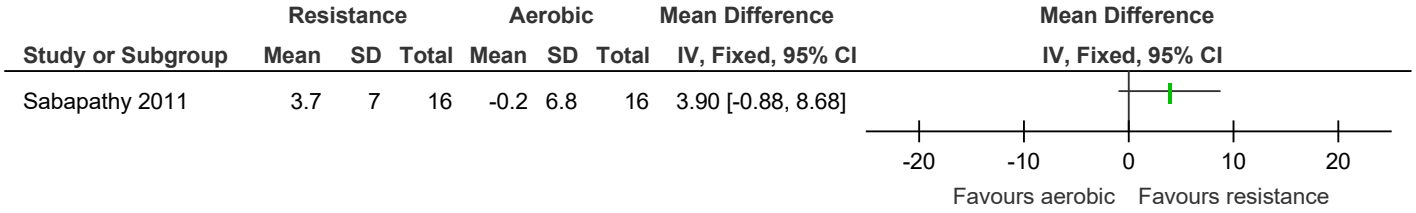


Figure 101: SF-36 mental composite (0-100; higher better)

Study or Subgroup	Resistance Mean	SD	Total	Aerobic Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sabapathy 2011	-1.9	9.7	16	2.3	10.6	16	-4.20 [-11.24, 2.84]

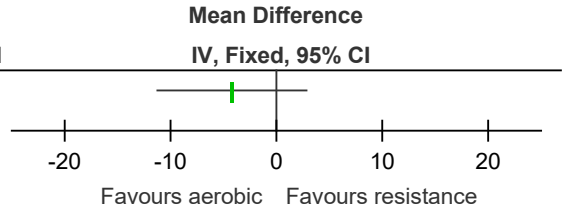


Figure 102: Beck Depression Inventory (0-63; lower better)

Study or Subgroup	Resistance Mean	SD	Total	Aerobic Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sabapathy 2011	-2.3	5.4	16	0.6	3.9	16	-2.90 [-6.16, 0.36]

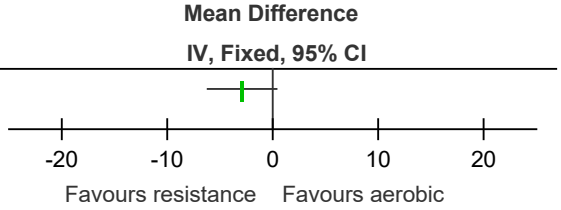
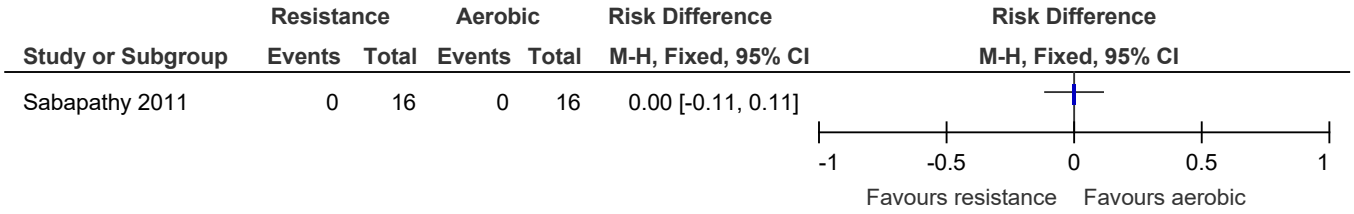


Figure 103: Incidence of adverse events



E.9 Vestibular/balance training vs. aerobic exercise – outcomes up to 6 months

Figure 104: Modified Fatigue Impact Scale – total (0-84; lower better)

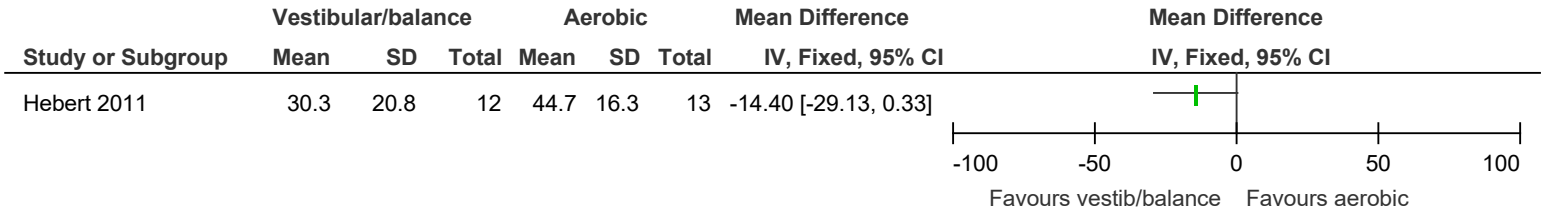


Figure 105: Fatigue Severity Scale (9-63; lower better)

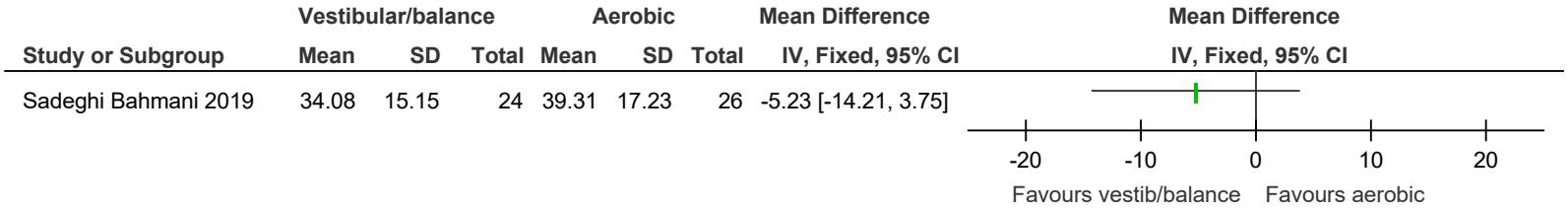


Figure 106: Improvement in Modified Fatigue Impact Scale (total) from baseline

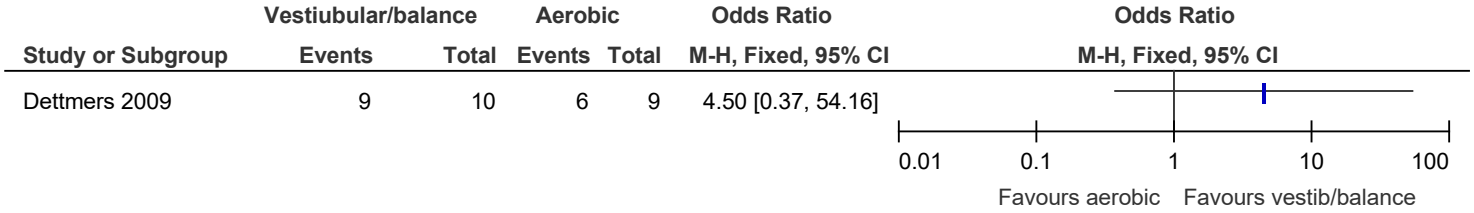


Figure 107: Improvement in Modified Fatigue Impact Scale (motor) from baseline

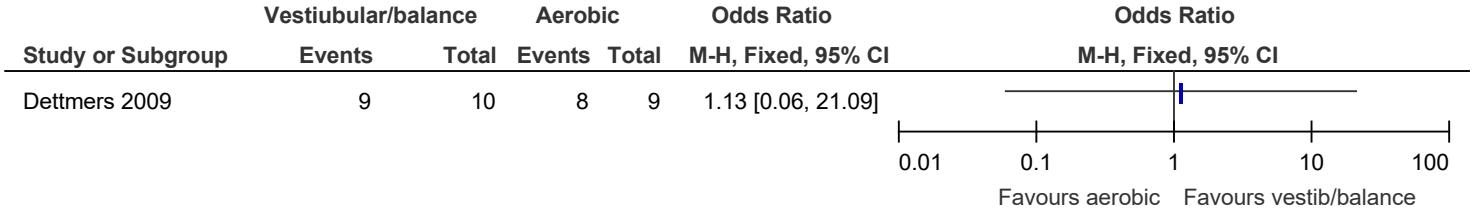


Figure 108: Improvement in Hamburg Quality of Life in MS Scale (HAQUAMS) motor from baseline

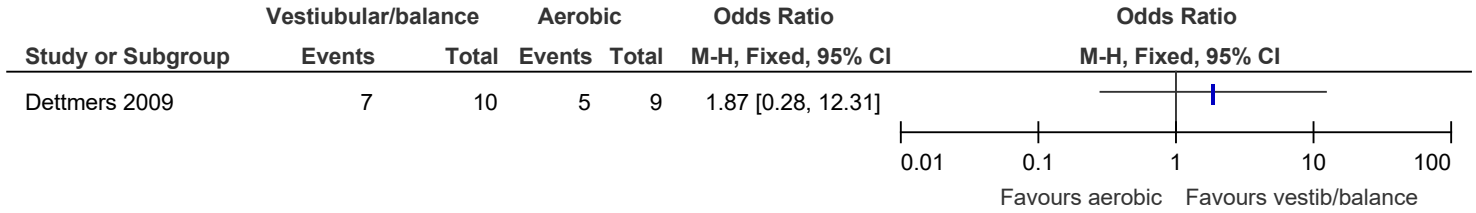


Figure 109: EDSS score (0-10; lower better)

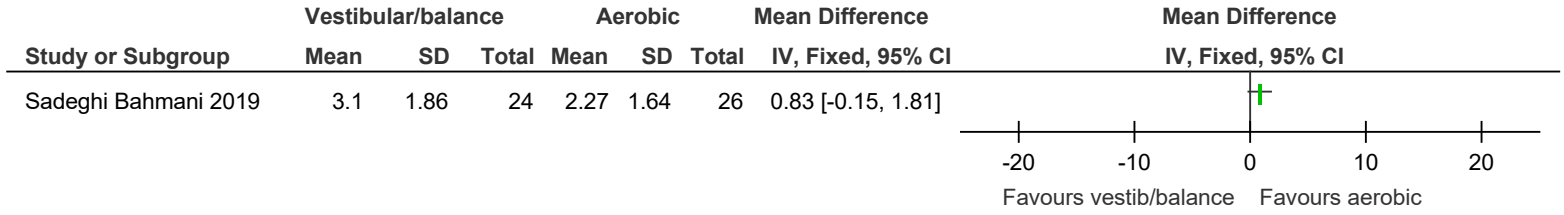


Figure 110: Beck Depression Inventory (0-63; lower better)

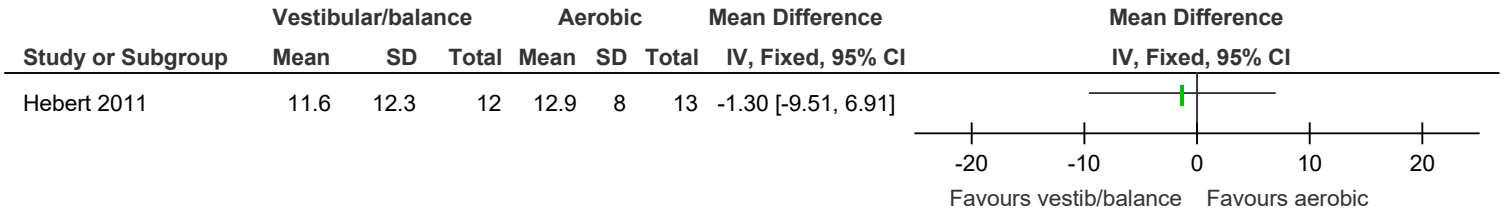


Figure 111: Beck Depression Inventory – fast screen (0-21; lower better)

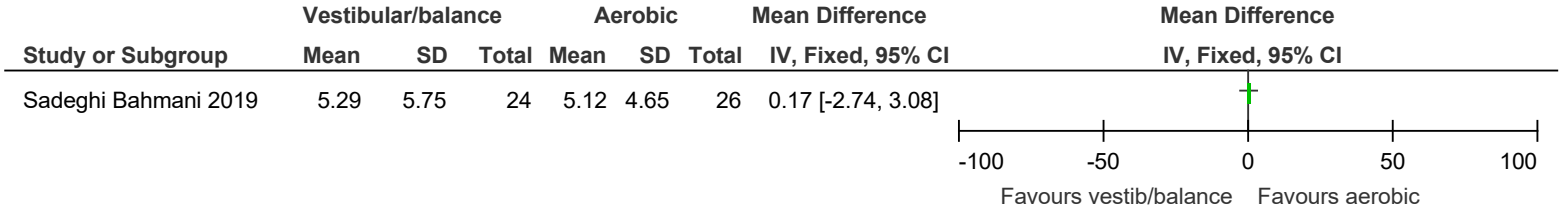


Figure 112: Improvement in Beck Depression Inventory from baseline

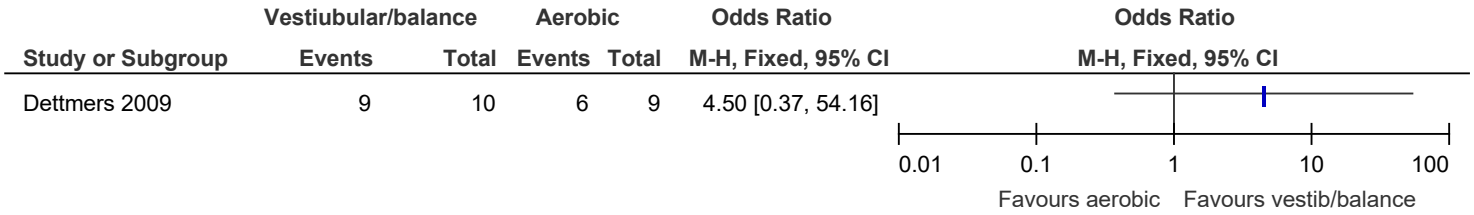
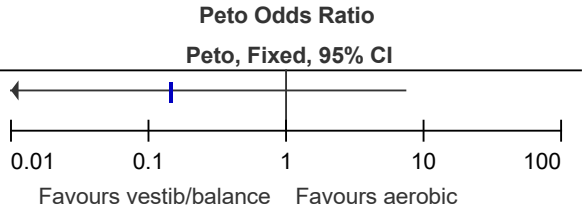


Figure 113: Adverse events

Study or Subgroup	Vestiubular/balance Events	Total	Aerobic Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Hebert 2011	0	12	1	13	0.15 [0.00, 7.39]



E.10 Vestibular/balance training vs. resistance training – outcomes up to 6 months

Figure 114: Modified Fatigue Impact Scale – total (0-84; lower better)

Study or Subgroup	Vestibular/balance Mean	SD	Total	Resistance Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Callesen 2020	-11.1	10.8315	28	-12.8	11.3313	23	1.70 [-4.43, 7.83]

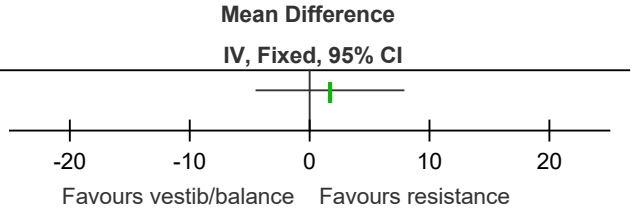
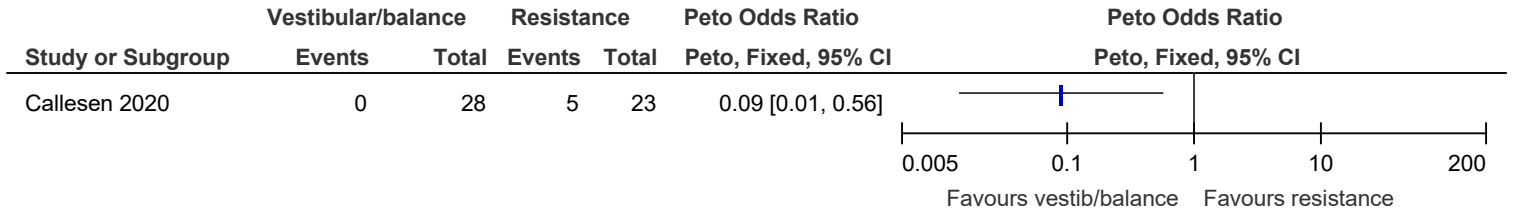


Figure 115: Adverse events leading to withdrawal



E.11 Resistance training + aerobic exercise vs. control (waitlist control, no intervention, information only) – outcomes up to 6 months

Figure 116: Modified Fatigue Impact Scale (0-84, 0-36 or 0-40; lower better)

Study or Subgroup	resist + aerobic Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
11.1.1 Total score (0-84)								
Correale 2021	-16.3	16.6	14	-4.5	5.8	9	16.7%	-11.80 [-21.29, -2.31]
Garrett 2013	-7.5	14.2944	63	-1.1	11.8371	49	36.6%	-6.40 [-11.24, -1.56]
Maurer 2018	-4.2	11.5563	93	-1.81	11.4279	84	46.7%	-2.39 [-5.78, 1.00]
Subtotal (95% CI)			**170**			**142**	**100.0%**	**-5.43 [-9.93, -0.92]**
Heterogeneity: Tau² = 8.33; Chi² = 4.34, df = 2 (P = 0.11); I² = 54%								
Test for overall effect: Z = 2.36 (P = 0.02)								
11.1.2 Physical subscale (0-36)								
Garrett 2013	-3.9	6.7501	63	0.4	4.7	49	100.0%	-4.30 [-6.42, -2.18]
Subtotal (95% CI)			**63**			**49**	**100.0%**	**-4.30 [-6.42, -2.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.97 (P < 0.0001)								
11.1.3 Cognitive subscale (0-40)								
Garrett 2013	-2.1	4.17	63	-0.51	4.18	49	100.0%	-1.59 [-3.15, -0.03]
Subtotal (95% CI)			**63**			**49**	**100.0%**	**-1.59 [-3.15, -0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.00 (P = 0.05)								

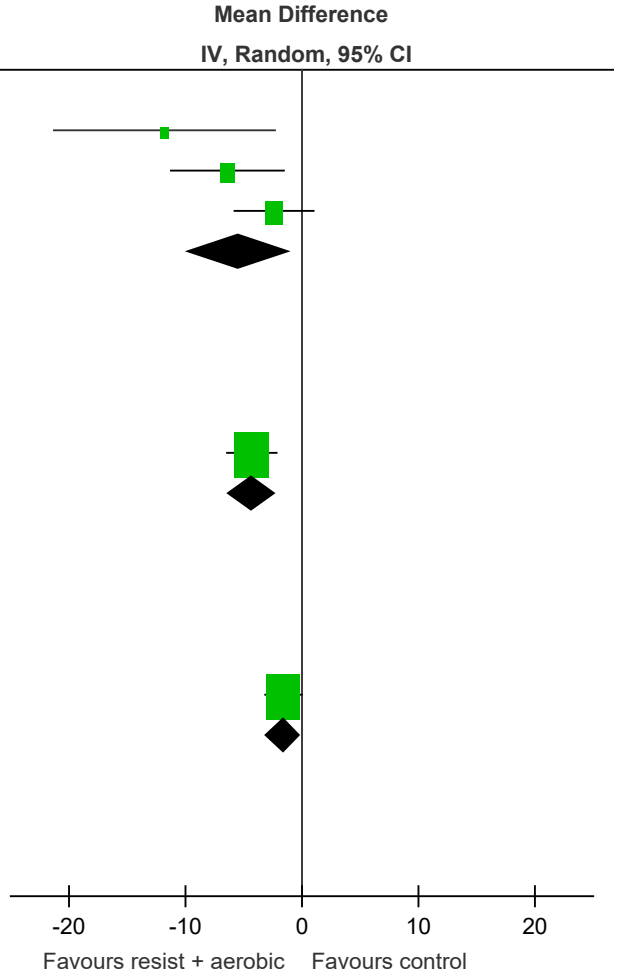


Figure 117: Fatigue Severity Scale (9-63; lower better)

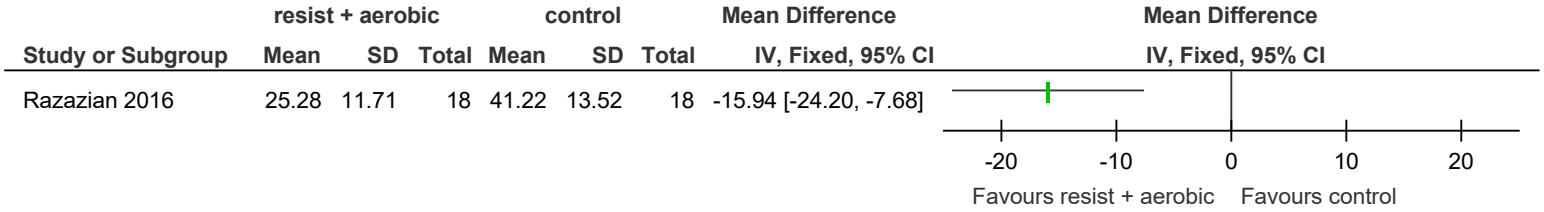


Figure 118: WEIMuS Fatigue scale (0-68; lower better)

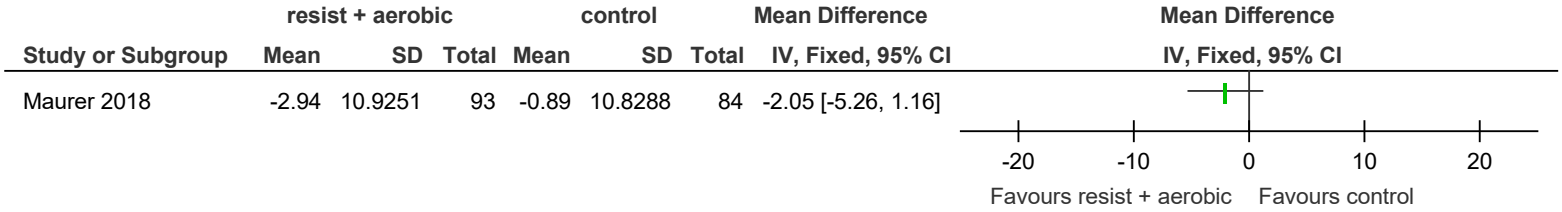


Figure 119: MSIS-29 physical subscale (0-100; lower better)

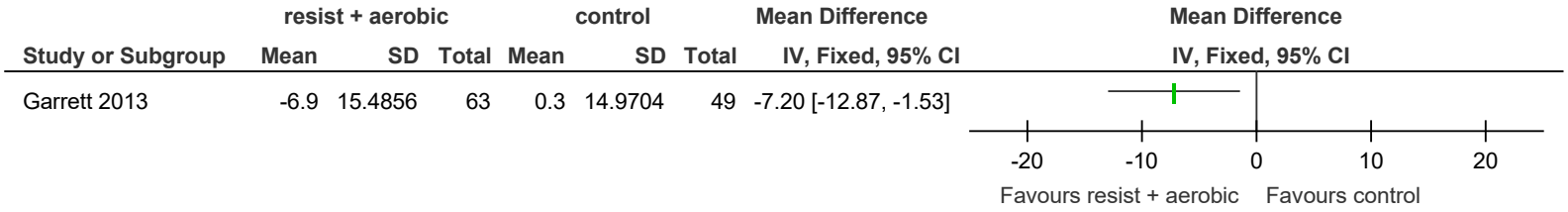


Figure 120: MSQoL-54 (0-100; higher better)

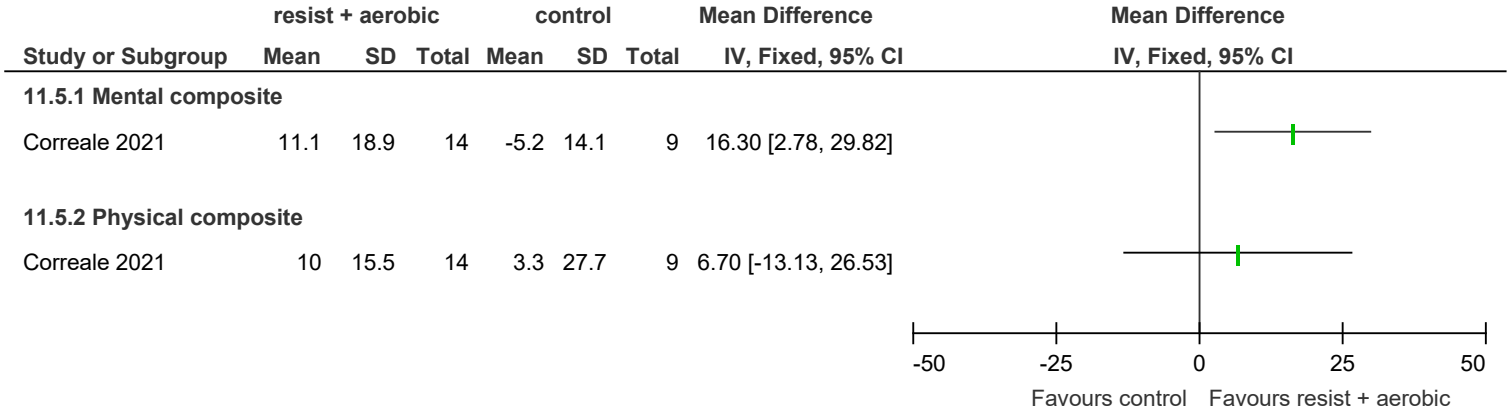


Figure 121: Beck Depression Inventory (0-63; lower better)

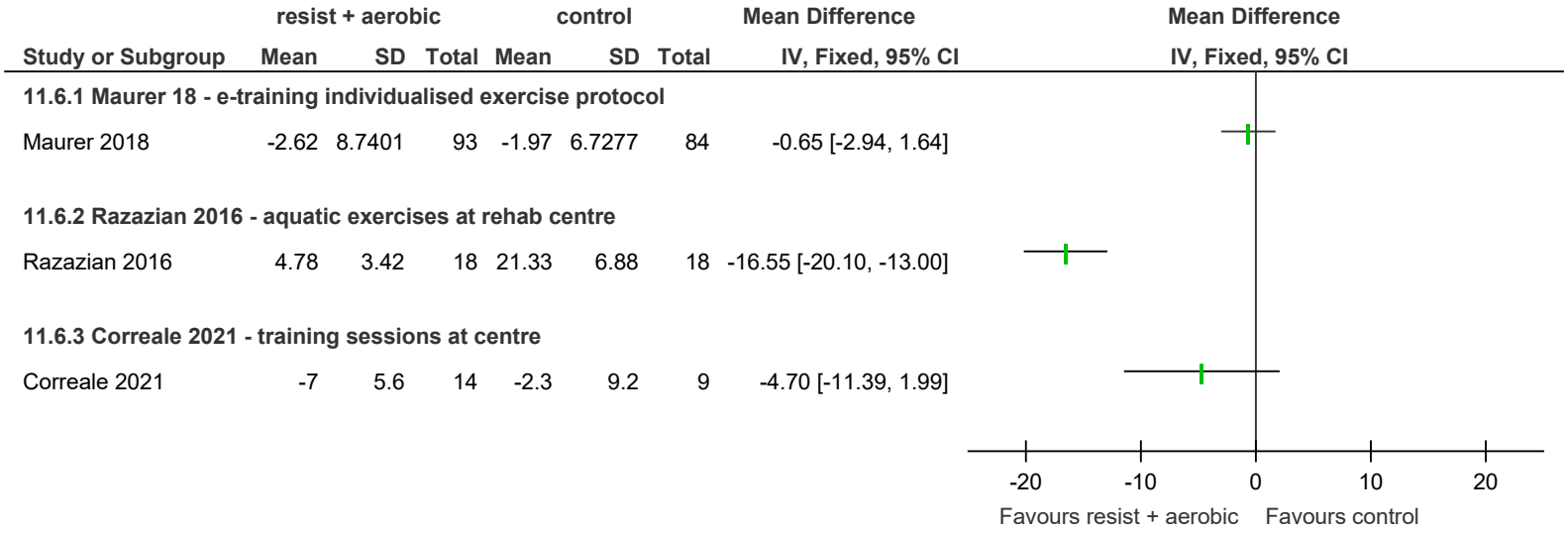


Figure 122: Any adverse event

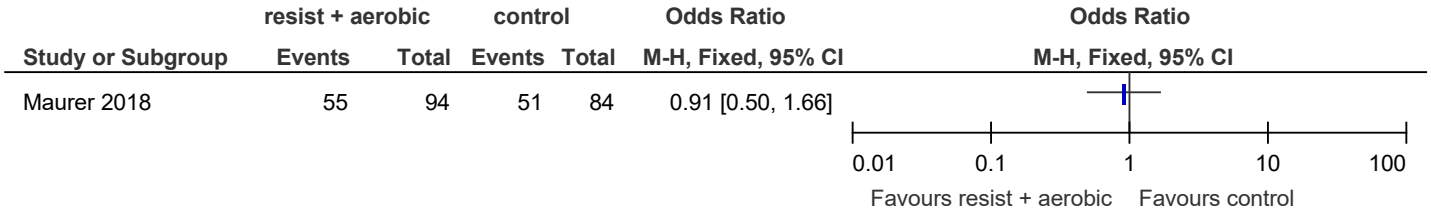
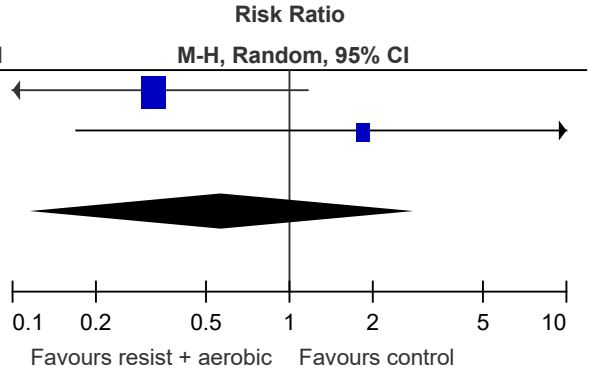


Figure 123: Adverse events leading to withdrawal

Study or Subgroup	resist + aerobic Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Garrett 2013	3	66	8	57	67.4%	0.32 [0.09, 1.16]
Maurer 2018	2	86	1	79	32.6%	1.84 [0.17, 19.87]
Total (95% CI)		**152**		**136**	**100.0%**	**0.57 [0.12, 2.81]**
Total events	5		9			

Heterogeneity: Tau² = 0.56; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%

Test for overall effect: Z = 0.69 (P = 0.49)



E.12 Resistance training + balance exercises vs. control (no intervention, waitlist control) – outcomes up to 6 months

Figure 124: Fatigue Severity Scale (9-63; lower better)

Study or Subgroup	resistance + balance Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cakit 2010	-5.7083	5.1515	24	-5.2	5.3	9	53.0%	-0.51 [-4.54, 3.52]
Taracki 2013	-8.26	16.9239	51	3.29	16.9239	48	47.0%	-11.55 [-18.22, -4.88]
Total (95% CI)			**75**			**57**	**100.0%**	**-5.70 [-16.50, 5.10]**

Heterogeneity: Tau² = 53.05; Chi² = 7.71, df = 1 (P = 0.005); I² = 87%

Test for overall effect: Z = 1.03 (P = 0.30)

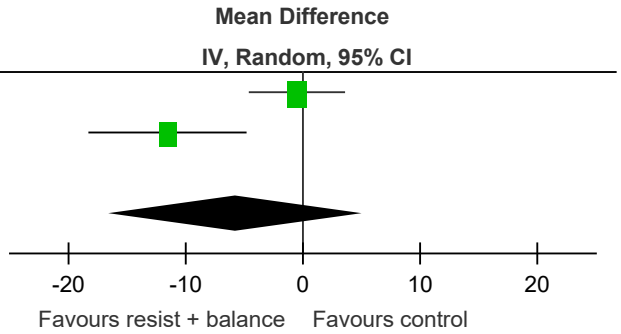


Figure 125: SF-36 quality of life (0-100 for each domain; higher better)

Study or Subgroup	resistance + balance Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
10.2.1 Physical functioning							
Cakit 2010	17.408	12.493	24	7.7	7.4	9	9.71 [2.75, 16.66]
10.2.2 Role-physical functioning							
Cakit 2010	17.75	32.866	24	5	44.7	9	12.75 [-19.28, 44.78]
10.2.3 Bodily pain							
Cakit 2010	5.9667	5.7184	24	4	4	9	1.97 [-1.51, 5.44]
10.2.4 General health							
Cakit 2010	3.5083	9.856	24	3.2	11.7	9	0.31 [-8.29, 8.91]
10.2.5 Mental component							
Cakit 2010	10.25	20.746	24	11	20.4	9	-0.75 [-16.45, 14.95]
10.2.6 Social functioning							
Cakit 2010	6.15	19.973	24	5	16.7	9	1.15 [-12.37, 14.67]
10.2.7 Role-emotional functioning							
Cakit 2010	11.325	44.6	24	19.9	50.5	9	-8.57 [-46.08, 28.93]
10.2.8 Mental health							
Cakit 2010	5.45	11.302	24	7	6.7	9	-1.55 [-7.84, 4.74]

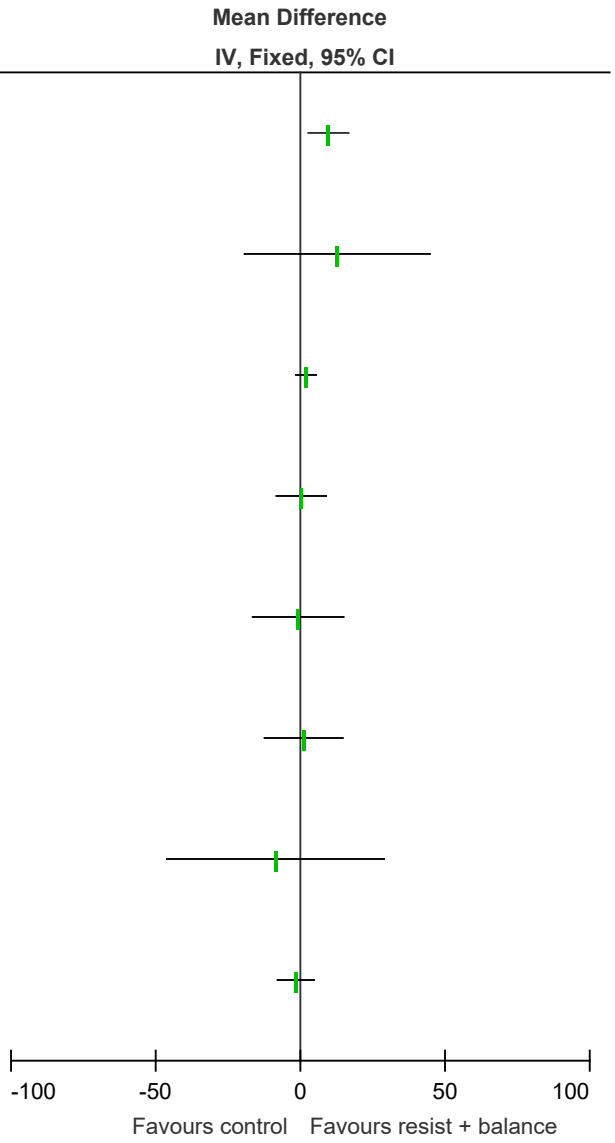


Figure 126: Multiple Sclerosis International Quality of Life questionnaire (MusiQoL; 0-100; higher better)

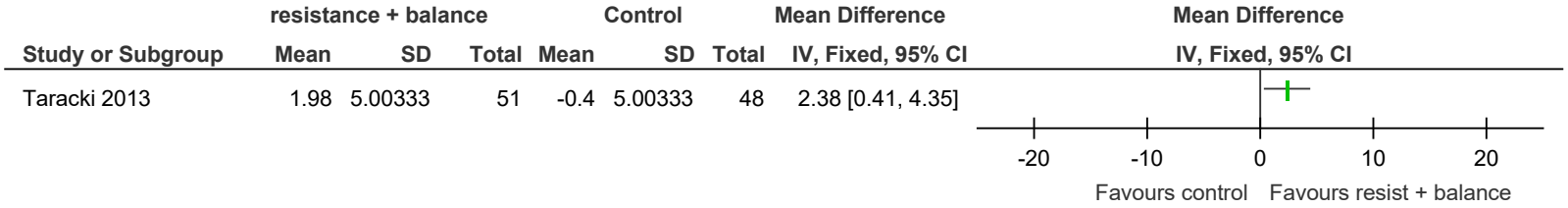


Figure 127: Beck Depression Inventory (0-63; lower better)

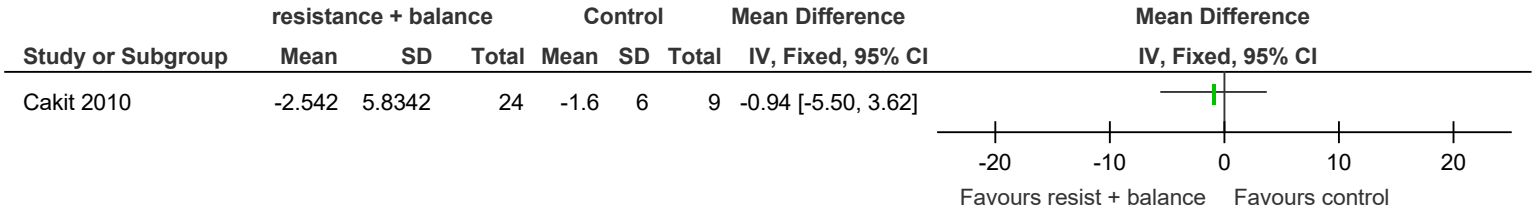
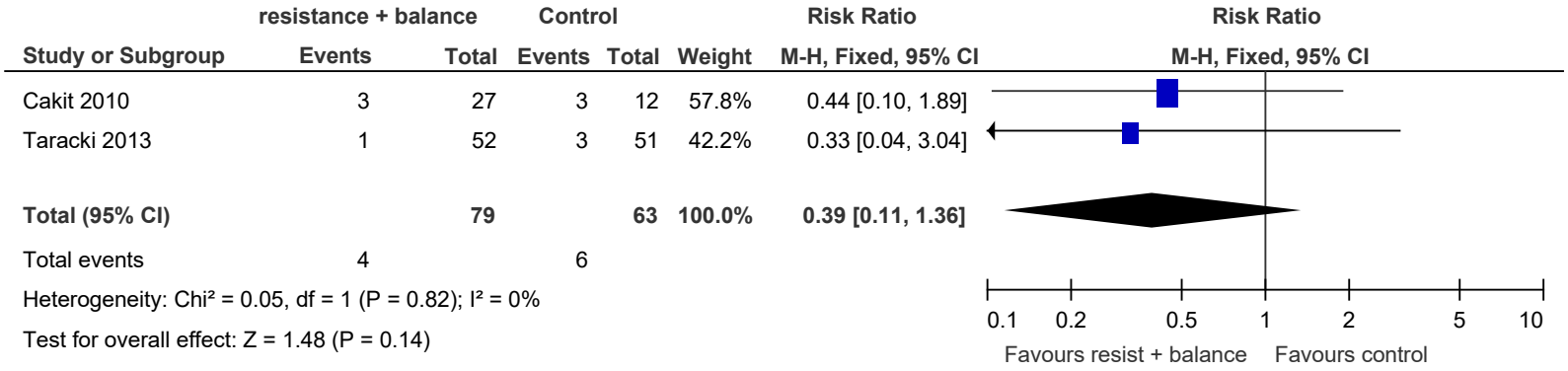


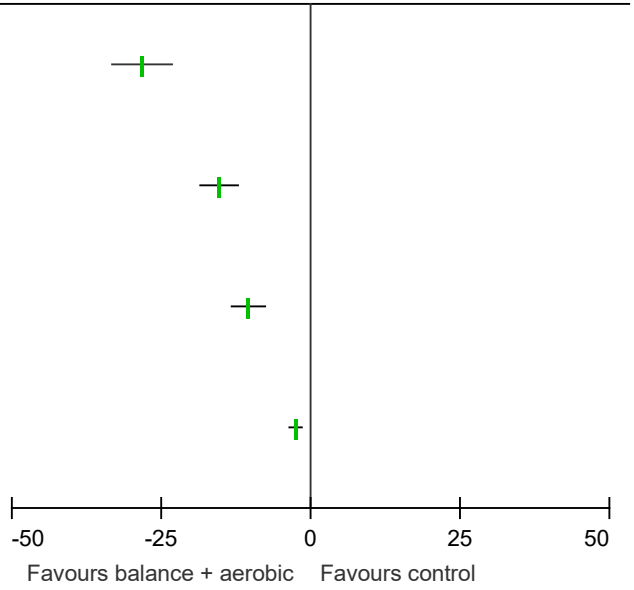
Figure 128: Adverse events leading to withdrawal



E.13 Vestibular/balance training + aerobic exercise vs. control (education only) – outcomes up to 6 months

Figure 129: Modified Fatigue Impact Scale (0-84, 0-36, 0-40 or 0-8; lower better)

	balance + aerobic			control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
13.1.1 Total score (0-84)								
Kargarfard 2018	32.8	5.9	17	61	8.2	15	-28.20 [-33.21, -23.19]	
13.1.2 Physical subscale (0-36)								
Kargarfard 2018	14.1	3.1	17	29.4	5.5	15	-15.30 [-18.45, -12.15]	
13.1.3 Cognitive subscale (0-40)								
Kargarfard 2018	14.5	2.7	17	24.9	4.9	15	-10.40 [-13.19, -7.61]	
13.1.4 Psychosocial scale (0-8)								
Kargarfard 2018	4.2	1.6	17	6.7	1.4	15	-2.50 [-3.54, -1.46]	



E.14 Resistance training + balance exercise + aerobic exercise vs. control (usual care, no intervention) – <u>outcomes up to 6 months</u>

Figure 130: Modified Fatigue Impact Scale (0-84, 0-36, 0-40 or 0-8; lower better)

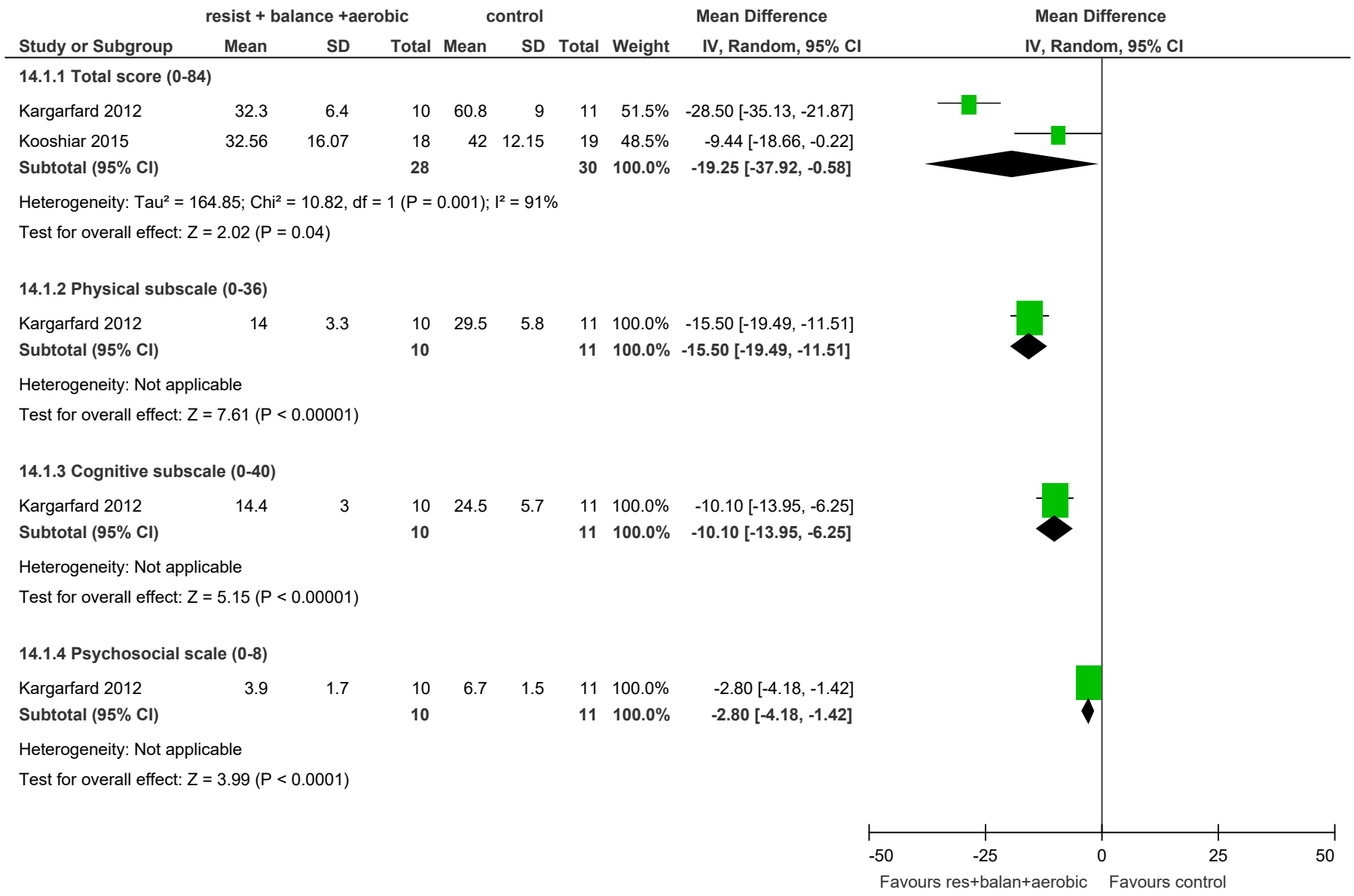

resist + balance +aerobic
control
Mean Difference
Mean Difference
Study or Subgroup
Mean
SD
Total
Mean
SD
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
14.1.1 Total score (0-84)
Kargarfard 2012 32.3 6.4 10 60.8 9 11 51.5% -28.50 [-35.13, -21.87]
Kooshiar 2015 32.56 16.07 18 42 12.15 19 48.5% -9.44 [-18.66, -0.22]
Subtotal (95% CI) 28 30 100.0% -19.25 [-37.92, -0.58]
Heterogeneity: Tau² = 164.85; Chi² = 10.82, df = 1 (P = 0.001); I² = 91%
Test for overall effect: Z = 2.02 (P = 0.04)
14.1.2 Physical subscale (0-36)
Kargarfard 2012 14 3.3 10 29.5 5.8 11 100.0% -15.50 [-19.49, -11.51]
Subtotal (95% CI) 10 11 100.0% -15.50 [-19.49, -11.51]
Heterogeneity: Not applicable
Test for overall effect: Z = 7.61 (P < 0.00001)
14.1.3 Cognitive subscale (0-40)
Kargarfard 2012 14.4 3 10 24.5 5.7 11 100.0% -10.10 [-13.95, -6.25]
Subtotal (95% CI) 10 11 100.0% -10.10 [-13.95, -6.25]
Heterogeneity: Not applicable
Test for overall effect: Z = 5.15 (P < 0.00001)
14.1.4 Psychosocial scale (0-8)
Kargarfard 2012 3.9 1.7 10 6.7 1.5 11 100.0% -2.80 [-4.18, -1.42]
Subtotal (95% CI) 10 11 100.0% -2.80 [-4.18, -1.42]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.99 (P < 0.0001)
-50
-25
0
25
50
Favours res+balan+aerobic
Favours control

Figure 131: Fatigue Severity Scale (9-63; lower better)

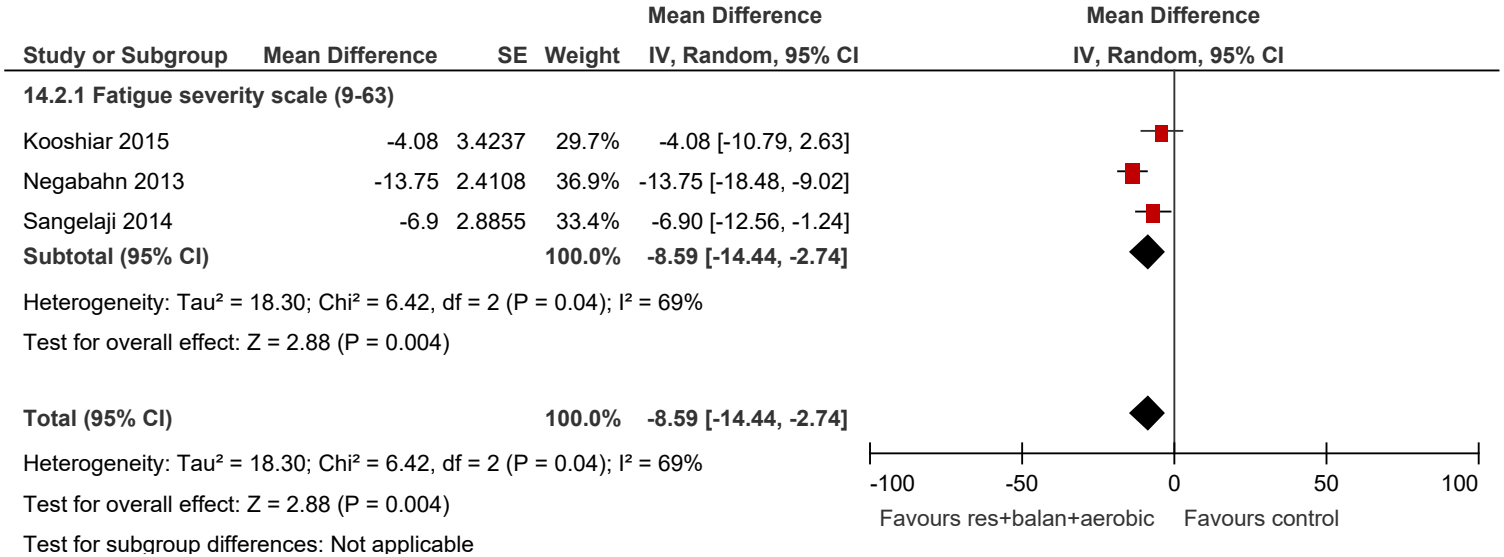


Figure 132: Fatigue Severity Scale (1-7; lower better)

Study or Subgroup	resist + balance +aerobic Mean	SD	Total	control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Learmonth 2012	5	1.8	15	6.2	0.7	10	31.1%	-1.20 [-2.21, -0.19]
Straudi 2014	5.63	0.78	12	6.01	0.91	12	68.9%	-0.38 [-1.06, 0.30]
Total (95% CI)			**27**			**22**	**100.0%**	**-0.64 [-1.20, -0.07]**

Heterogeneity: Chi² = 1.75, df = 1 (P = 0.19); I² = 43%

Test for overall effect: Z = 2.21 (P = 0.03)

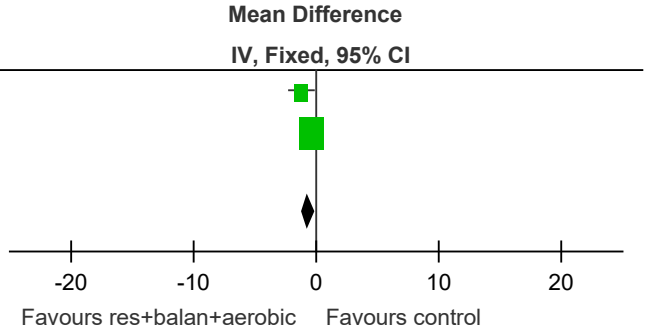


Figure 133: MSQOL-54 physical summary (0-100; higher better)

Study or Subgroup	resist + balance +aerobic Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Kargarfard 2012	65.4	6.6	10	44.2	4.4	11	21.20 [16.35, 26.05]

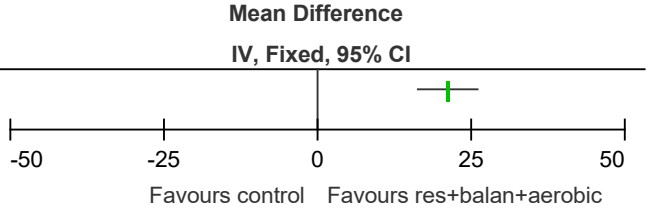


Figure 134: MSQOL-54 mental summary (0-100; higher better)

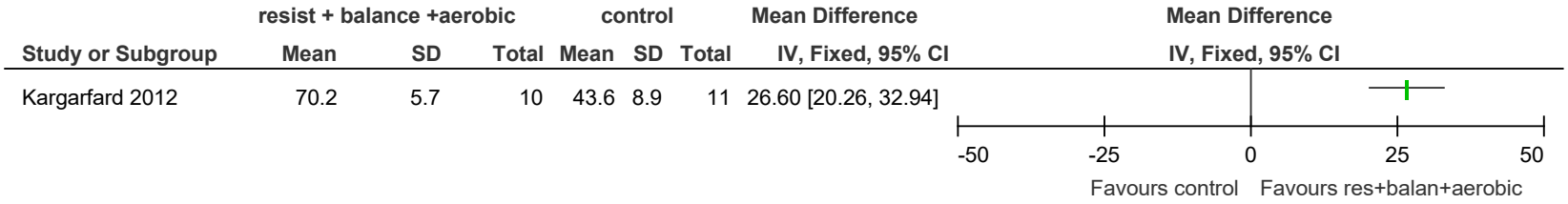


Figure 135: MSIS-29 physical summary (0-100; lower better)

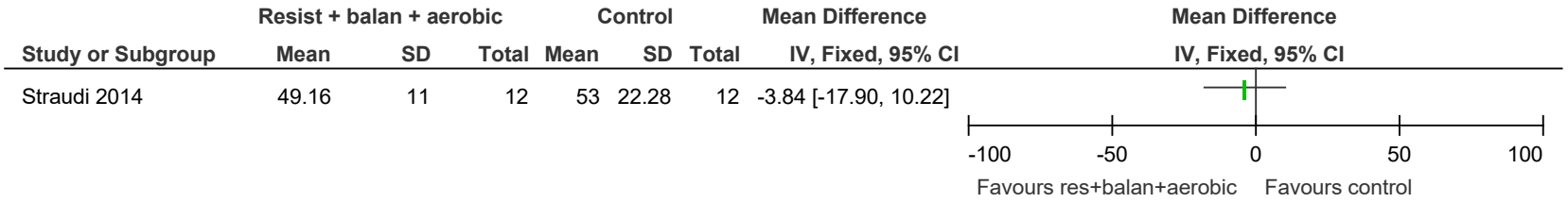


Figure 136: MSIS-29 psychological summary (0-100; lower better)

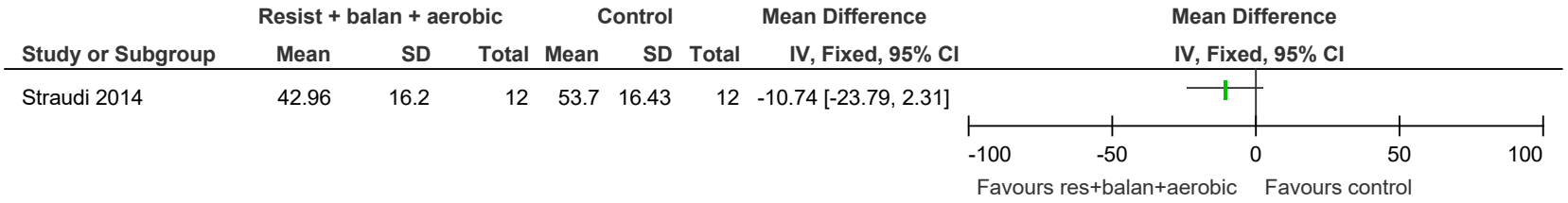


Figure 137: Multicultural Quality of Life Index (MQLIM; 0-100; higher better)

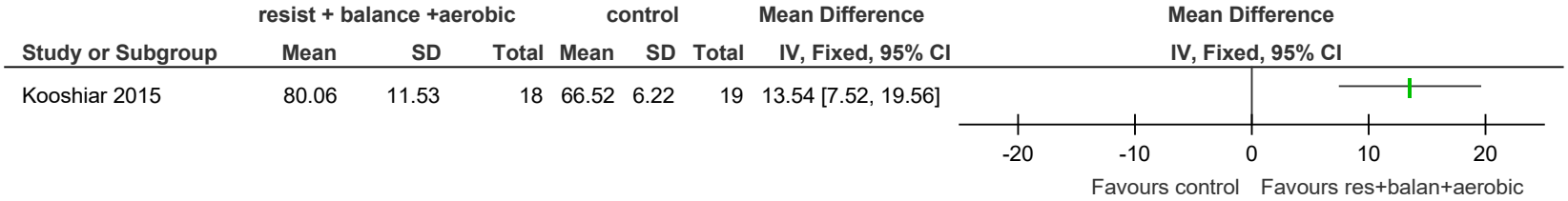


Figure 138: MS-specific quality of life measure (name and therefore scale unclear) mental health domain (higher better)

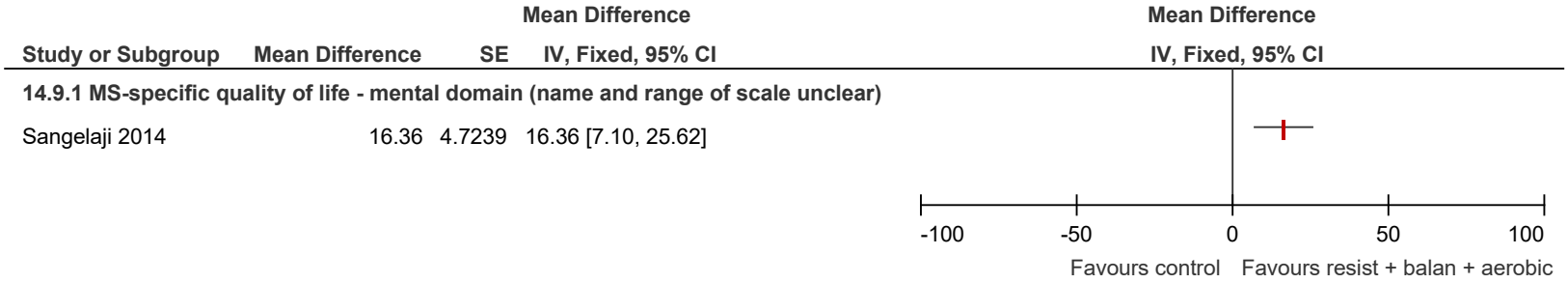


Figure 139: MS-specific quality of life measure (name and therefore scale unclear) physical domain (higher

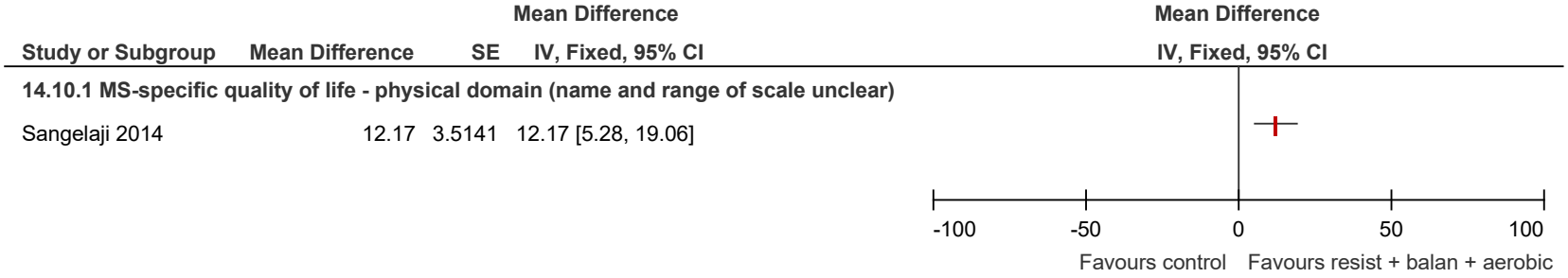


Figure 140: EDSS score (0-10; lower better)

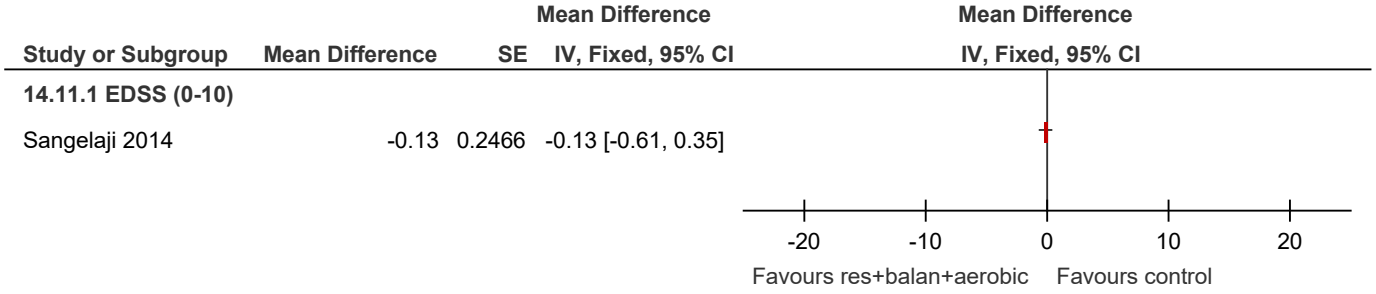


Figure 141: Hospital Anxiety and Depression Scale (0-21; lower better)

	resist + balance +aerobic			control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Learmonth 2012	11.7	5.9	15	13.8	6.6	10	-2.10 [-7.16, 2.96]

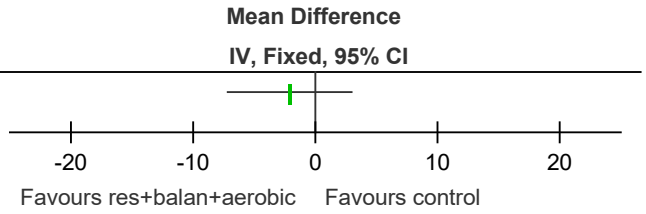


Figure 142: Leeds MS Quality of Life (0-24; lower better)

	resist + balance +aerobic			control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Learmonth 2012	10.9	3.9	15	12.4	3.1	10	-1.50 [-4.25, 1.25]

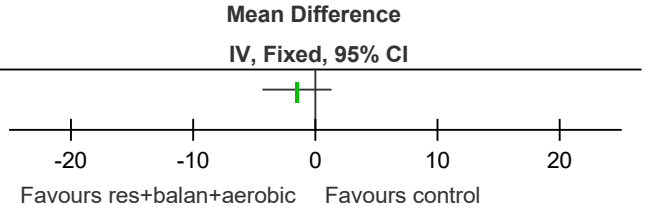
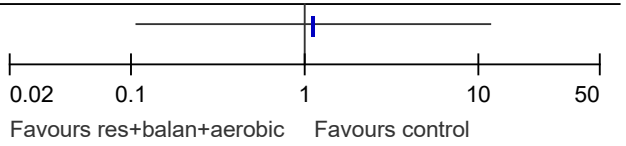


Figure 143: Adverse events leading to withdrawal

	resist + balan + aerobic		Control		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Sangelaji 2014	2	41	1	23	1.12 [0.11, 11.71]



E.15 Resistance training + balance exercise + aerobic exercise vs. control (usual care, no intervention) – outcomes >6 months

Figure 144: Fatigue Severity Scale (9-63; lower better)

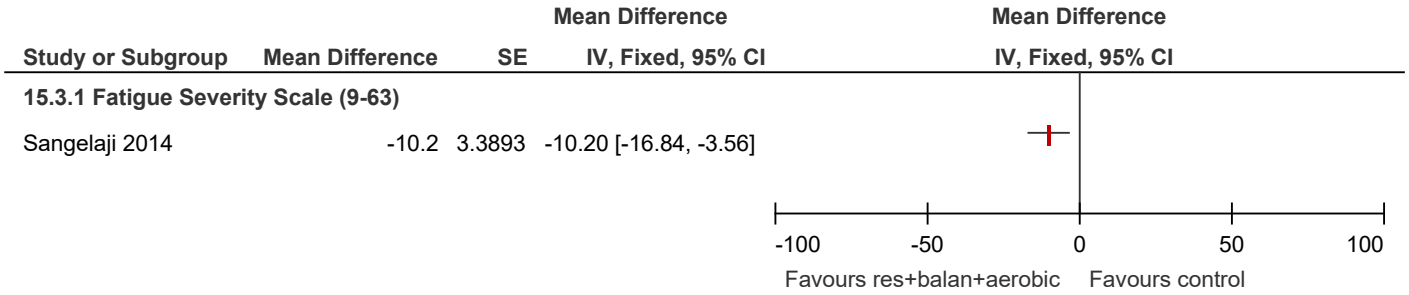


Figure 145: MS-specific quality of life measure (name and therefore scale unclear) mental health domain (higher better)

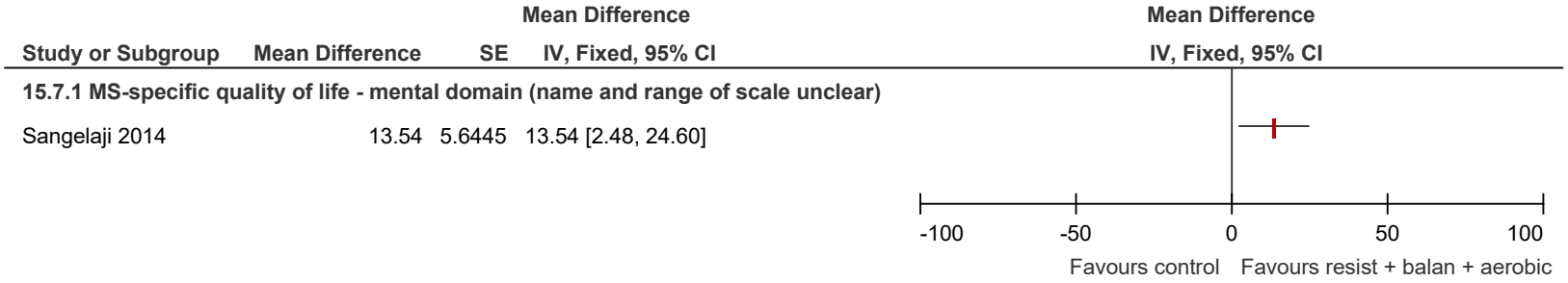


Figure 146: MS-specific quality of life measure (name and therefore scale unclear) physical domain (higher better)

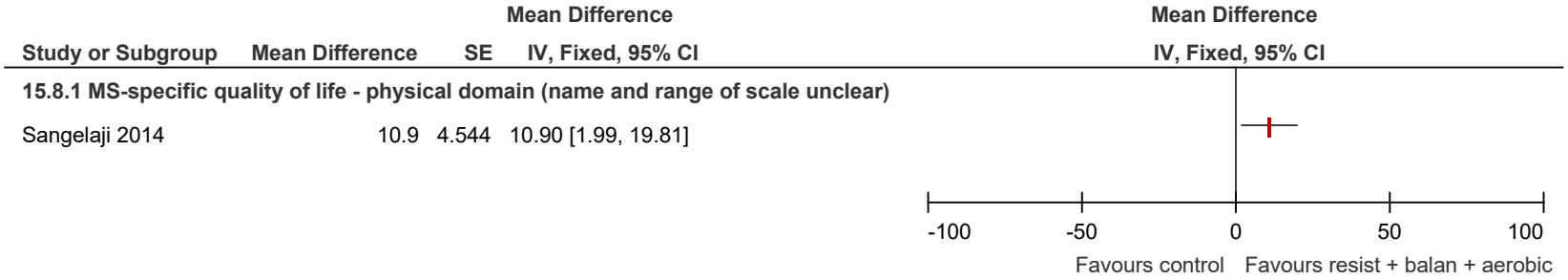
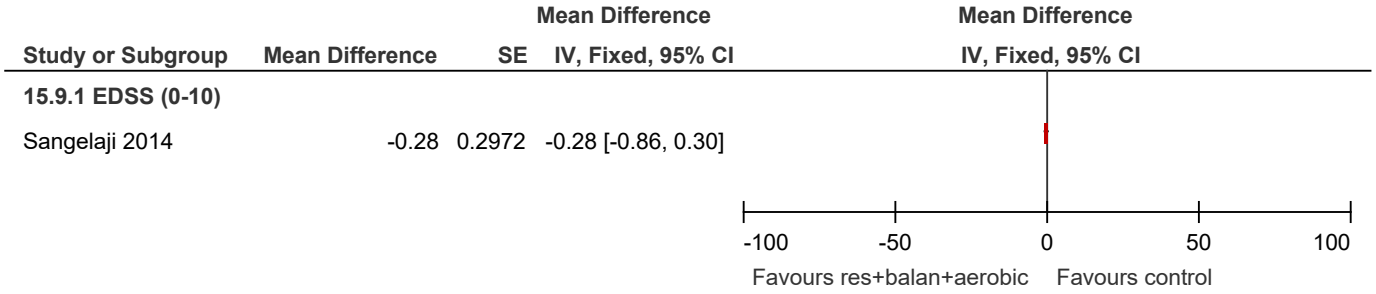


Figure 147: EDSS score (0-10; lower better)



E.16 Standard exercises (resistance + balance + aerobic) + high-intensity lower limb resistance training vs. standard exercises alone – outcomes up to 6 months

Figure 148: Fatigue Severity Scale (10 max score; lower better)

	standard ex + high resist			standard exercises			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Hayes 2011	-0.94	1.129	10	-1.38	0.957	9	0.44 [-0.50, 1.38]

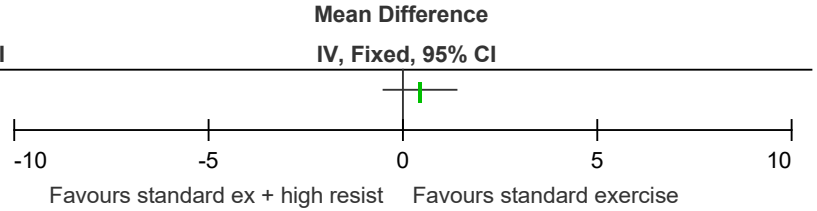
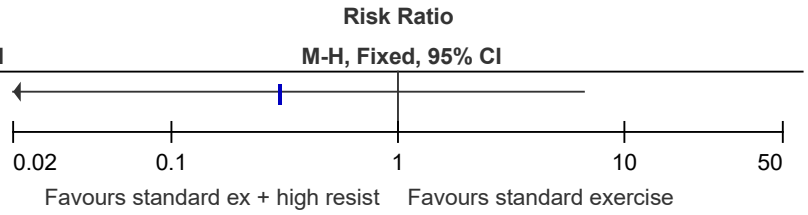


Figure 149: Adverse events

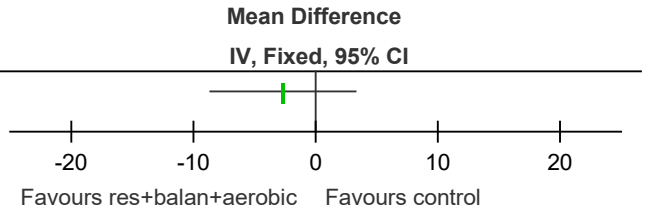
	standard ex + high resist		standard exercises		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Hayes 2011	0	10	1	9	0.30 [0.01, 6.62]



E.17 Resistance + balance + aerobic exercise vs. massage – outcomes up to 6 months

Figure 150: Fatigue Severity Scale (9-63; lower better)

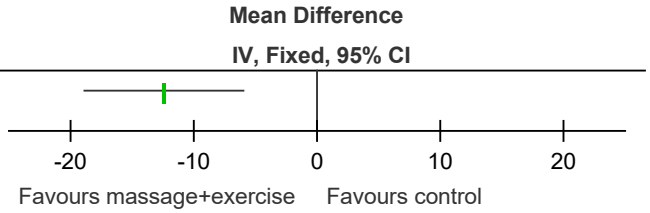
	resist + balance +aerobic			control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Negabahn 2013	-10.75	7.27	12	-8.08	7.58	12	-2.67 [-8.61, 3.27]



E.18 Massage + exercise (resistance, balance + aerobic) vs. control (no intervention) – outcomes up to 6 months

Figure 151: Fatigue Severity Scale (9-63; lower better)

	massage + exercise			control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Negabahn 2013	-9.419	10.63	12	3	4.11	12	-12.42 [-18.87, -5.97]



E.19 Massage + exercise (resistance, balance + aerobic) vs. exercise only – outcomes up to 6 months

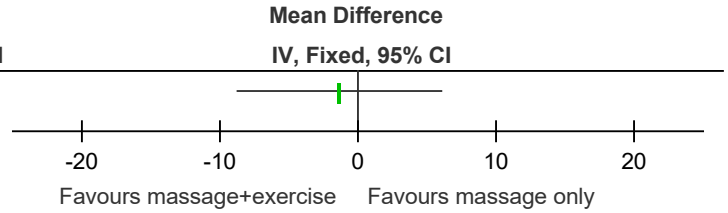
Figure 152: Fatigue Severity Scale (9-63; lower better)

	massage + exercise			exercise only			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Negabahn 2013	-9.419	10.63	12	-10.75	7.27	12	1.33 [-5.96, 8.62]

E.20 Massage + exercise (resistance, balance + aerobic) vs. massage only – outcomes up to 6 months

Figure 153: Fatigue Severity Scale (9-63; lower better)

	massage + exercise			massage only			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Negabahn 2013	-9.419	10.63	12	-8.08	7.58	12	-1.34 [-8.73, 6.05]



E.21 Resistance + aerobic exercise vs. yoga – outcomes up to 6 months

Figure 154: Modified Fatigue Impact Scale (0-84, 0-36 or 0-40; lower better)

	resistance + aerobic			yoga			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
12.1.1 Total score (0-84)								
Garrett 2013	32.9	14.6	41	33.9	19.2	37	-1.00 [-8.63, 6.63]	
12.1.2 Physical subscale (0-36)								
Garrett 2013	-3.9	6.7501	63	-2.1	6.35	63	-1.80 [-4.09, 0.49]	
12.1.3 Cognitive subscale (0-40)								
Garrett 2013	-2.1	4.17	63	-0.96	3.57	63	-1.14 [-2.50, 0.22]	

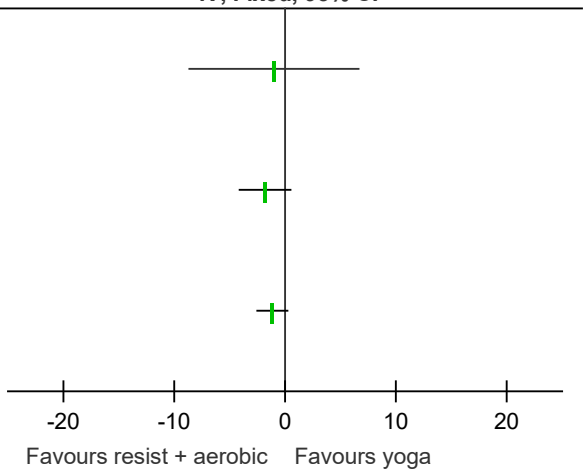


Figure 155: Fatigue Severity Scale (9-63; lower better)

	resistance + aerobic			yoga			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Razazian 2016	25.28	11.71	18	38.94	13.63	18	-13.66 [-21.96, -5.36]	

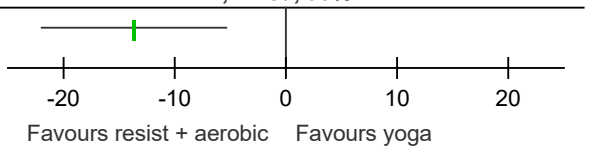


Figure 156: MSIS-29 (0-100 for each domain; lower better)

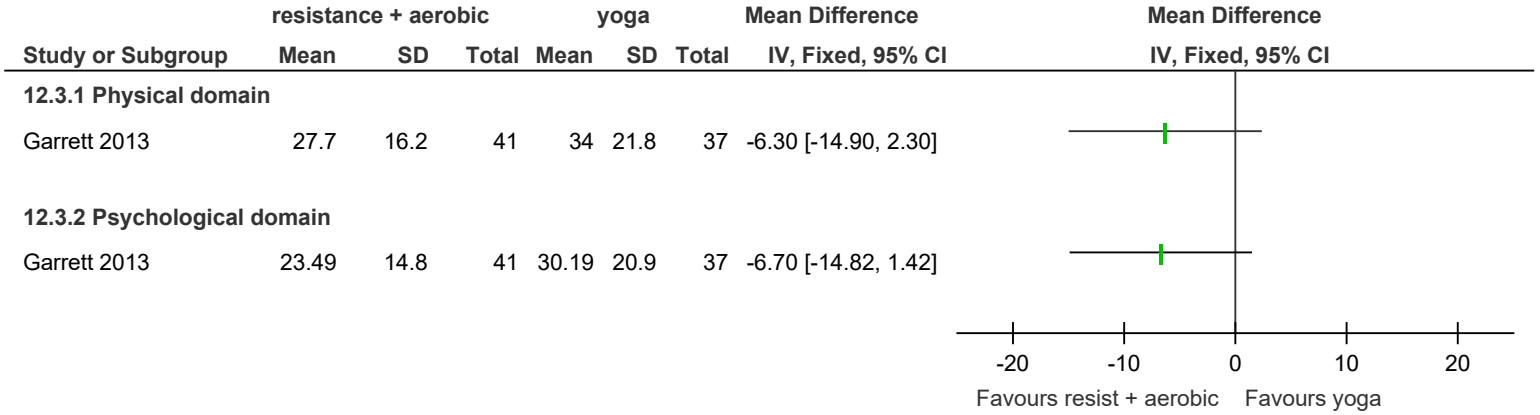


Figure 157: Beck Depression Inventory (0-63; lower better)

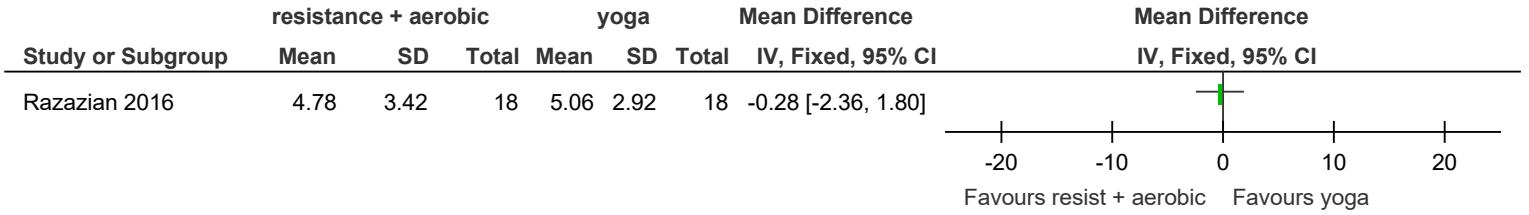


Figure 158: Adherence – classes attended out of a possible 10

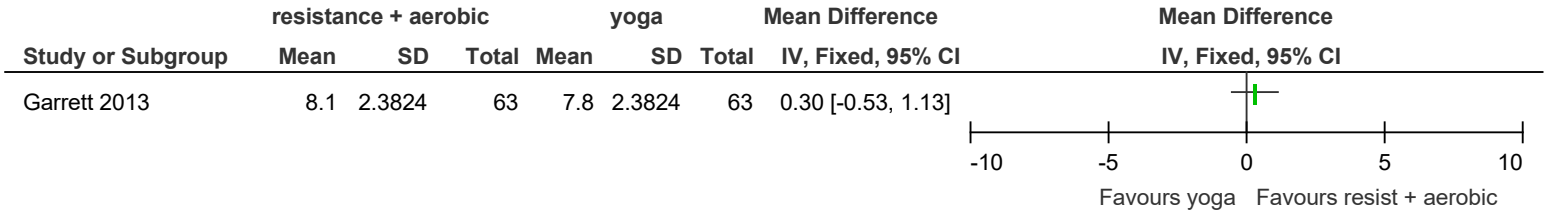
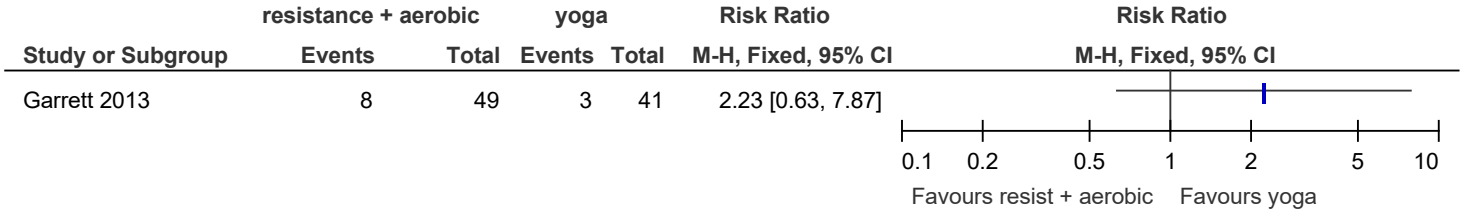


Figure 159: Adverse events leading to withdrawal



E.22 Fatigue/energy management programme vs. control (waitlist, no intervention, information only) – outcomes up to 6 months

Figure 160: Fatigue Severity Scale (1-7; lower better)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
29.1.1 Fatigue Severity Scale (1-7)				
Abonie 2020	-0.5	0.6702	2.7%	-0.50 [-1.81, 0.81]
Blikman 2017	0.06	0.1735	40.8%	0.06 [-0.28, 0.40]
Finlayson 2011	-0.18	0.153	52.4%	-0.18 [-0.48, 0.12]
Garcia Jalon 2013	0.31	0.5468	4.1%	0.31 [-0.76, 1.38]
Subtotal (95% CI)			**100.0%**	**-0.07 [-0.29, 0.15]**

Heterogeneity: Chi² = 1.97, df = 3 (P = 0.58); I² = 0%

Test for overall effect: Z = 0.64 (P = 0.52)

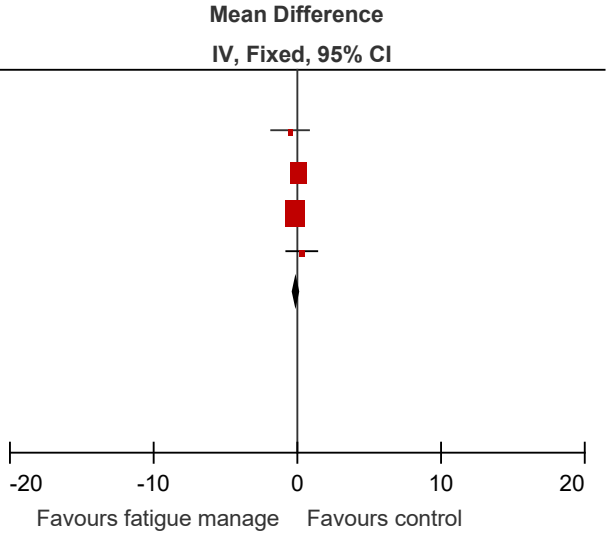


Figure 161: Fatigue Severity Scale (9-63; lower better)

Study or Subgroup	Fatigue management Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hugos 2010	48.6	5.8095	15	45.82	5.9644	15	2.78 [-1.43, 6.99]

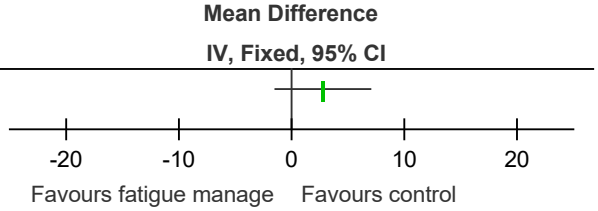


Figure 162: Modified Fatigue Impact Scale – total (0-84; lower better)

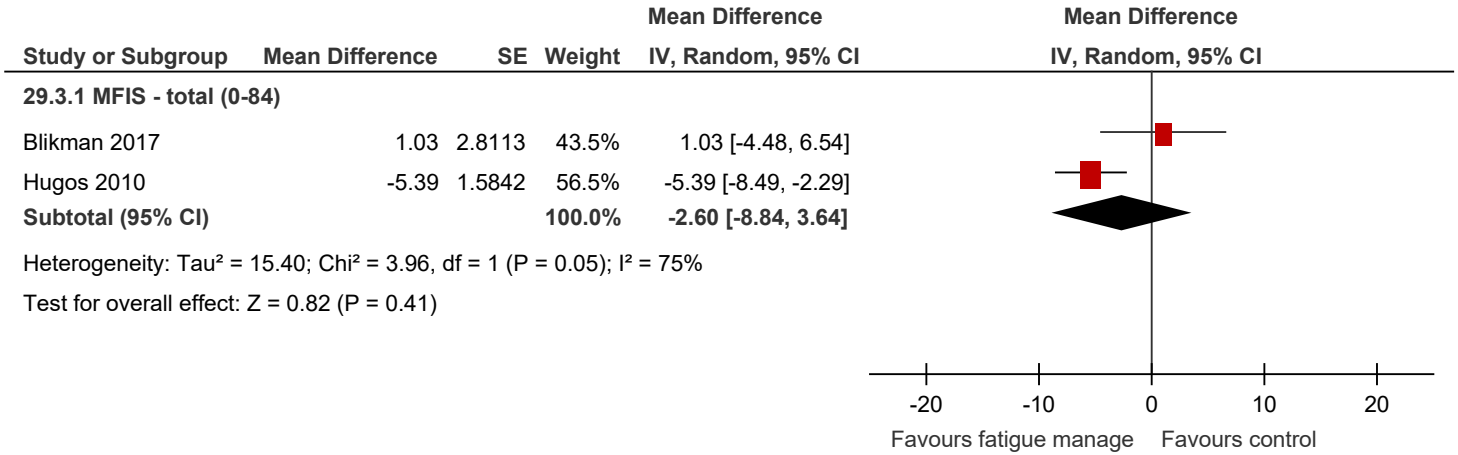


Figure 163: Modified Fatigue Impact Scale – physical (0-36; lower better)

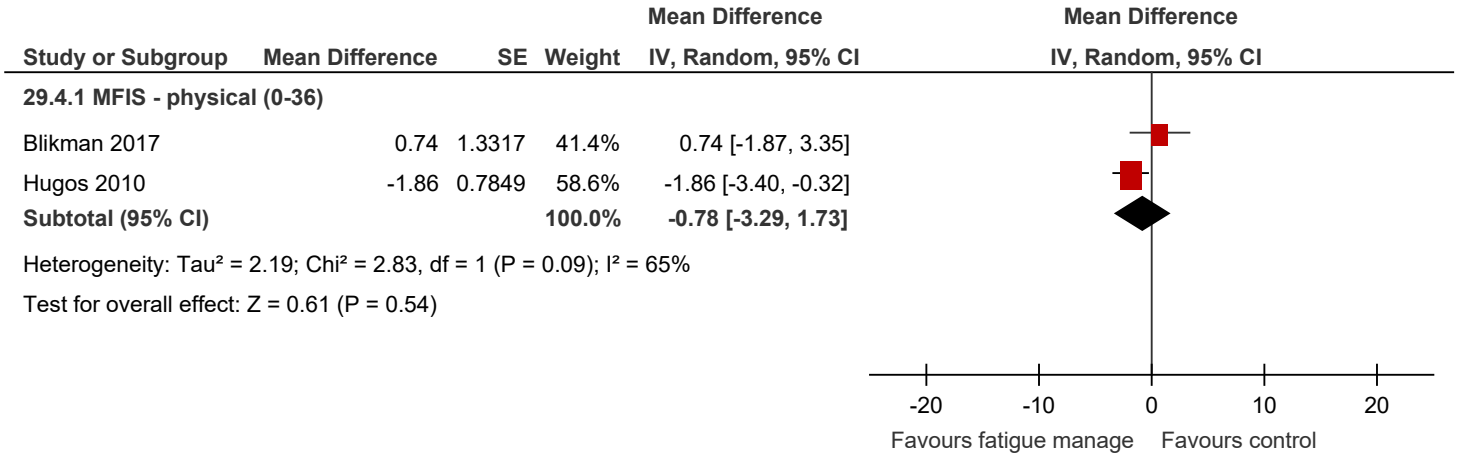


Figure 164: Modified Fatigue Impact Scale – physical (0-40; lower better)

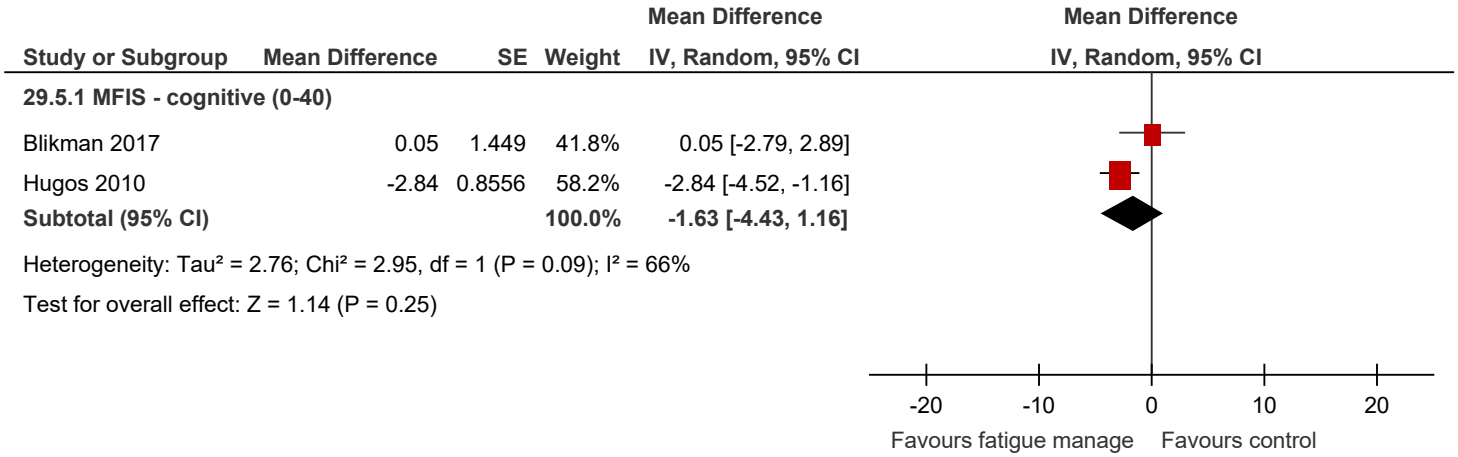


Figure 165: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

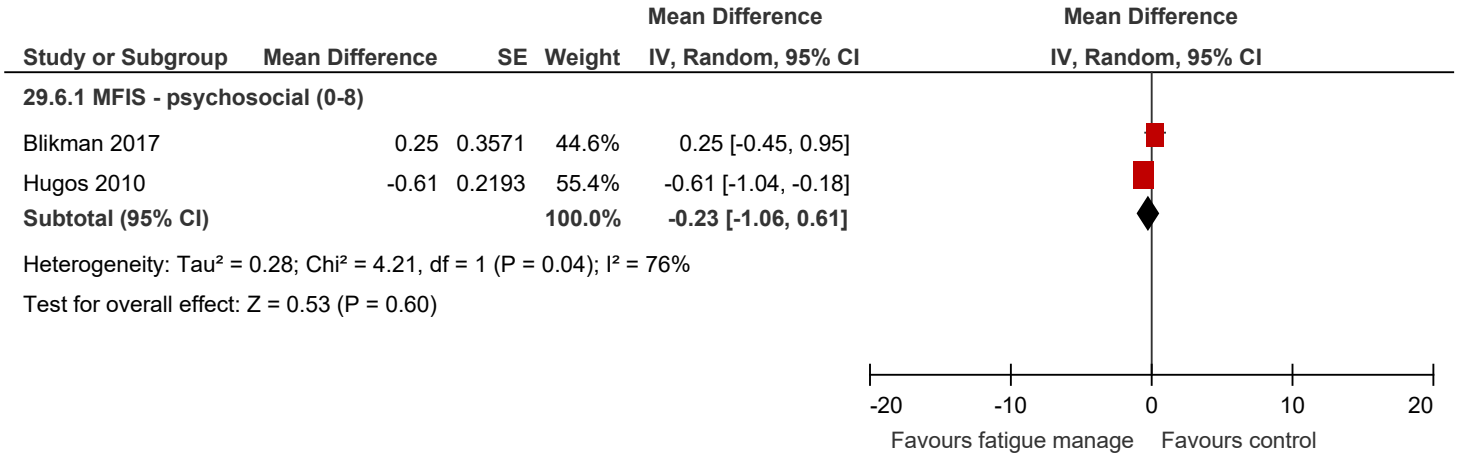


Figure 166: Fatigue Impact Scale – total (0-160; lower better)

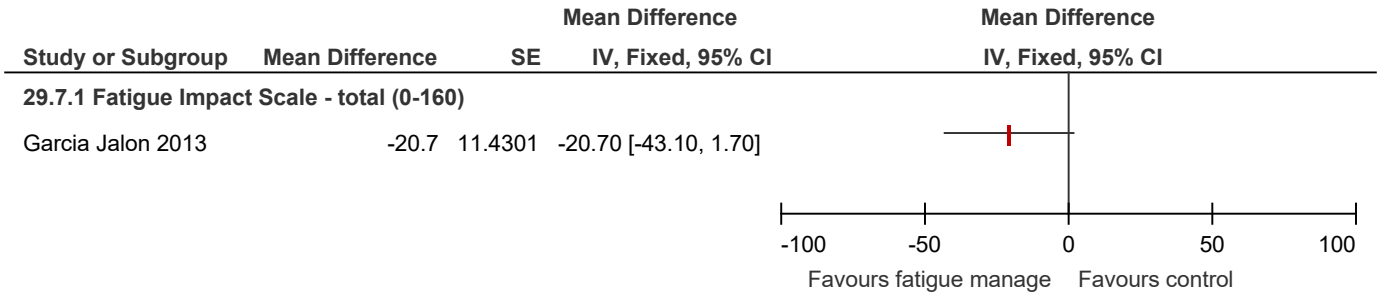


Figure 167: Fatigue Impact Scale – cognitive (0-40; lower better)

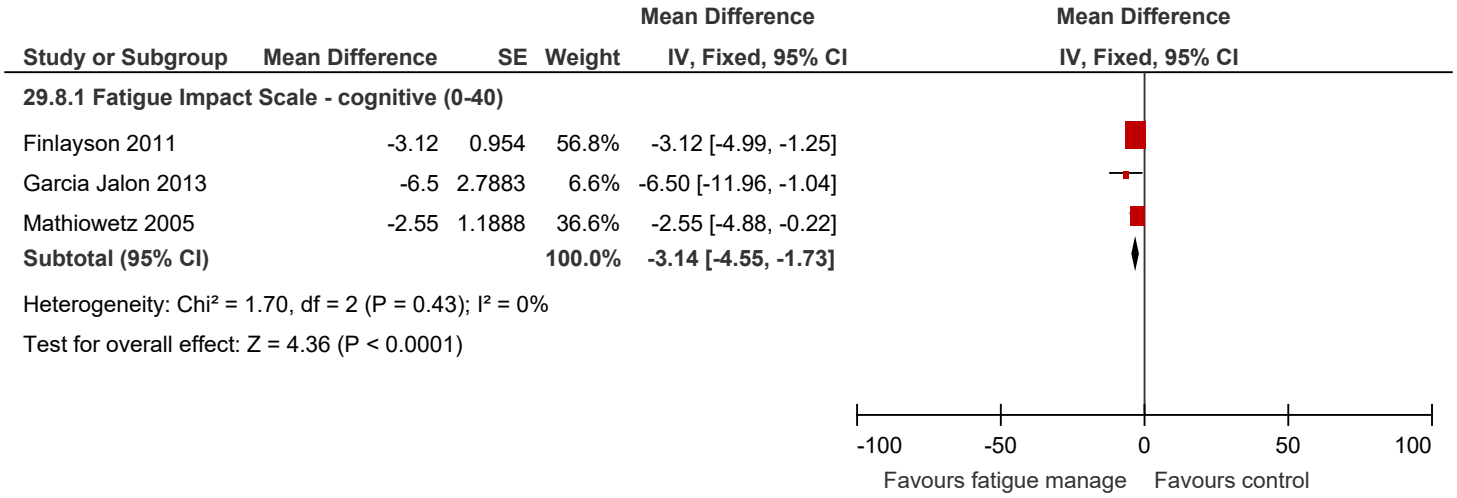


Figure 168: Fatigue Impact Scale – physical (0-40; lower better)

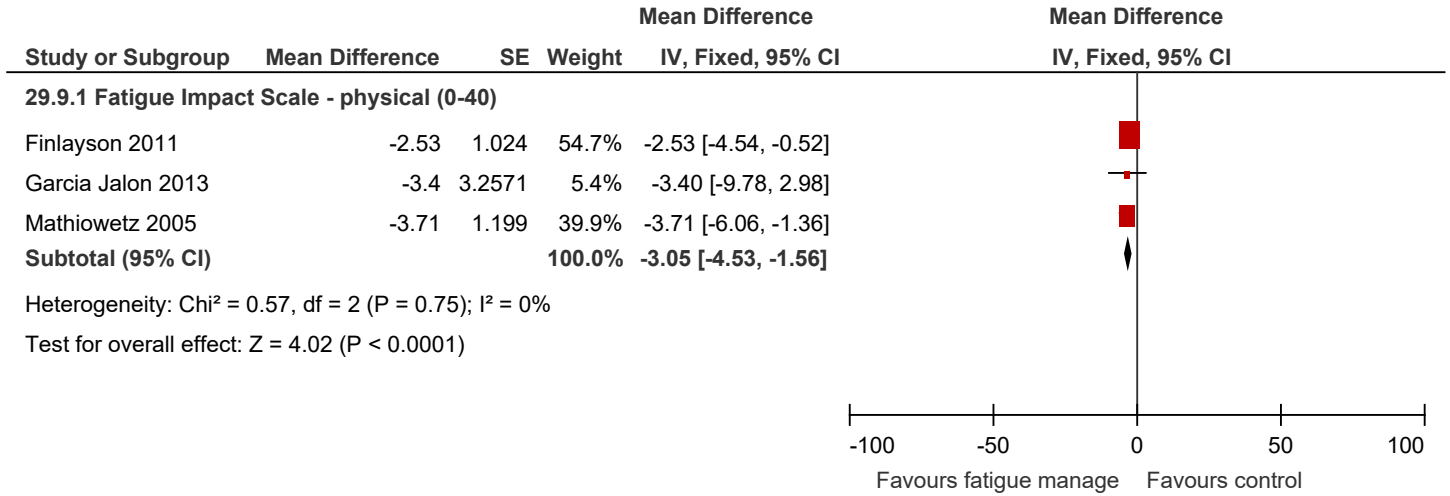


Figure 169: Fatigue Impact Scale – psychosocial (0-80; lower better)

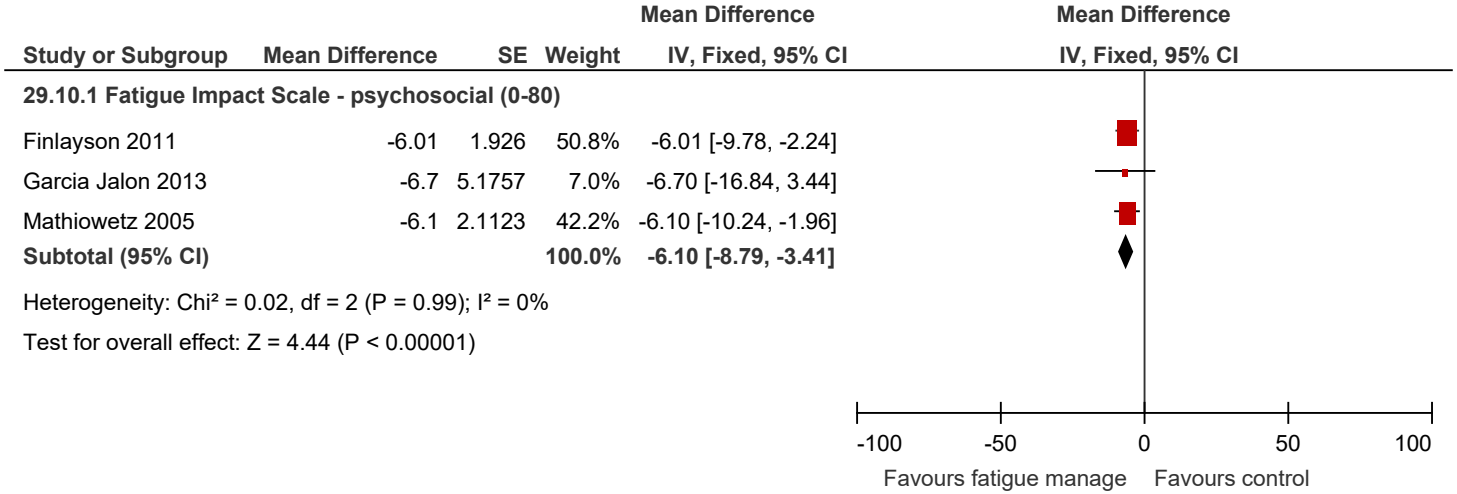


Figure 170: Checklist Individual Strength (CIS)20r – fatigue subscale (8-56; lower better)

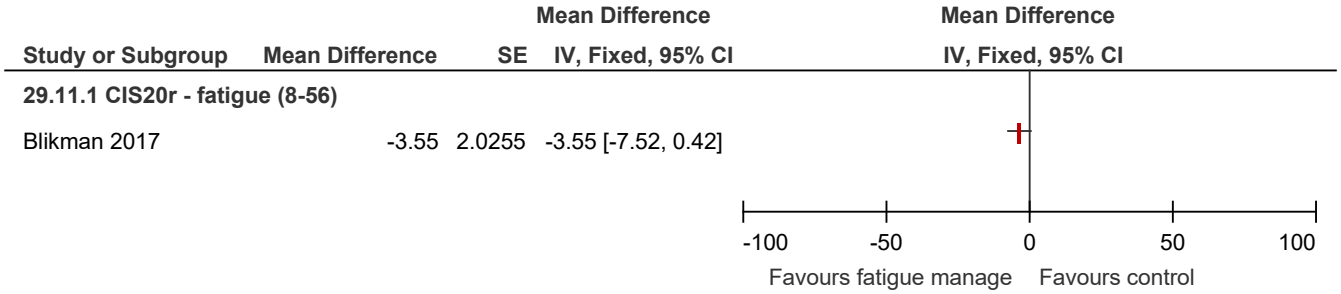


Figure 171: Clinically significant improvement in fatigue score from baseline

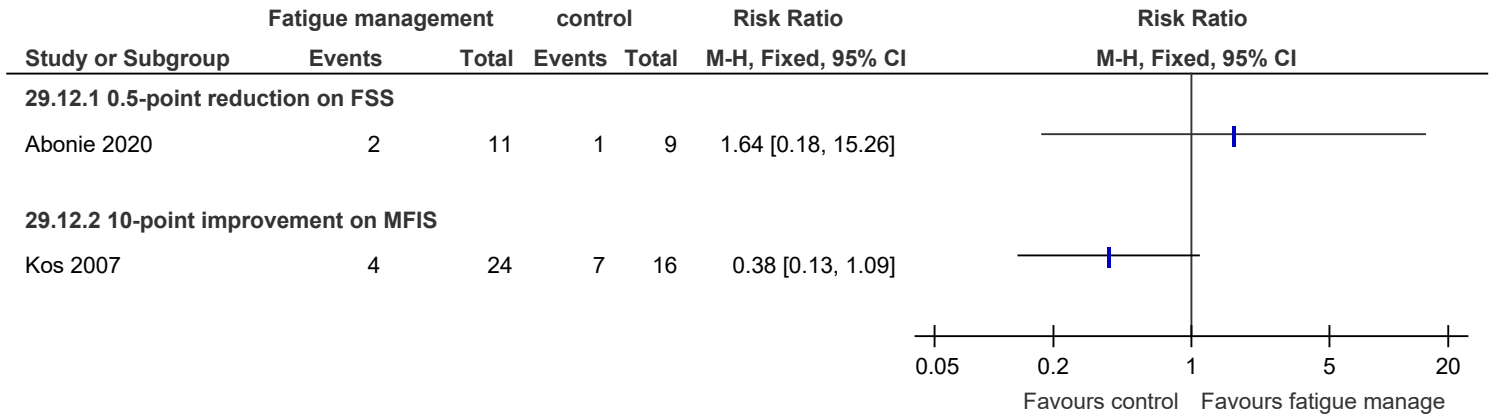


Figure 172: SF-36 physical function (0-100; higher better)

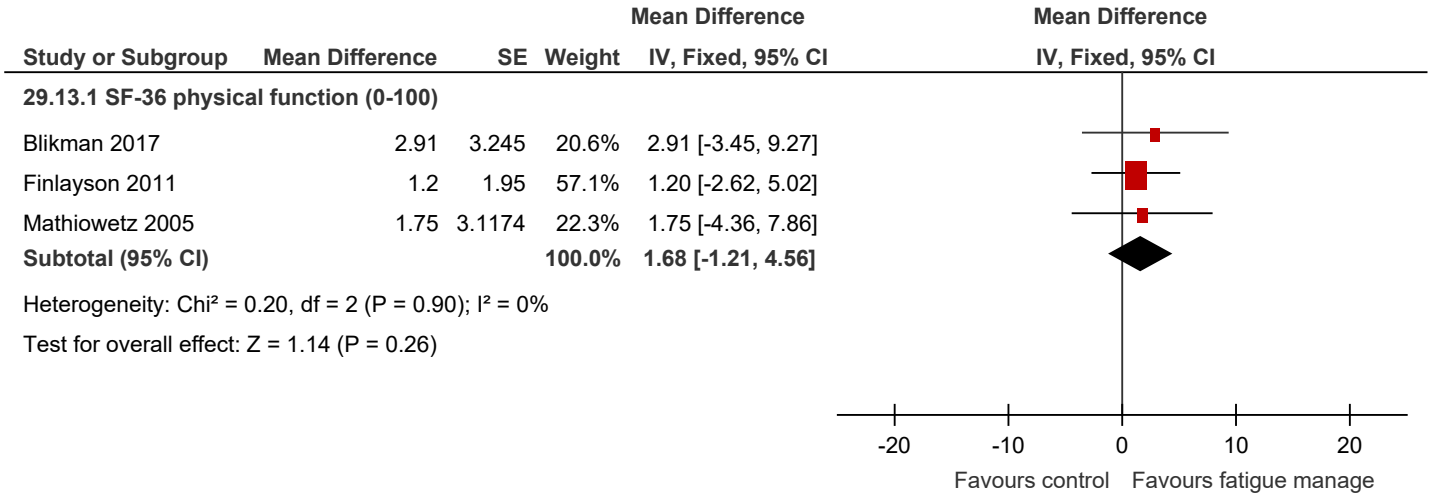


Figure 173: SF-36 role physical (0-100; higher better)

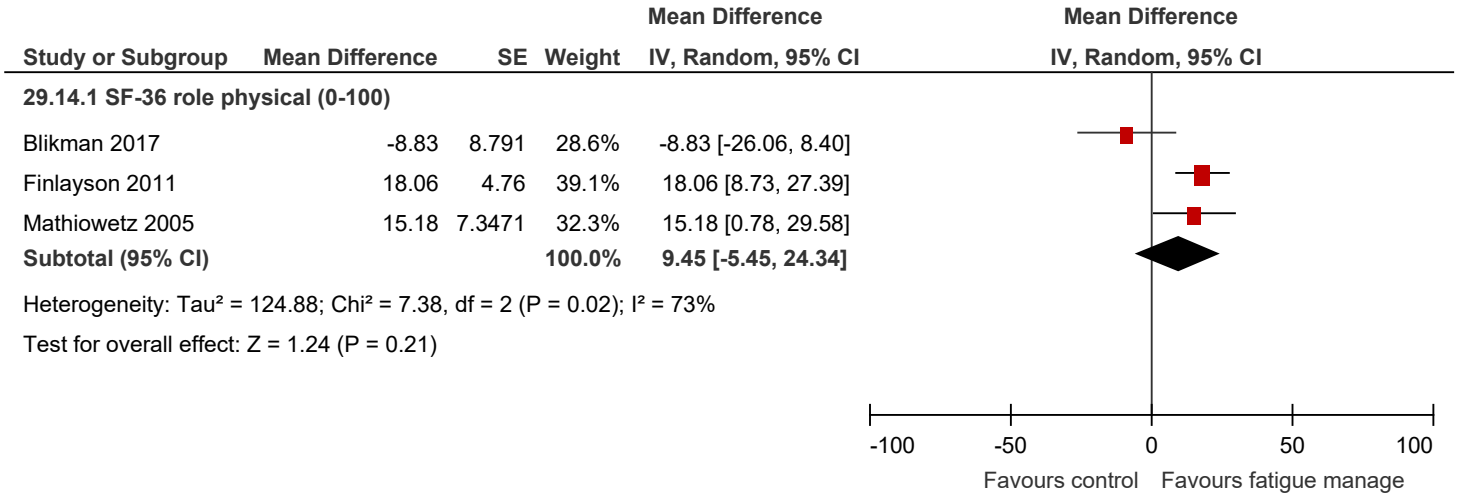


Figure 174: SF-36 body pain (0-100; higher better)

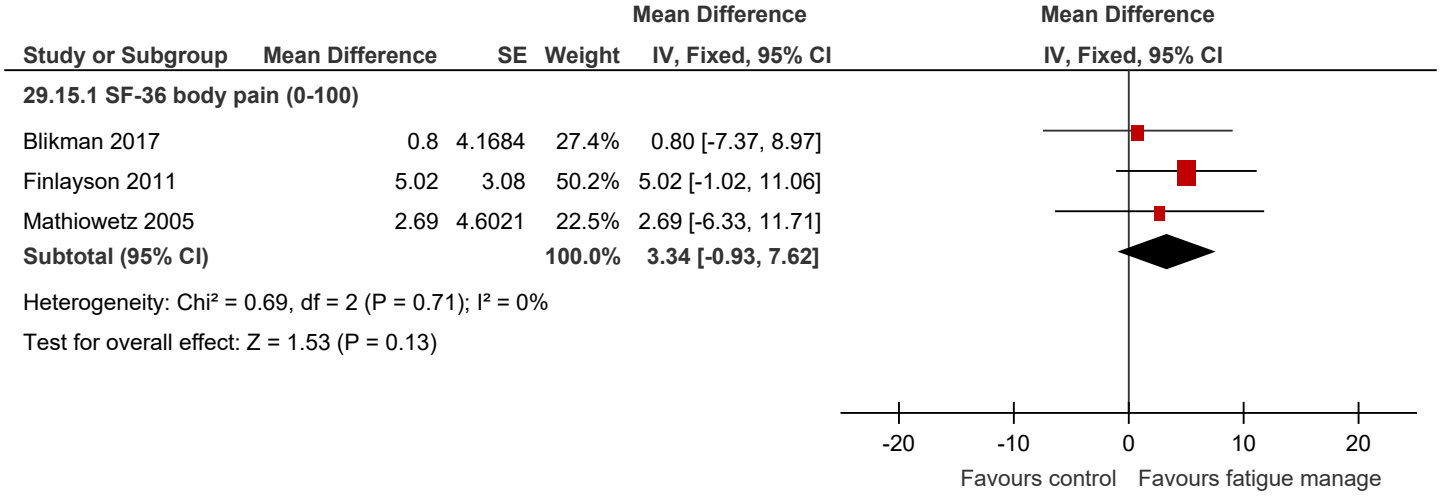


Figure 175: SF-36 general health (0-100; higher better)

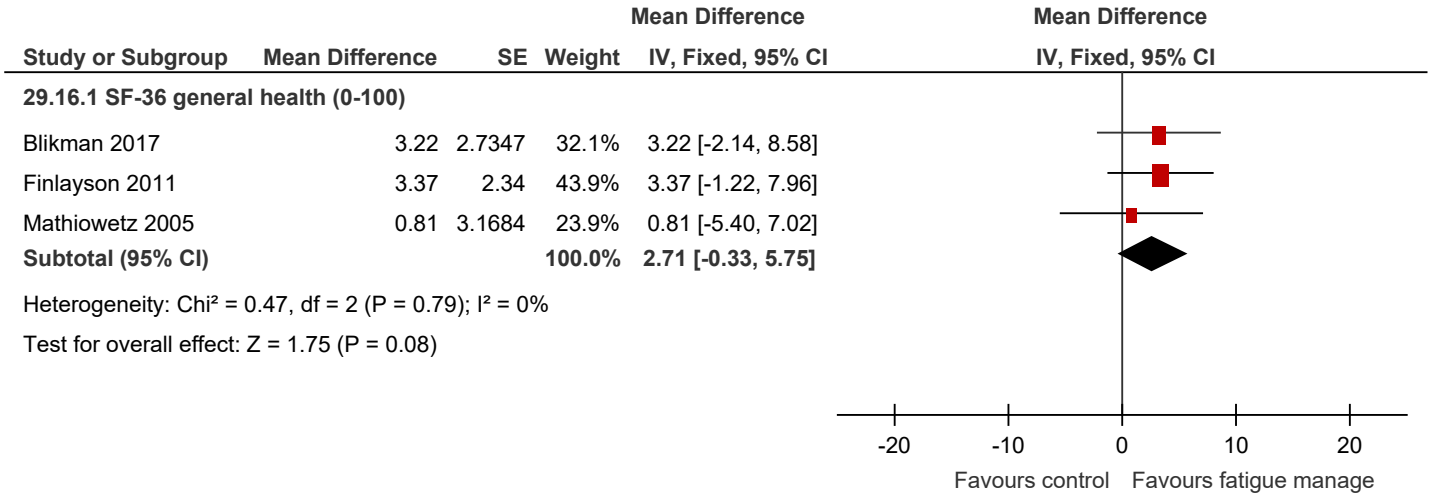


Figure 176: SF-36 vitality (0-100; higher better)

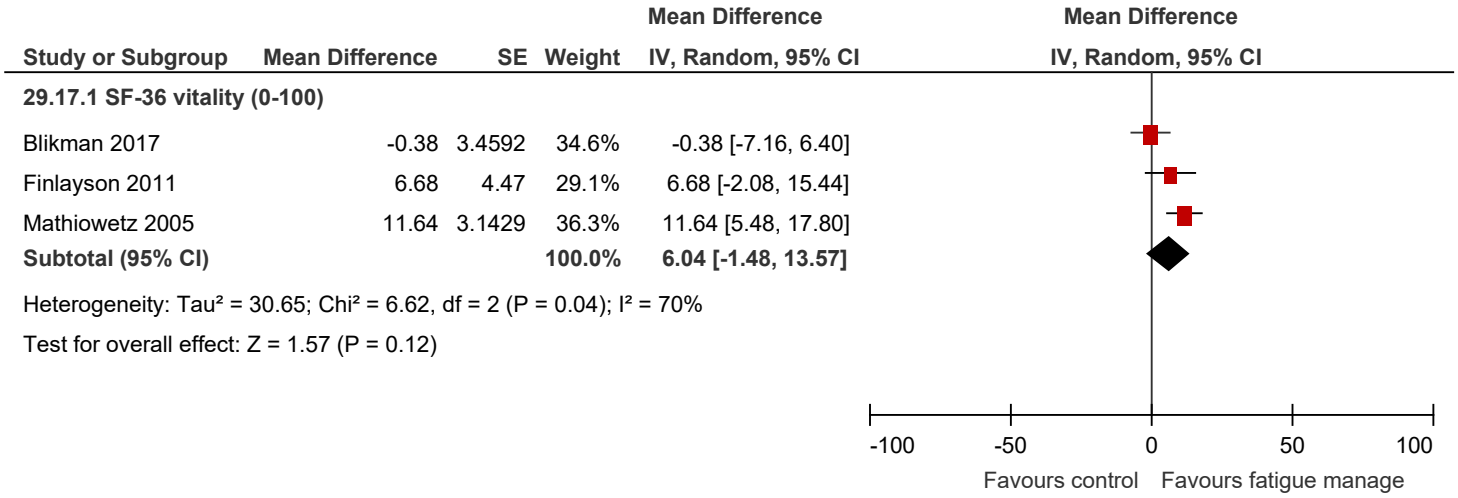


Figure 177: SF-36 social function (0-100; higher better)

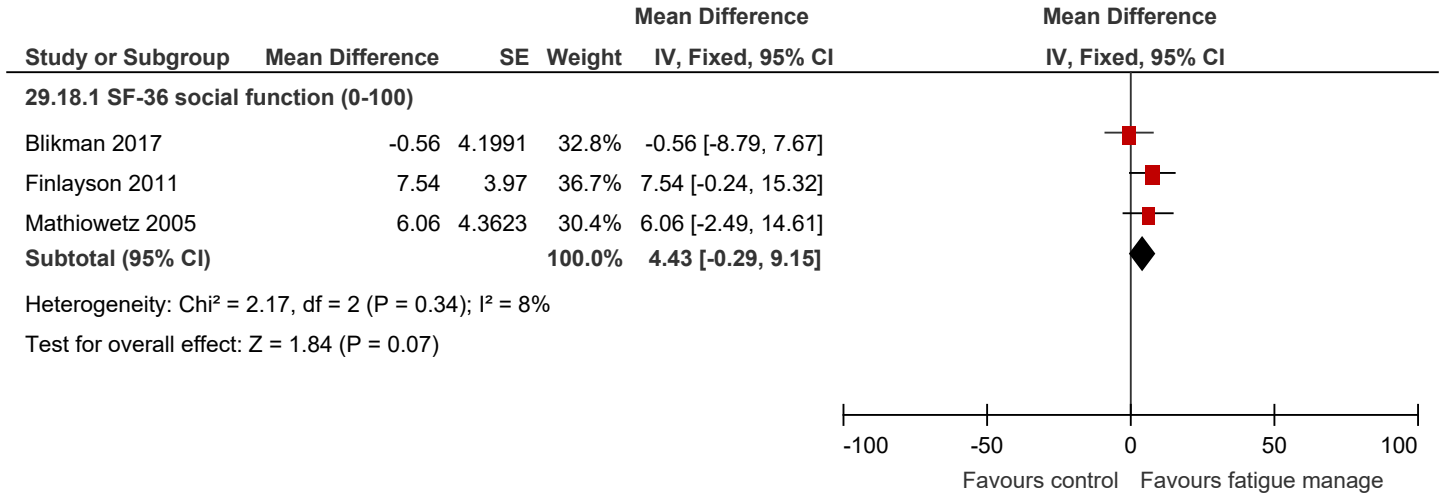


Figure 178: SF-36 role emotional (0-100; higher better)

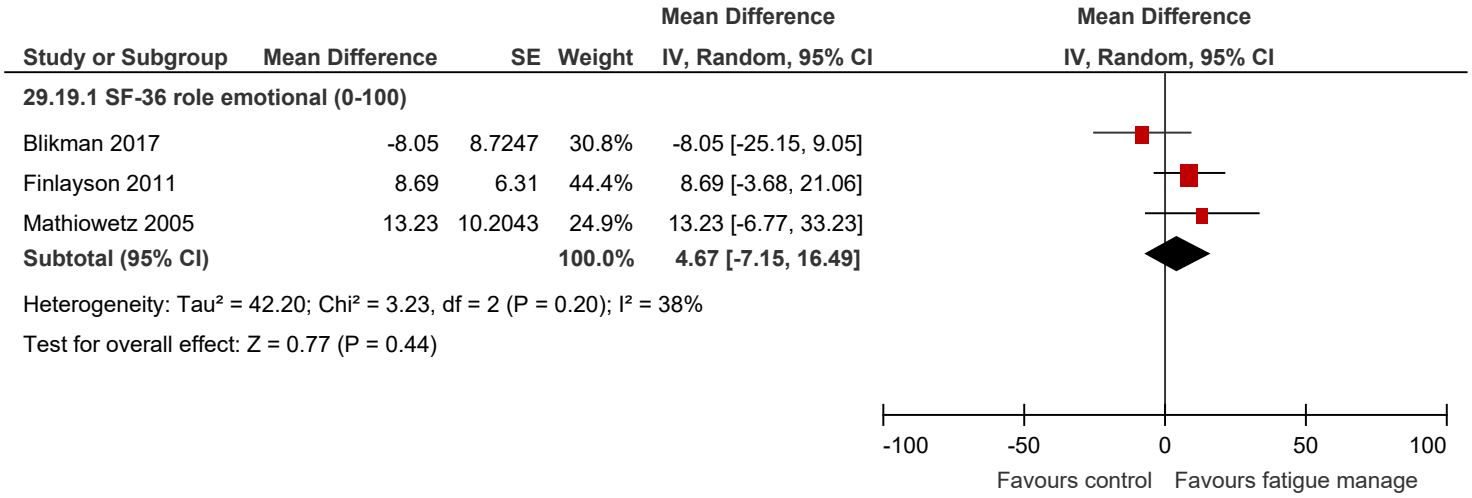


Figure 179: SF-36 mental health (0-100; higher better)

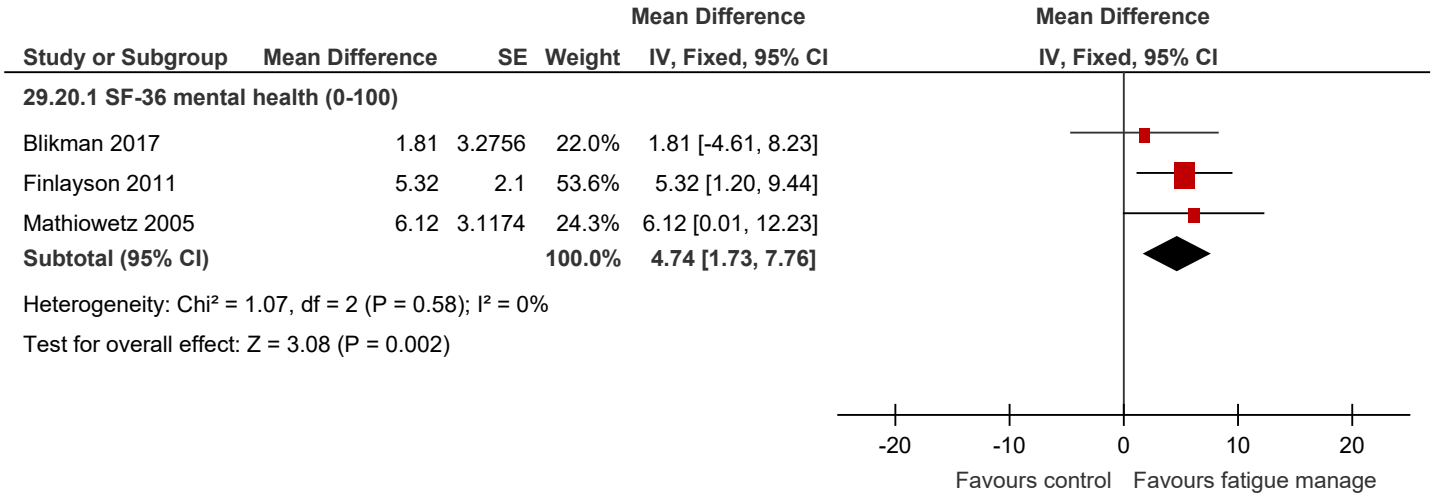


Figure 180: MSIS-29 – total (0-100; lower better)

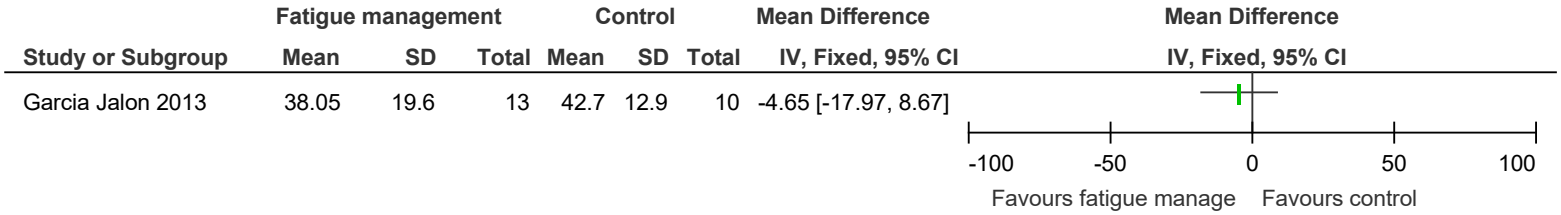


Figure 181: MSIS-29 – physical (0-100; lower better)

	Fatigue management			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Garcia Jalon 2013	38.46	21.06	13	45.12	14.51	10	-6.66 [-21.22, 7.90]	

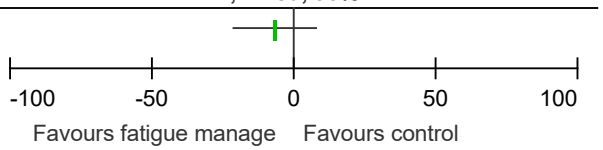


Figure 182: MSIS-29 – psychological (0-100; lower better)

	Fatigue management			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Garcia Jalon 2013	36.32	23.55	13	37.49	14.88	10	-1.17 [-16.95, 14.61]	

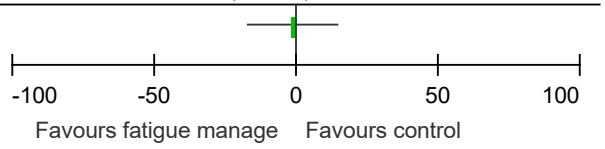


Figure 183: Cognitive - Checklist Individual Strength (CIS)20r – concentration (5-35; lower better)

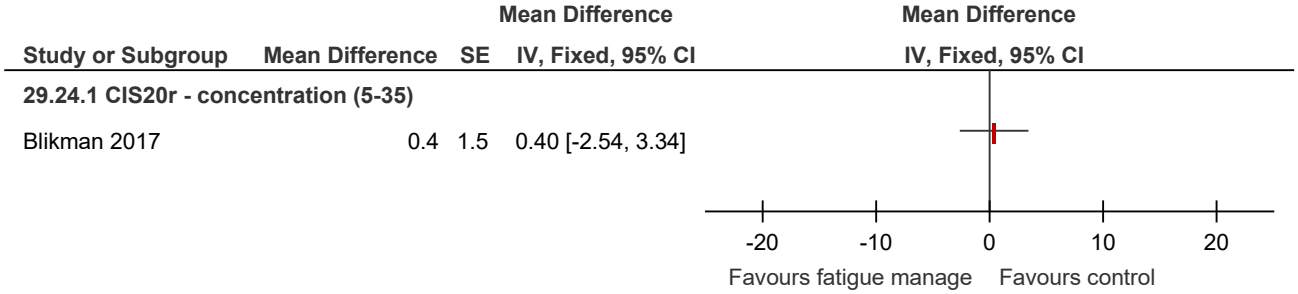


Figure 184: Beck Depression Inventory – fast screen (0-21; lower better)

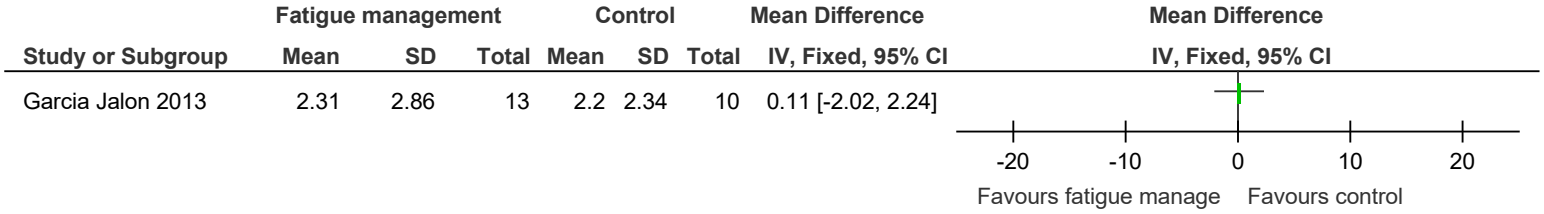
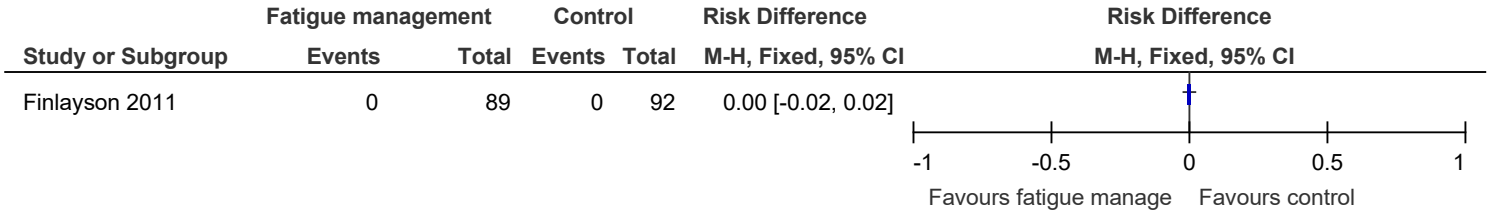


Figure 185: Adverse events



E.23 Fatigue/energy management programme vs. control (waitlist, no intervention, information only) – outcomes >6 months

Figure 186: Fatigue Severity Scale (1-7; lower better)

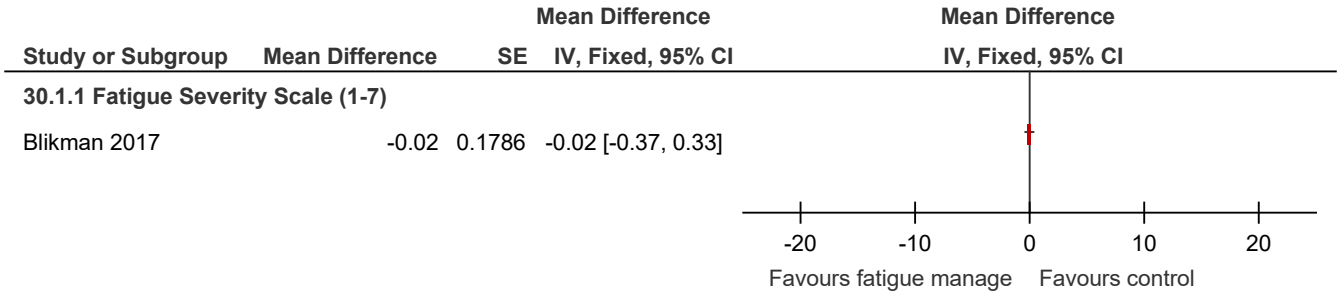


Figure 187: Modified Fatigue Impact Scale – total (0-84; lower better)

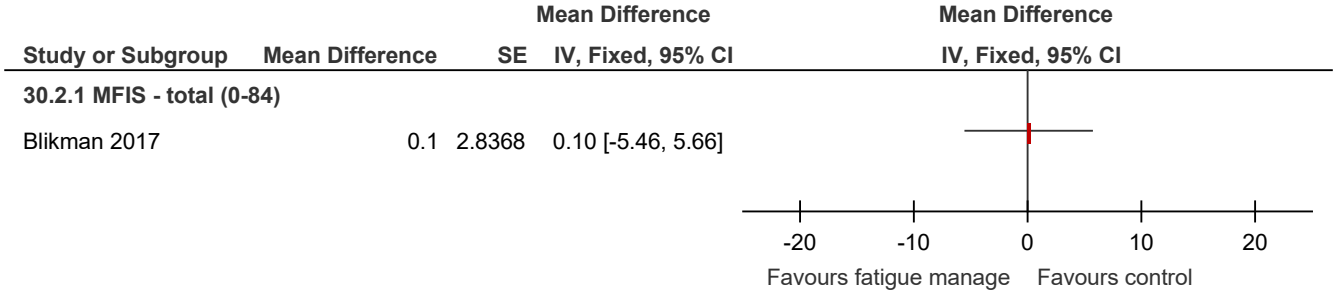


Figure 188: Modified Fatigue Impact Scale – physical (0-36; lower better)

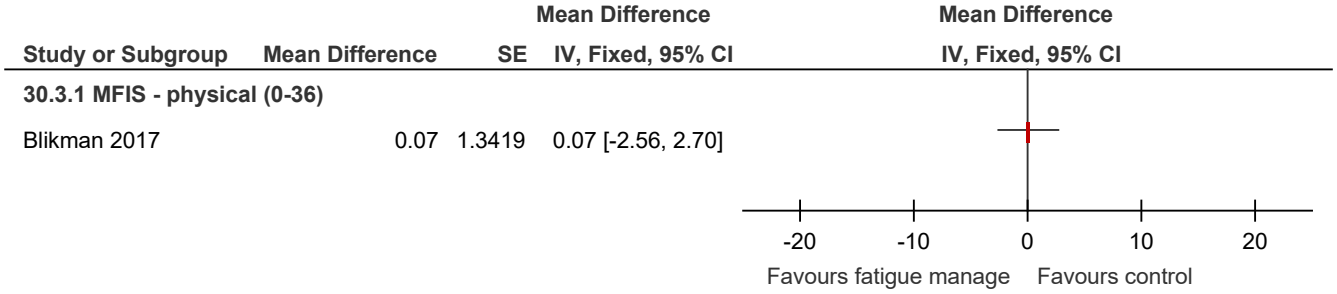


Figure 189: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

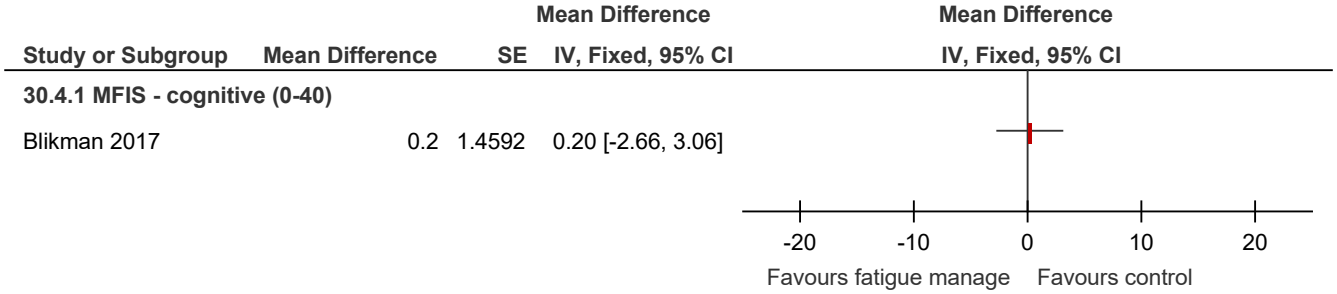


Figure 190: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

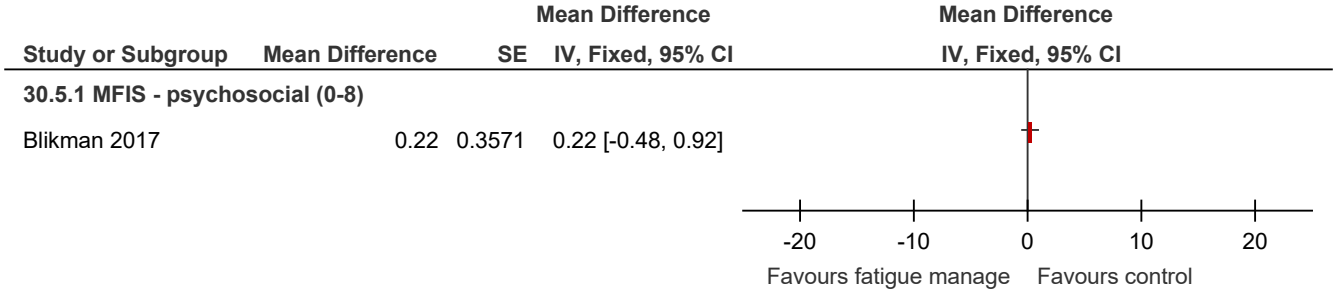


Figure 191: Checklist Individual Strength (CIS)20r – fatigue subscale (8-56; lower better)

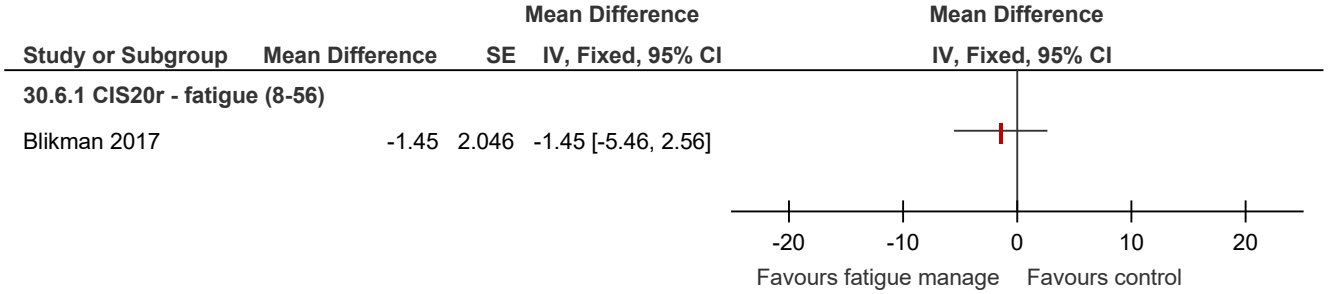


Figure 192: SF-36 physical function (0-100; higher better)

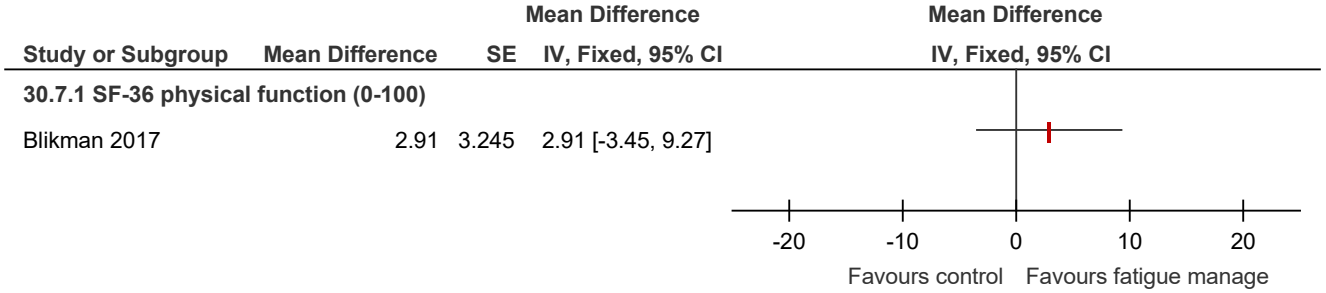


Figure 193: SF-36 role physical (0-100; higher better)

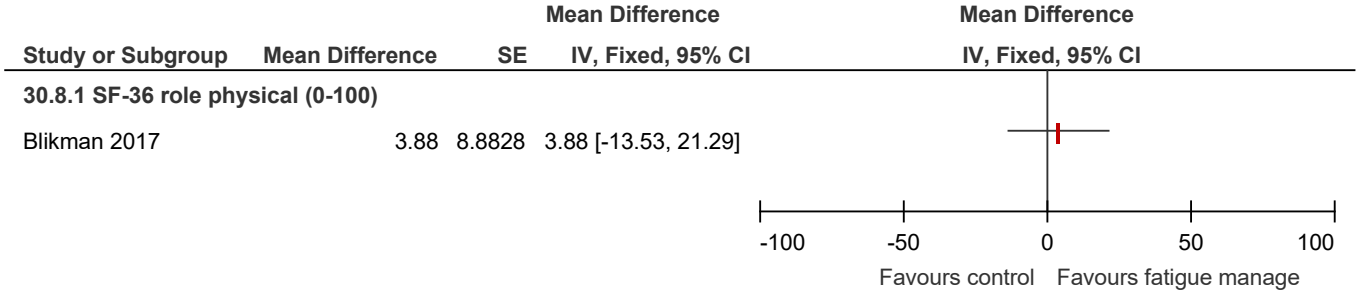


Figure 194: SF-36 body pain (0-100; higher better)

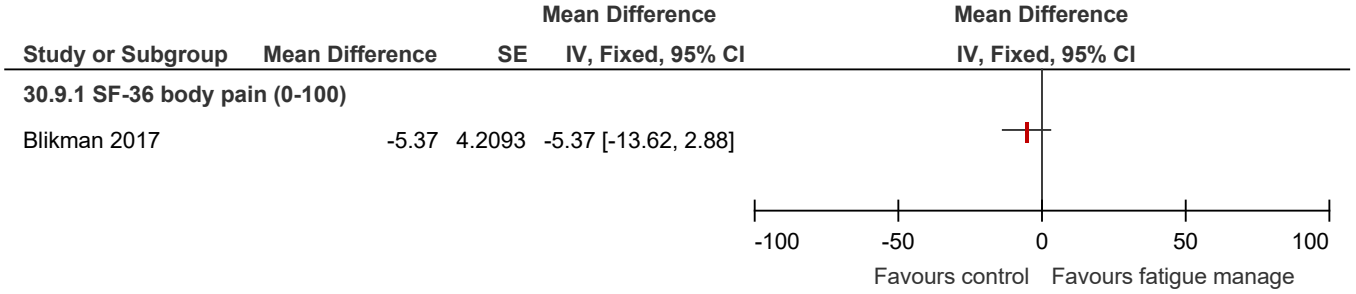


Figure 195: SF-36 general health (0-100; higher better)

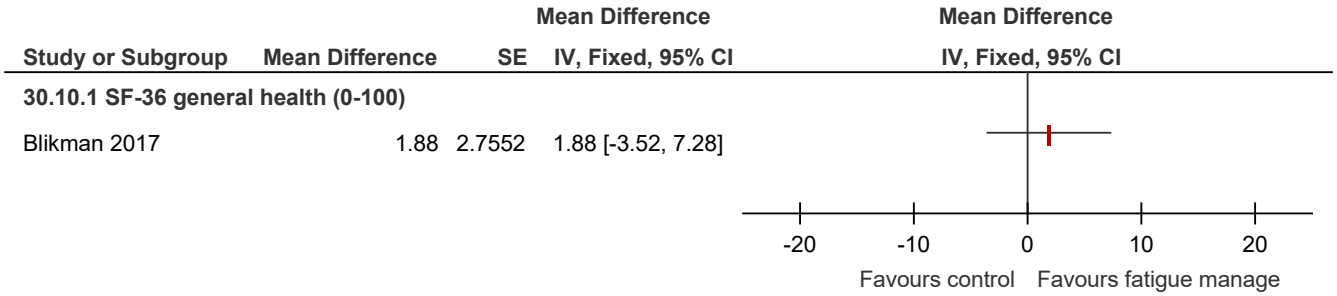


Figure 196: SF-36 vitality (0-100; higher better)

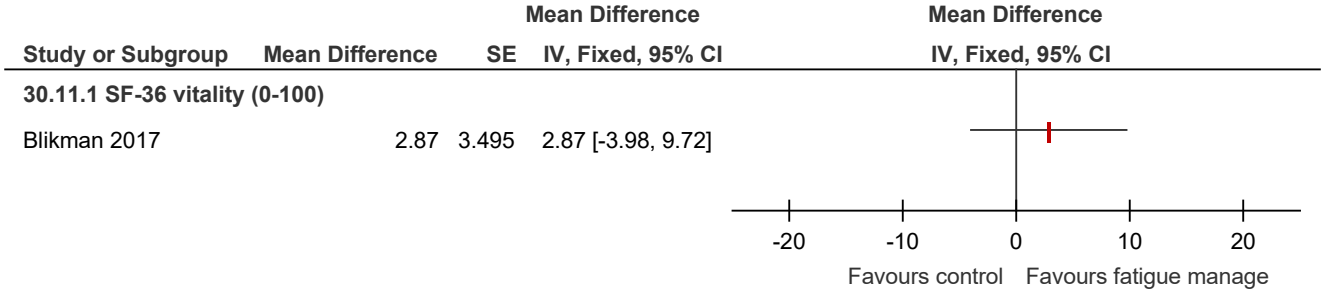


Figure 197: SF-36 social function (0-100; higher better)

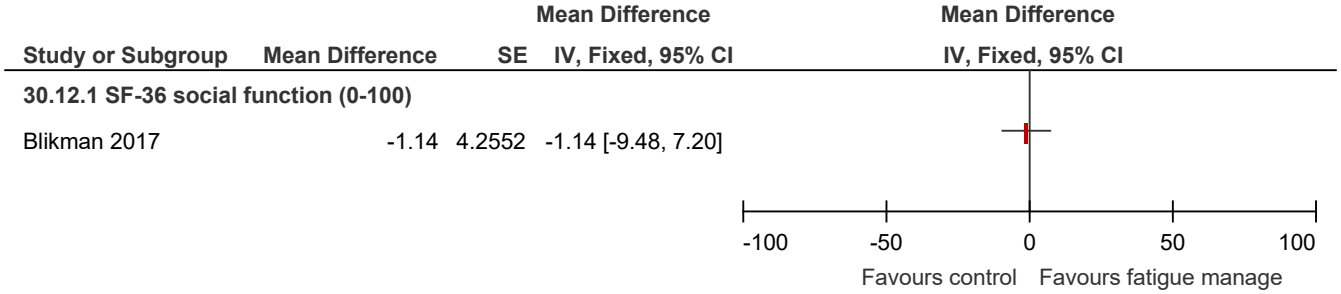


Figure 198: SF-36 role emotional (0-100; higher better)

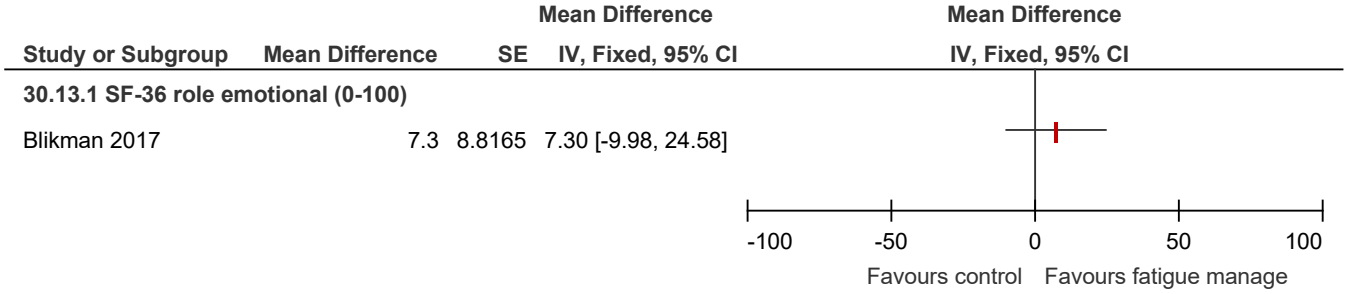


Figure 199: SF-36 mental health (0-100; higher better)

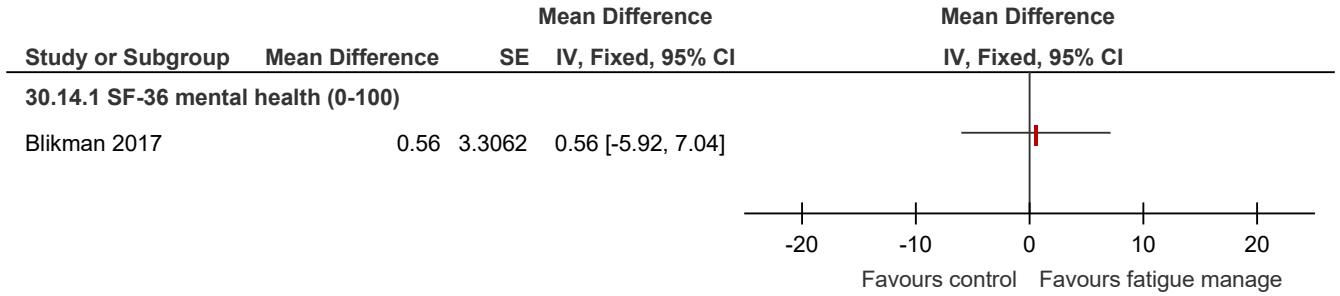


Figure 200: Cognitive - Checklist Individual Strength (CIS)20r – concentration (5-35; lower better)

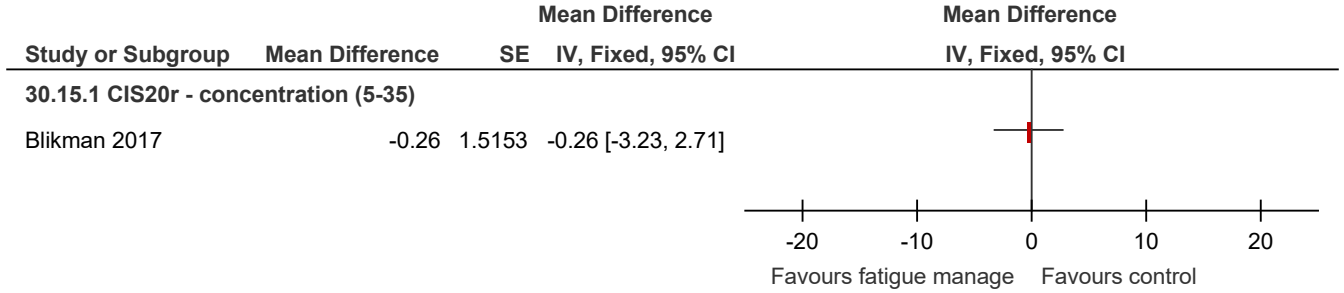


Figure 201: Adverse events (serious)

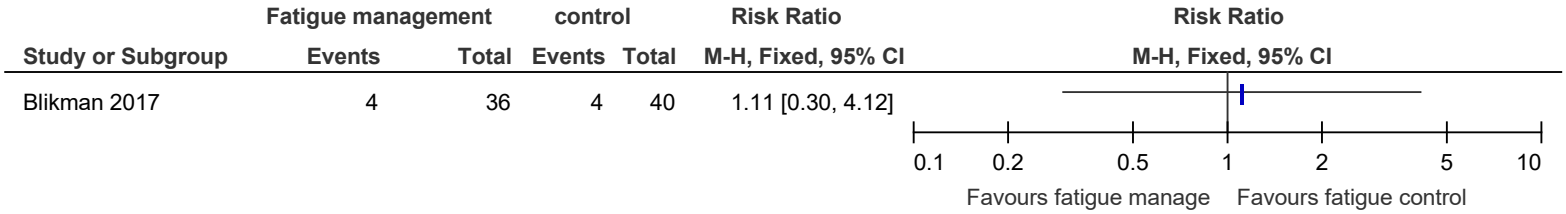


Figure 202: Adverse events leading to withdrawal

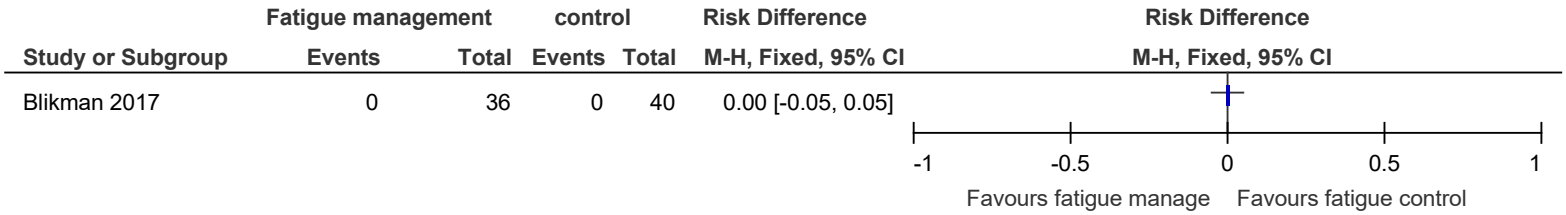
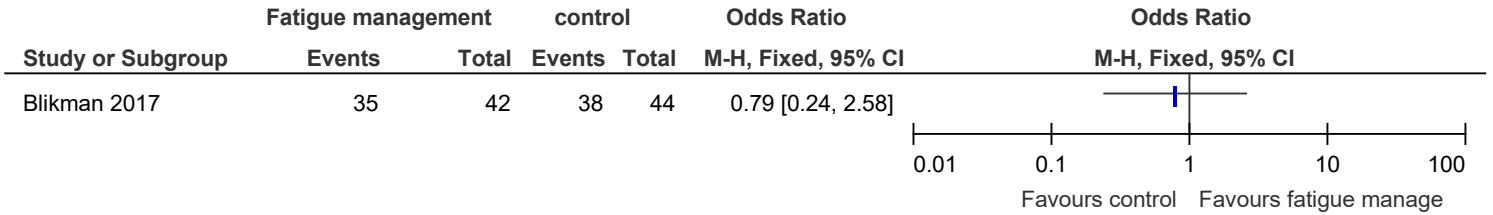


Figure 203: Adherence to programme



E.24 Fatigue/energy management programme vs. general self-management programme – up to 6 months and >6 months outcomes

Figure 204: Modified Fatigue Impact Scale – total (0-84; lower better)

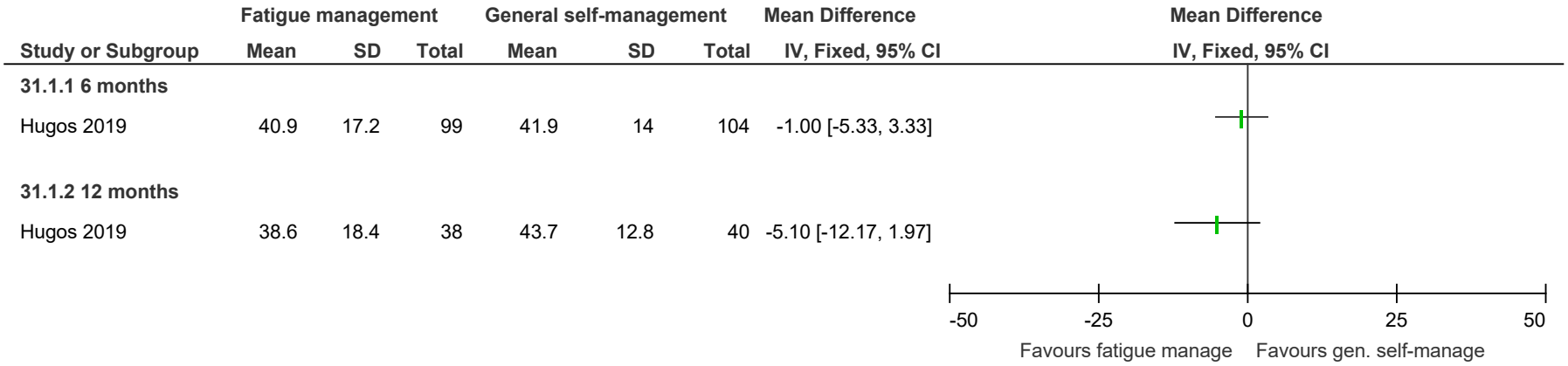


Figure 205: Beck Depression Inventory (0-63; lower better) – 6 weeks

	Fatigue management			General self-management			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Hugos 2019	9.5	7.7	100	10.7	7.7	104	-1.20 [-3.31, 0.91]

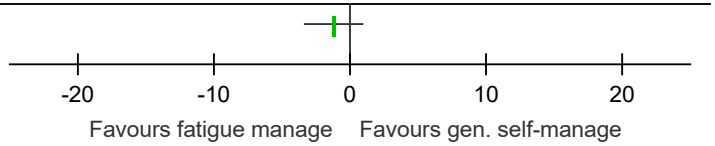


Figure 206: Adverse events (all relapses) – 6 weeks

	Fatigue management		General self-management		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Hugos 2019	4	100	4	104	1.04 [0.27, 4.05]

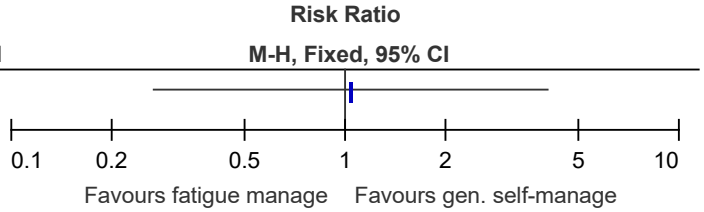
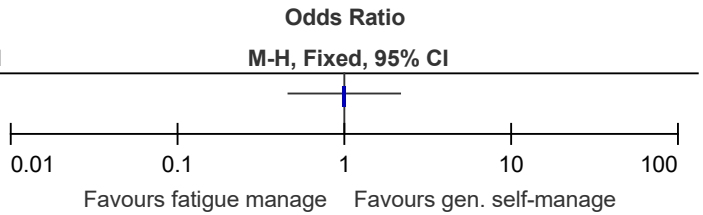


Figure 207: Adherence – completed at least 4 sessions

	Fatigue management		General self-management		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Hugos 2019	94	109	94	109	1.00 [0.46, 2.16]



E.25 Fatigue/energy management programme vs. relaxation – up to 6 months outcomes

Figure 208: Modified Fatigue Impact Scale (0-84, 0-36, 0-40 or 0-8; lower better)

	Fatigue management			Relaxation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
32.1.1 Total (0-84)								
Kos 2016	32.3	11.1	14	41.9	15.4	11	-9.60 [-20.40, 1.20]	
32.1.2 Physical (0-36)								
Kos 2016	16.6	5.4	14	20.4	7.5	11	-3.80 [-9.06, 1.46]	
32.1.3 Cognitive (0-40)								
Kos 2016	12.8	6.7	14	17.7	8.3	11	-4.90 [-10.93, 1.13]	
32.1.4 Psychosocial (0-8)								
Kos 2016	2.9	1	14	3.8	2.4	11	-0.90 [-2.41, 0.61]	

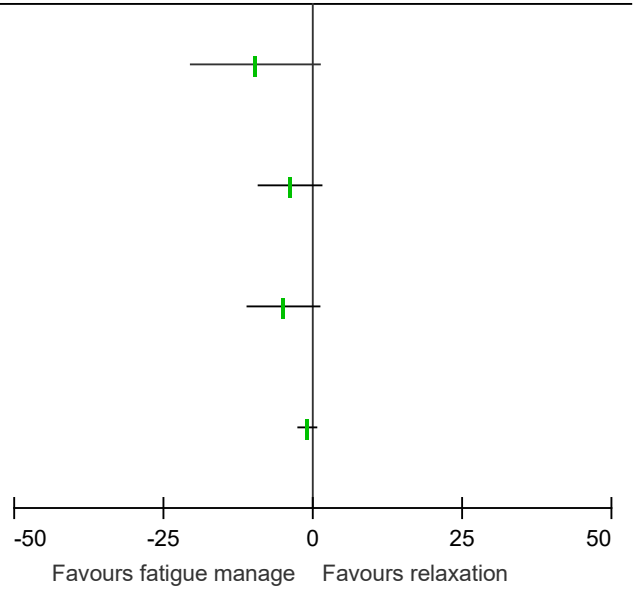


Figure 209: Checklist Individual Strength (CIS)20r – scales indicated in plot (lower better)

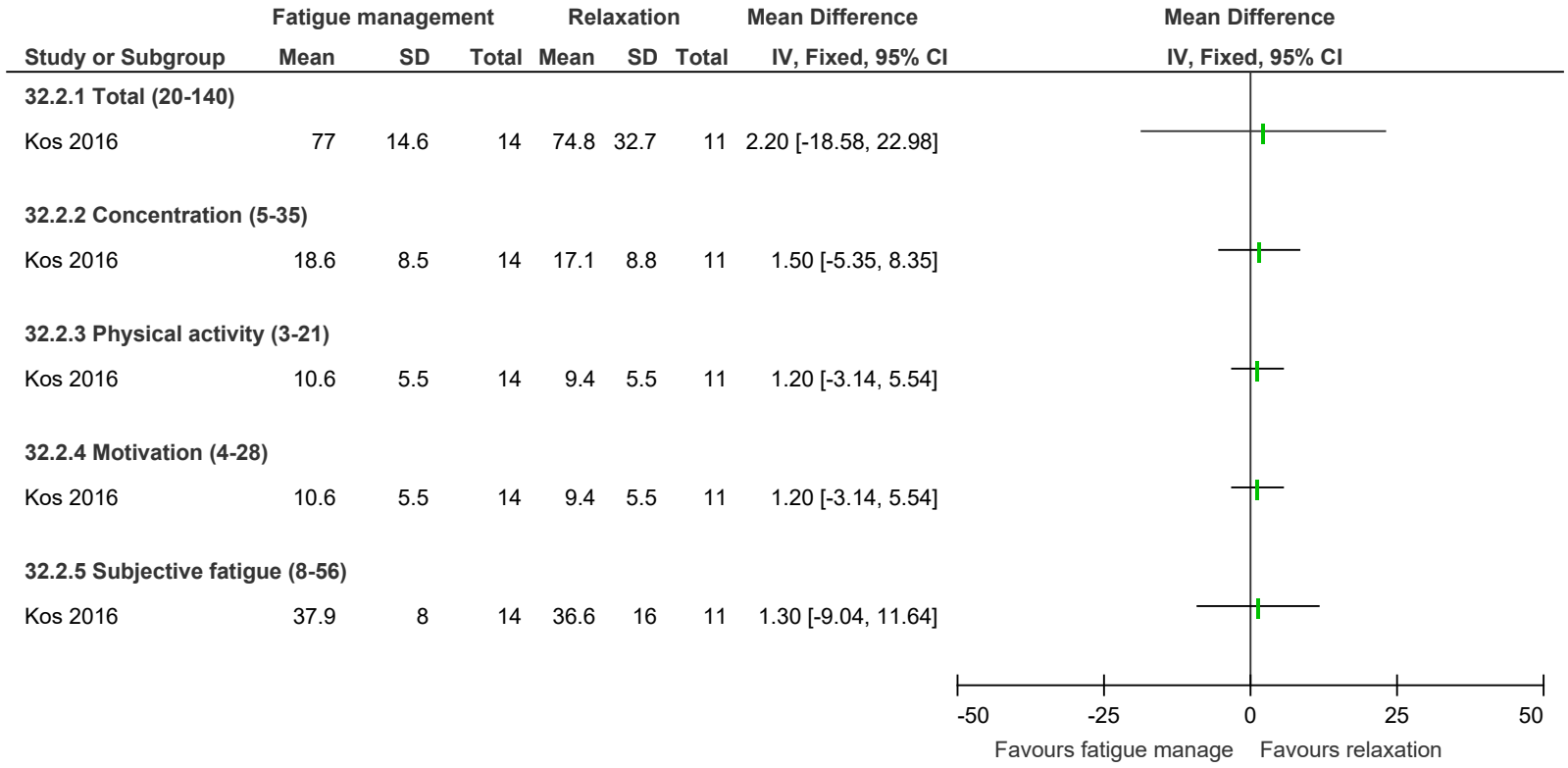
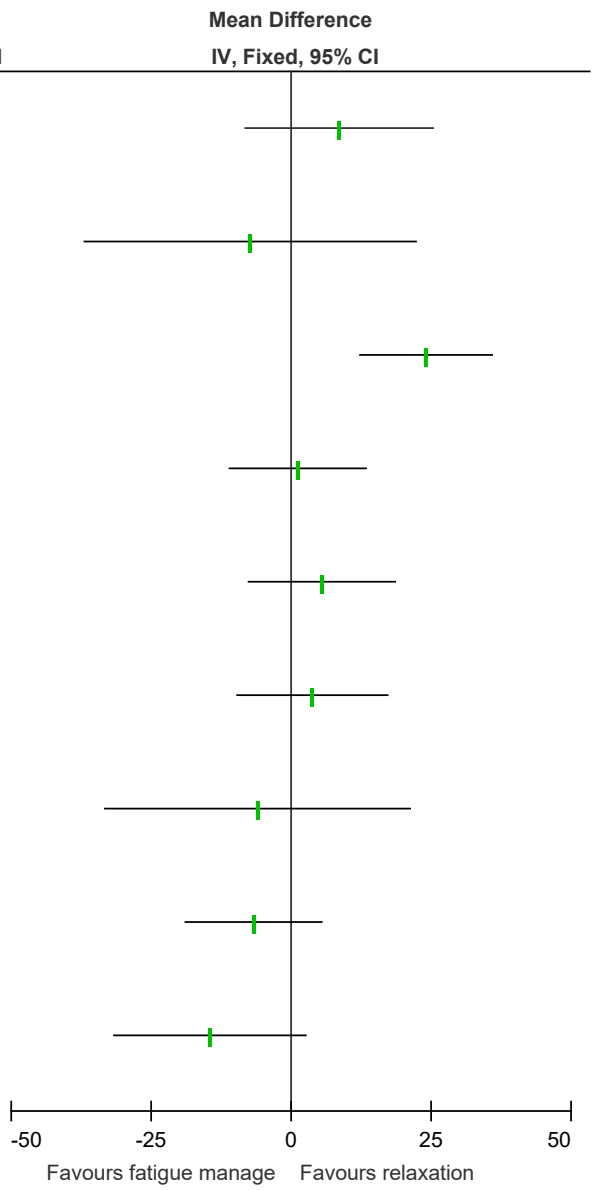


Figure 210: SF-36 quality of life (0-100; higher better)

Study or Subgroup	Fatigue management Mean	SD	Total	Relaxation Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
32.3.1 Physical functioning							
Kos 2016	66.9	16.9	14	58.3	24.1	11	8.60 [-8.17, 25.37]
32.3.2 Role physical function							
Kos 2016	59.4	40	14	66.7	35.4	11	-7.30 [-36.91, 22.31]
32.3.3 Physical pain							
Kos 2016	83.3	11.4	14	59.2	17.2	11	24.10 [12.31, 35.89]
32.3.4 General health							
Kos 2016	48.8	16.9	14	47.6	14.2	11	1.20 [-11.00, 13.40]
32.3.5 Vitality							
Kos 2016	54.4	16.8	14	48.9	16.4	11	5.50 [-7.59, 18.59]
32.3.6 Social functioning							
Kos 2016	71.9	17.4	14	68.1	16.7	11	3.80 [-9.63, 17.23]
32.3.7 Role emotional function							
Kos 2016	79.2	35.4	14	85.2	33.8	11	-6.00 [-33.25, 21.25]
32.3.8 Mental health							
Kos 2016	64	11.7	14	70.7	17.8	11	-6.70 [-18.87, 5.47]
32.3.9 Health change							
Kos 2016	43.8	25.9	14	58.3	17.7	11	-14.50 [-31.63, 2.63]



E.26 Aerobic exercise + fatigue self-management vs. control (information only) – up to 6 months outcomes

Figure 211: Fatigue Impact Scale – total (0-160; lower better)

	Aerobic + fatigue SM			Control			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Plow 2019	53.95	28.72	70	62.63	35	69	-8.68 [-19.33, 1.97]

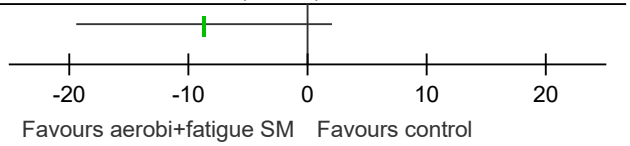


Figure 212: MSIS-29 (0-100; lower better)

Study or Subgroup	Aerobic + fatigue SM Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
26.2.1 Physical function							
Plow 2019	31.11	18.04	70	37.81	22.18	69	-6.70 [-13.43, 0.03]
26.2.2 Mental function							
Plow 2019	29.56	19.07	70	35.77	21.3	69	-6.21 [-12.93, 0.51]

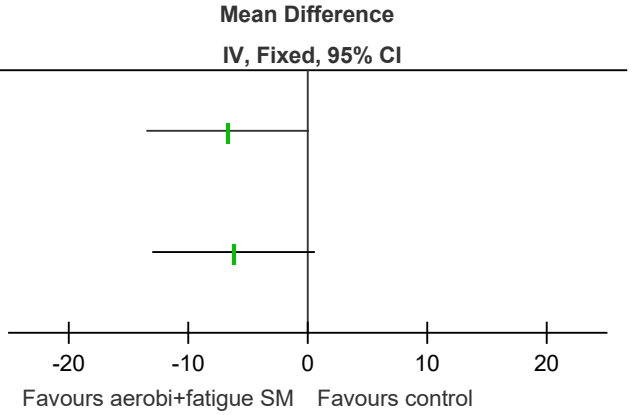


Figure 213: Adverse events (exacerbations)

Study or Subgroup	Aerobic + fatigue SM Events	Total	Control Events	Total	Risk Ratio M-H, Fixed, 95% CI
Plow 2019	14	70	17	69	0.81 [0.43, 1.52]

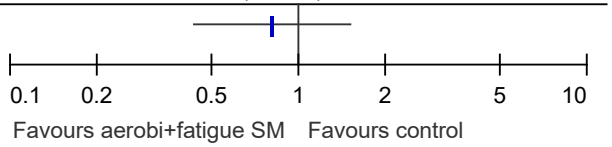


Figure 214: Adverse events (orthopaedic problems)

	Aerobic + fatigue SM		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Plow 2019	28	70	24	69	1.15 [0.75, 1.77]	

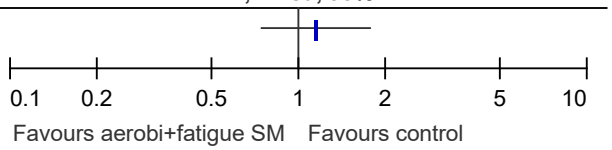


Figure 215: Adverse events (at least one fall)

	Aerobic + fatigue SM		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Plow 2019	22	70	21	69	1.03 [0.63, 1.70]	

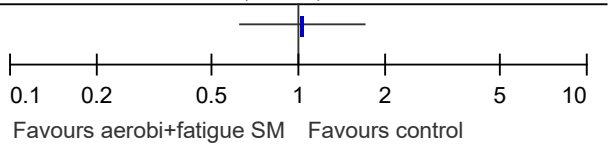


Figure 216: Adherence – completed all 1-1 calls

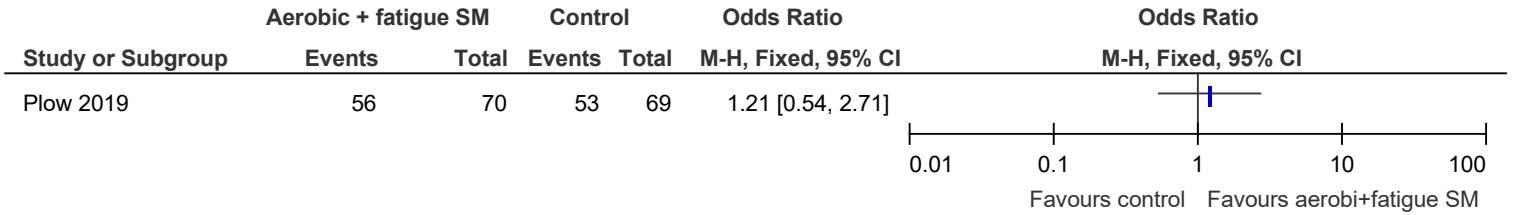
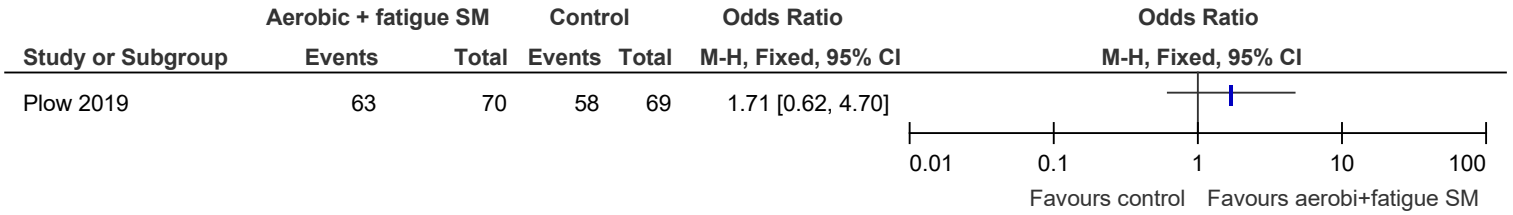


Figure 217: Adherence – completed all group calls with or without at least one makeup call



E.27 Aerobic exercise + fatigue self-management vs. aerobic exercise only – up to 6 months outcomes

Figure 218: Fatigue Impact Scale – total (0-160; lower better)

Study or Subgroup	Aerobic + fatigue SM Mean	SD	Total	Aerobic only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Plow 2019	53.95	28.72	70	68.03	31.31	69	-14.08 [-24.07, -4.09]

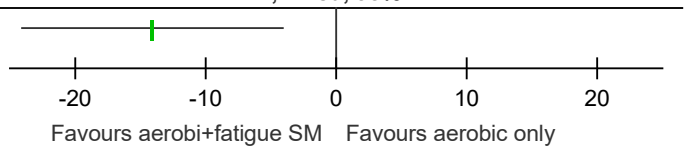


Figure 219: MSIS-29 (0-100; lower better)

Study or Subgroup	Aerobic + fatigue SM Mean	SD	Total	Aerobic only Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
27.2.1 Physical function							
Plow 2019	31.11	18.04	70	32.19	20.47	69	-1.08 [-7.50, 5.34]
27.2.2 Mental function							
Plow 2019	29.56	19.07	70	31.08	20.39	69	-1.52 [-8.09, 5.05]

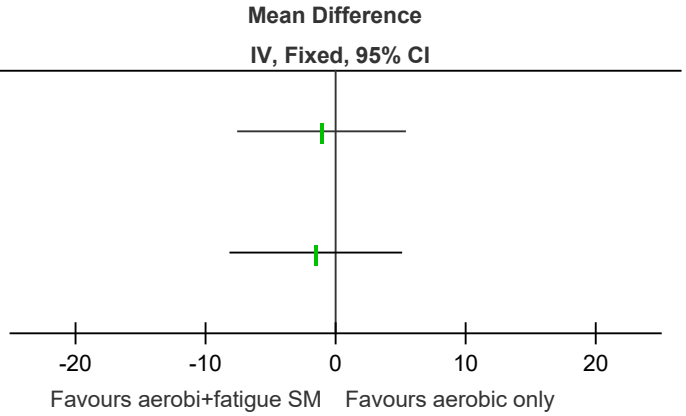


Figure 220: Adverse events (exacerbations)

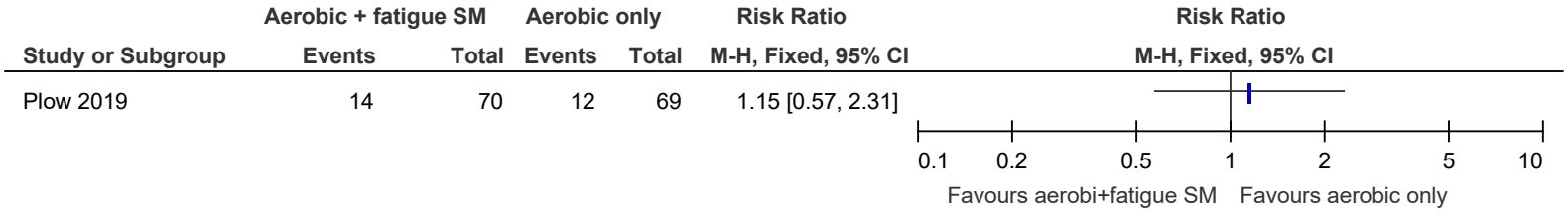


Figure 221: Adverse events (orthopaedic problems)

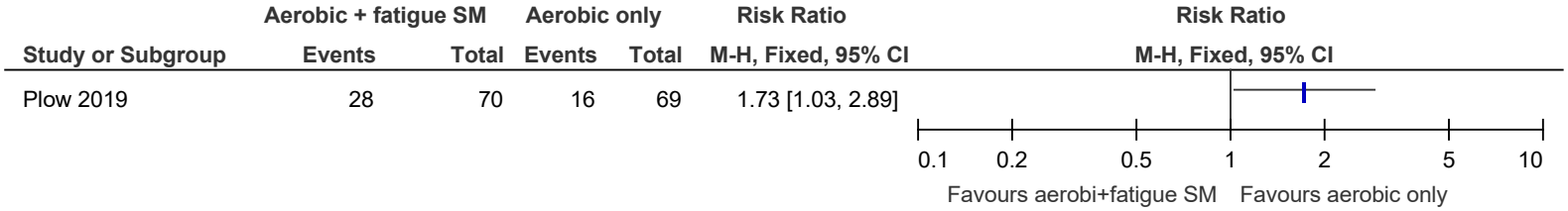


Figure 222: Adverse events (at least one fall)

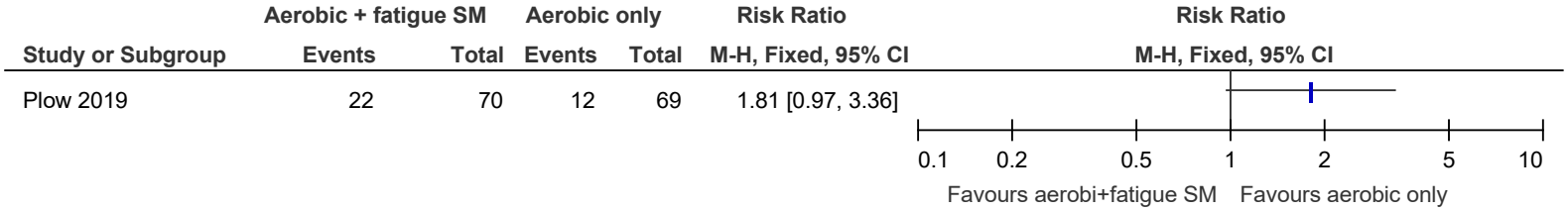


Figure 223: Adherence – completed all 1-1 calls

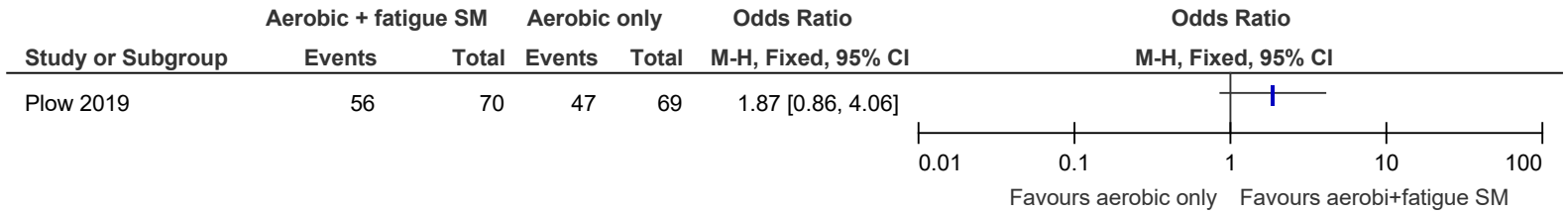
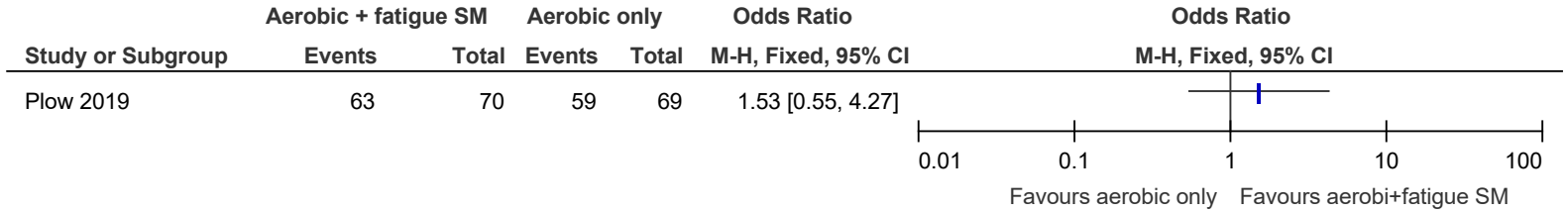


Figure 224: Adherence – completed all group calls with or without at least one makeup call



E.28 Fatigue management + CBT vs. control (local/standard care) – up to 6 months and >6 months outcomes (<6 months unless indicated otherwise in plot)

Figure 225: Global Fatigue Severity (1-7; lower better)

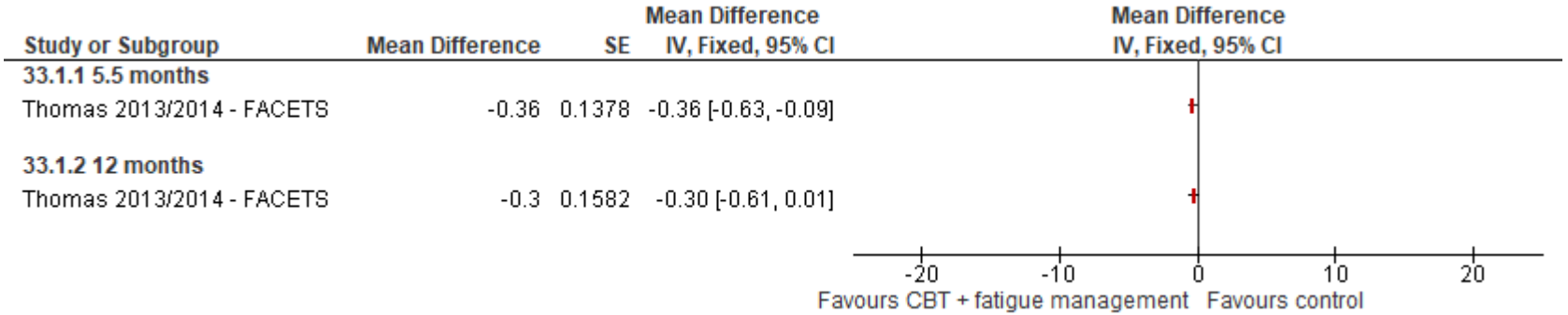


Figure 226: Modified Fatigue Impact Scale – total (0-84; lower better)

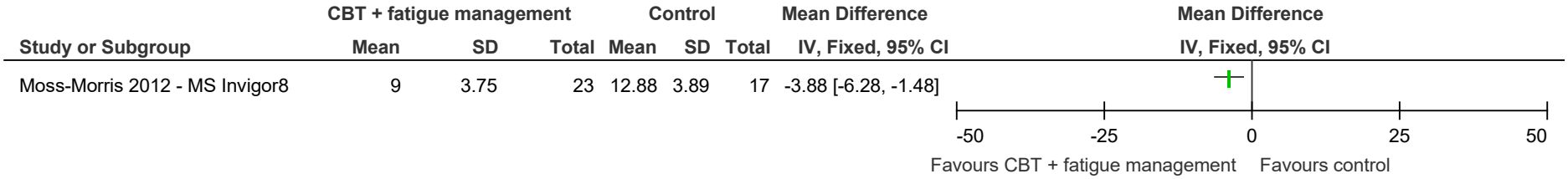


Figure 227: Chalder Fatigue Scale (0-33; lower better)

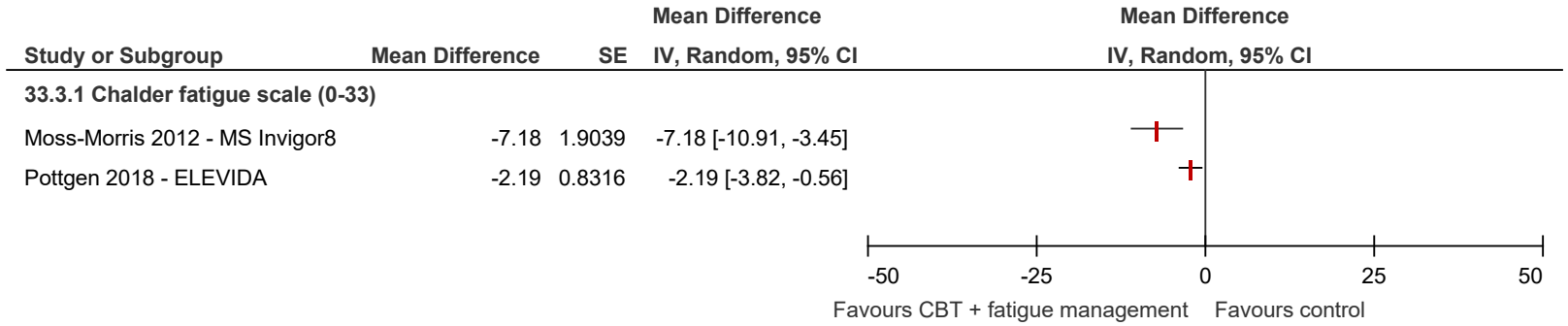


Figure 228: MS Fatigue Self-Efficacy Scale (10-100; higher better)

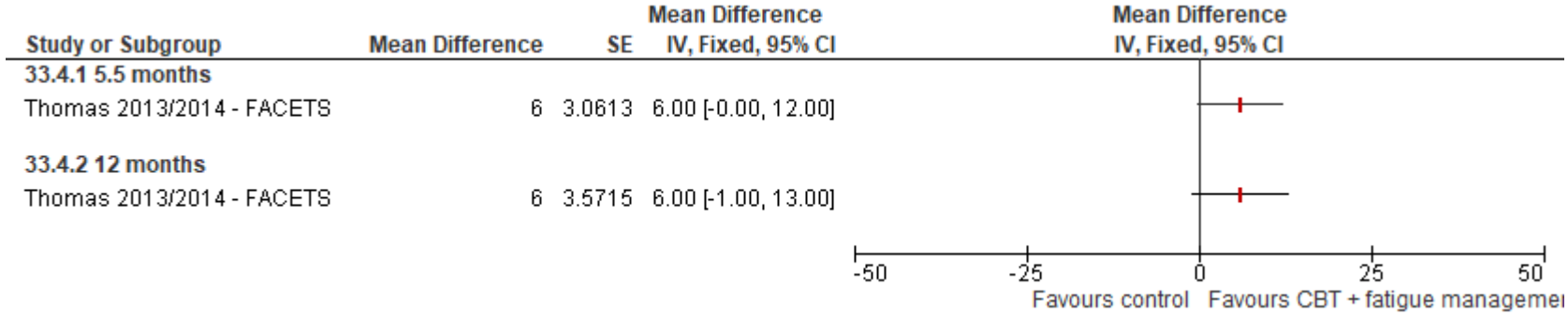


Figure 229: Fatigue Scale of Motor and Cognition (20-100 or 10-50; lower better)

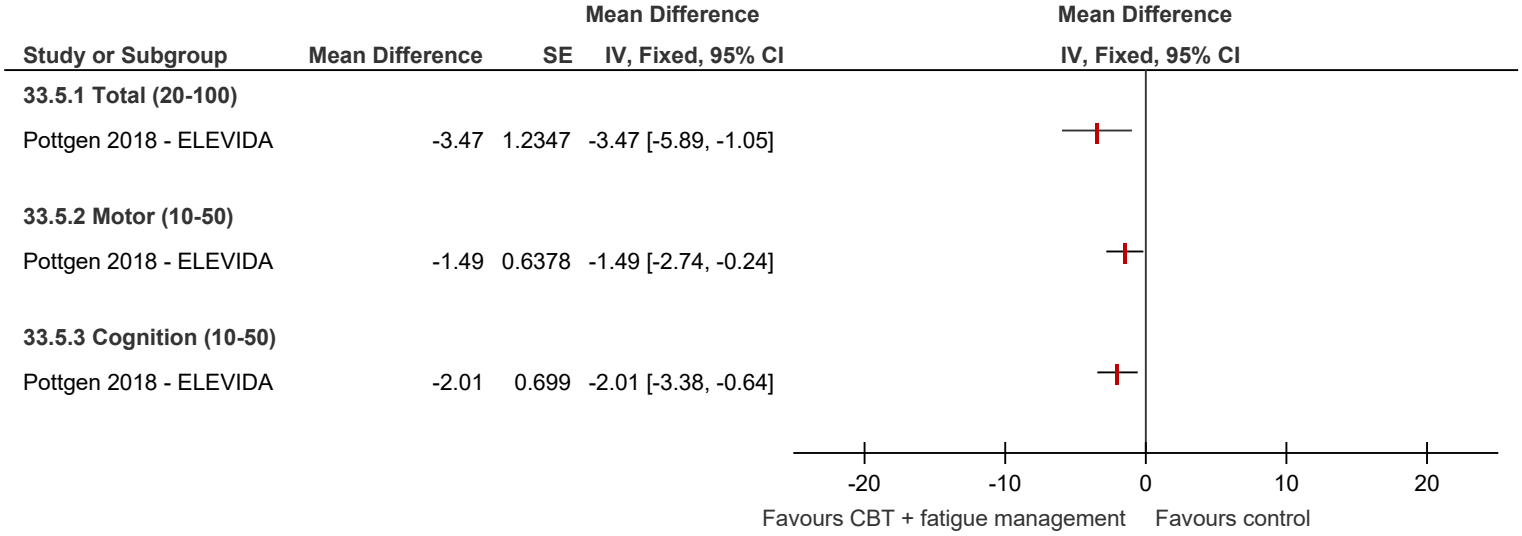


Figure 230: SF-36 vitality (0-100; higher better)

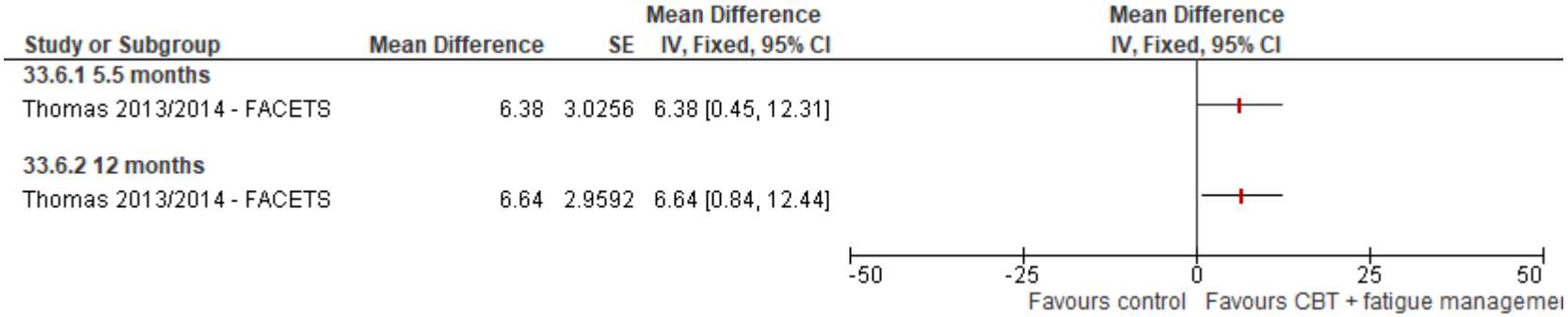


Figure 231: MSIS-29 – total (0-100; lower better)

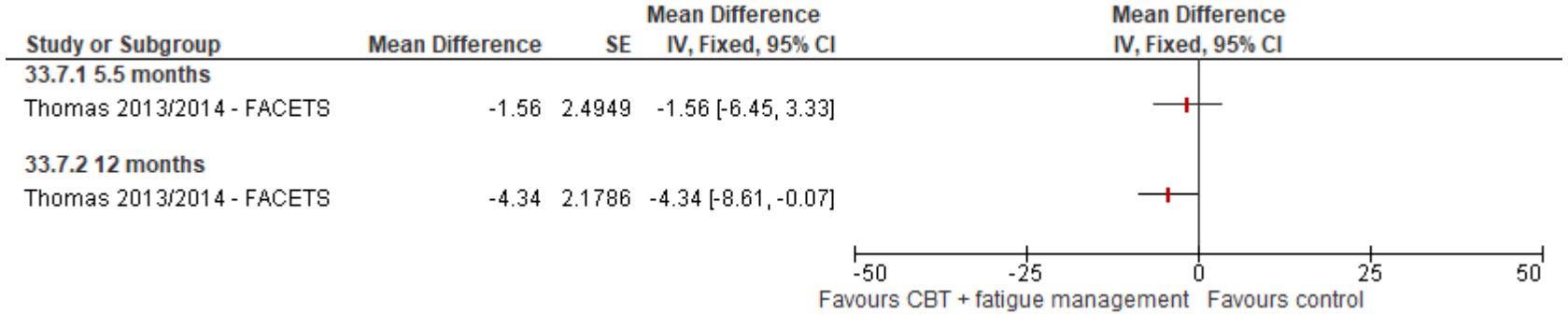


Figure 232: MSIS-29 – physical (0-100; lower better)

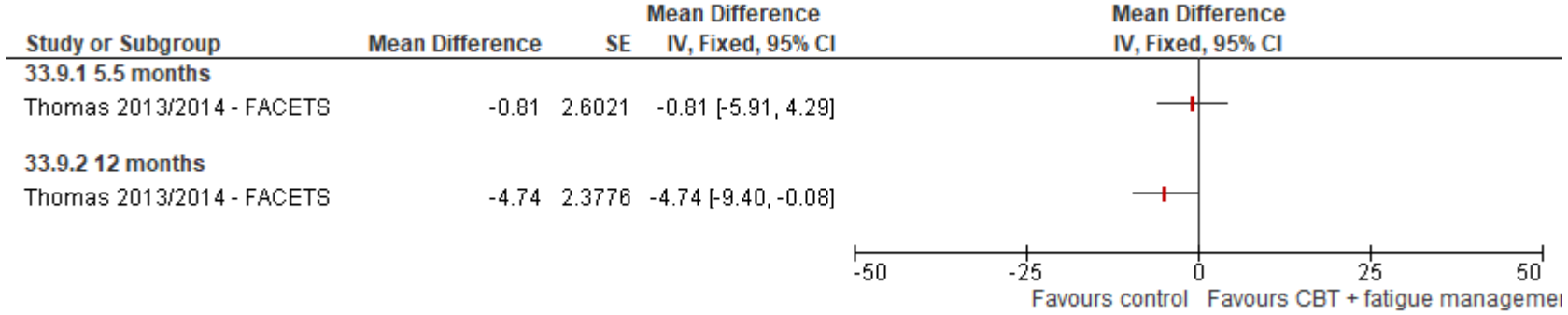


Figure 233: MS Neurological Screening Questionnaire (0-60?; lower better)

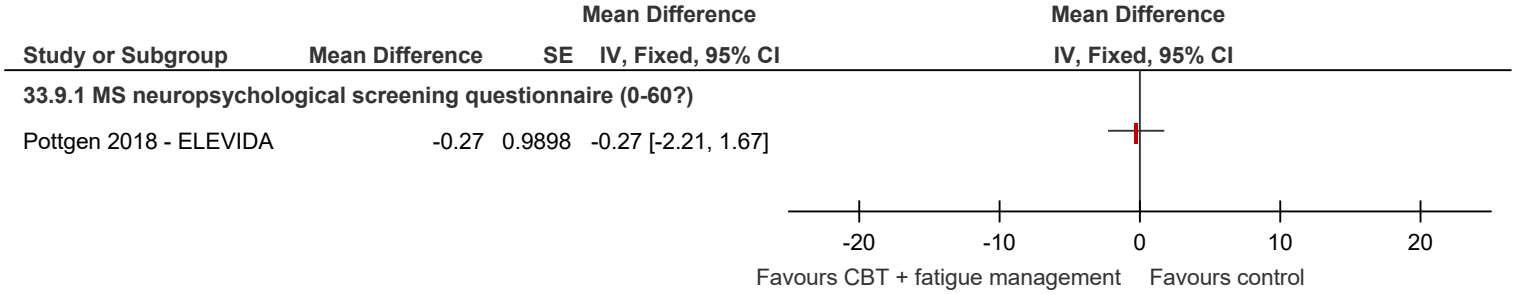


Figure 234: HADS – anxiety (0-21; lower better)

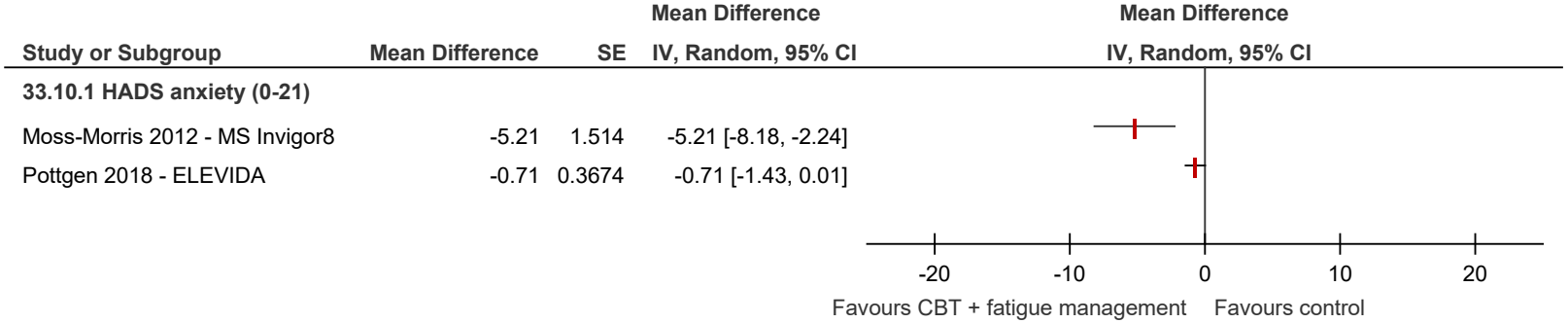


Figure 235: HADS – depression (0-21; lower better)

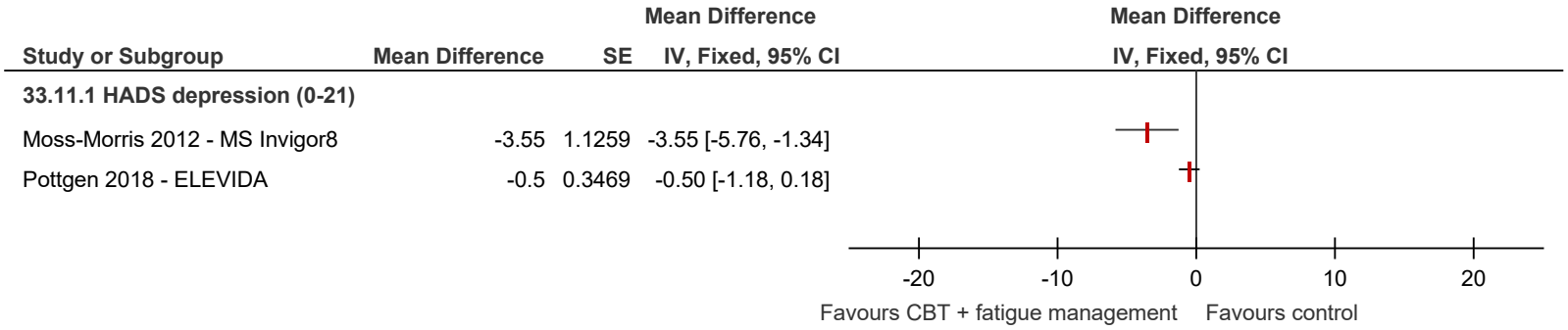
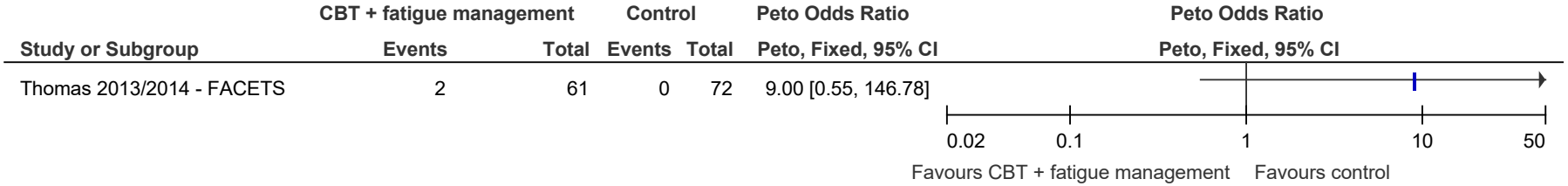


Figure 236: Withdrawal due to adverse events (relapse) – 5.5 months



E.29 Multidisciplinary rehabilitation + fatigue self-management vs. control (consultation only) – up to 6 months outcomes

Figure 237: Modified Fatigue Impact Scale (0-84, 0-36, 0-40 or 0-8; lower better)

	Multi rehab + fatigue SM			control			Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
28.1.1 Total score (0-84)								
Rietberg 2014	1.2	9.5	22	-0.6	13.8	24	1.80 [-5.00, 8.60]	
28.1.2 Physical subscale (0-36)								
Rietberg 2014	1.1	4.4	22	-0.6	6.3	24	1.70 [-1.42, 4.82]	
28.1.3 Cognitive subscale (0-40)								
Rietberg 2014	-0.1	6.3	22	0.1	7.4	24	-0.20 [-4.16, 3.76]	
28.1.4 Psychosocial scale (0-8)								
Rietberg 2014	0.1	1.5	22	-0.1	1.9	24	0.20 [-0.79, 1.19]	

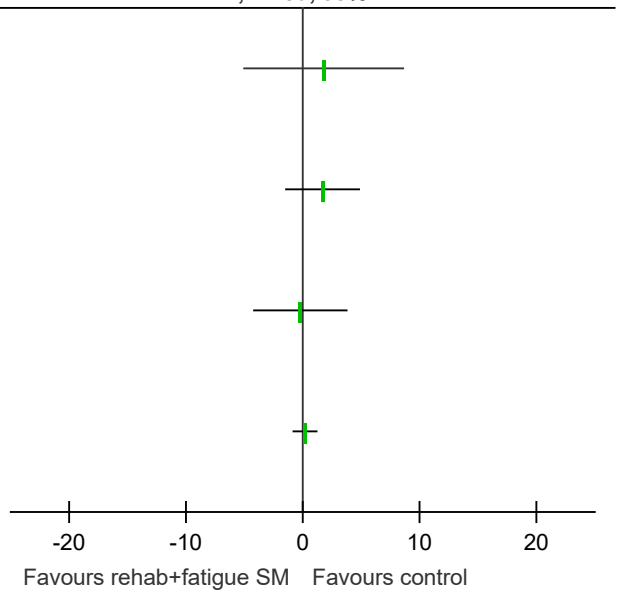


Figure 238: Fatigue Severity Scale (1-7; lower better)

Study or Subgroup	Multi rehab + fatigue SM Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Rietberg 2014	-1.6	7.1	22	0.3	8.5	24	-1.90 [-6.41, 2.61]

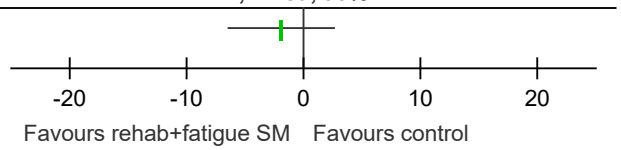


Figure 239: MSIS-29 (0-100; lower better)

Study or Subgroup	Multi rehab + fatigue SM Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
28.3.1 Physical function							
Rietberg 2014	1	1.7	22	2	9	24	-1.00 [-4.67, 2.67]
28.3.2 Mental function							
Rietberg 2014	0	6	22	1	5	24	-1.00 [-4.21, 2.21]

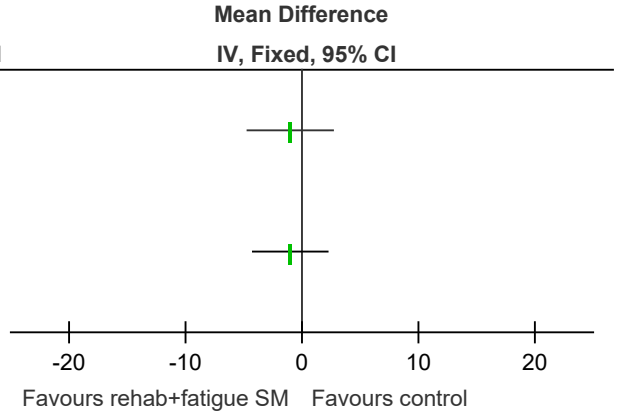


Figure 240: Functional Independence Measure (1-7; higher better)

	Multi rehab + fatigue SM			control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Rietberg 2014	2	4	22	-1	5	24	3.00 [0.39, 5.61]	

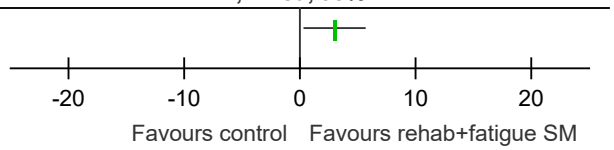
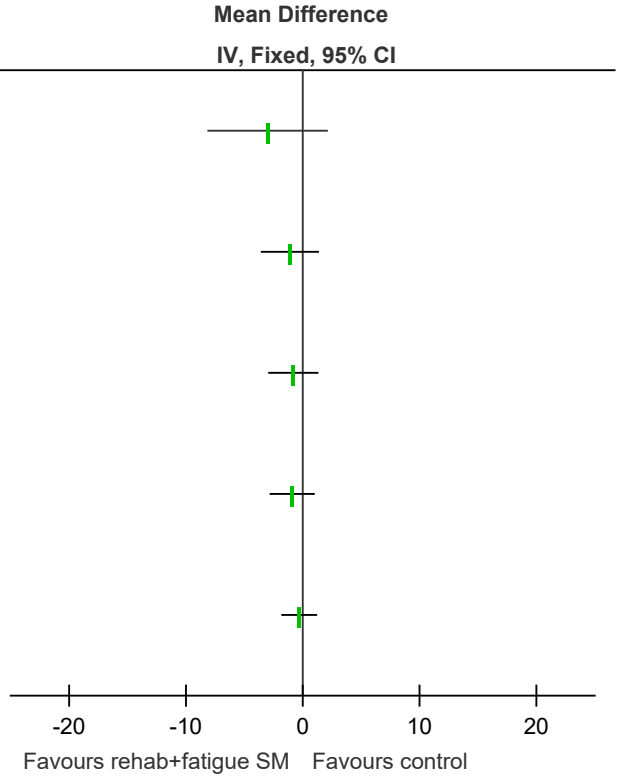


Figure 241: Checklist Individual Strength (CIS)20r (scales indicated in plot; lower better)

	Multi rehab + fatigue SM			control			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
28.5.1 Total (0-140)							
Rietberg 2014	-0.8	7.1	22	2.2	10.3	24	-3.00 [-8.08, 2.08]
28.5.2 Subjective fatigue (8-56)							
Rietberg 2014	0.6	3.2	22	1.7	5	24	-1.10 [-3.51, 1.31]
28.5.3 Concentration (5-35)							
Rietberg 2014	-1.1	3.8	22	-0.3	3.3	24	-0.80 [-2.87, 1.27]
28.5.4 Motivation (4-28)							
Rietberg 2014	-0.6	3.1	22	0.3	3.3	24	-0.90 [-2.75, 0.95]
28.5.5 Physical activity (3-21)							
Rietberg 2014	0.3	2.1	22	0.6	2.9	24	-0.30 [-1.75, 1.15]



E.30 Multidisciplinary rehabilitation + fatigue self-management vs. relaxation – up to 6 months outcomes

Figure 242: Modified Fatigue Impact Scale – total (0-84; lower better)

	Rehab + fatigue SM			Relaxation			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Hersche 2019	34.5	16.6	14	34.5	10.9	15	0.00 [-10.30, 10.30]

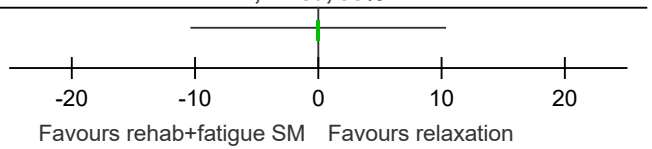


Figure 243: SF-36 physical functioning (0-100; higher better)

	Rehab + fatigue SM			Relaxation			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Hersche 2019	44.8	24.7	14	30	16.5	15	14.80 [-0.60, 30.20]

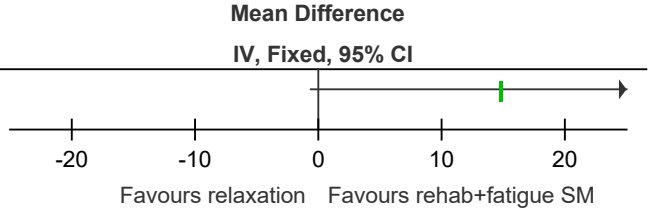
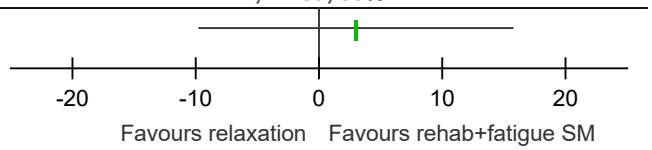


Figure 244: SF-36 fatigue/vitality (0-100; higher better)

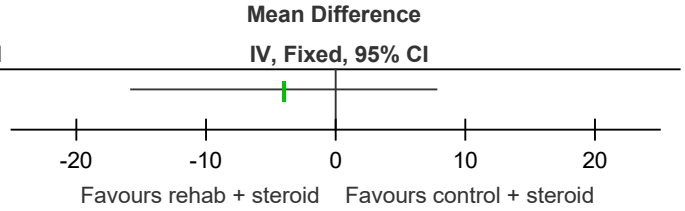
Study or Subgroup	Rehab + fatigue SM Mean	SD	Total	Relaxation Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Hersche 2019	46.5	16.6	14	43.5	18.3	15	3.00 [-9.70, 15.70]



E.31 Multidisciplinary rehabilitation (medical, exercise, counselling and fatigue self-management) vs. no rehabilitation in those treated with methylprednisolone for a relapse – up to 6 months outcomes

Figure 245: Fatigue Severity Scale (9-63; lower better)

Study or Subgroup	Multidis. rehab + steroid Mean	SD	Total	Control + steroid Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Nedeljkovic 2016	36.6	21.1	19	40.6	15.9	20	-4.00 [-15.77, 7.77]



E.32 Self-management programme vs. control – up to 6 months and >6 months outcomes (<6 months unless indicated in the plot)

Figure 246: Fatigue Severity Scale (1-7; lower better)

	Self-management programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Afrasiabifar 2016	-5.45	0.52	32	0.41	0.38	31	-5.86 [-6.08, -5.64]	

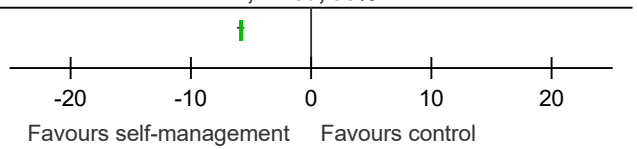


Figure 247: Fatigue VAS (0-10; lower better)

	Self-management programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Barlow 2009	-0.3	3.1047	78	-0.8	3.2027	64	0.50 [-0.54, 1.54]	

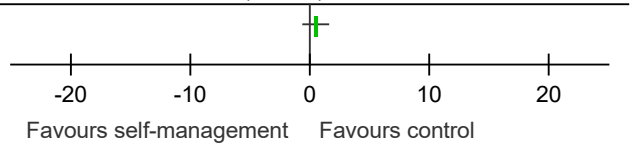


Figure 248: Modified Fatigue Impact Scale – total (0-84; lower better)

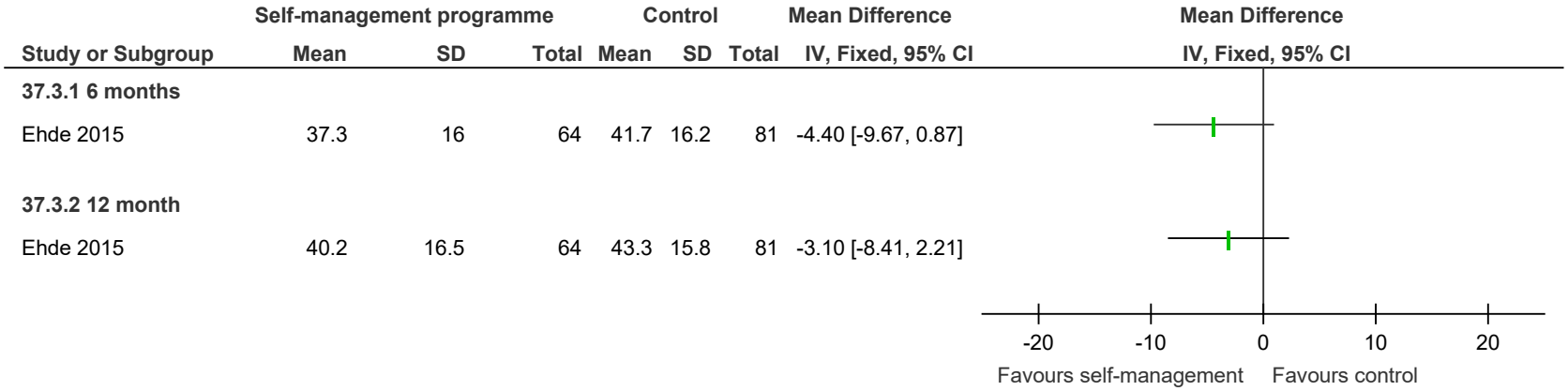


Figure 249: At least 10-point reduction on MFIS total from baseline

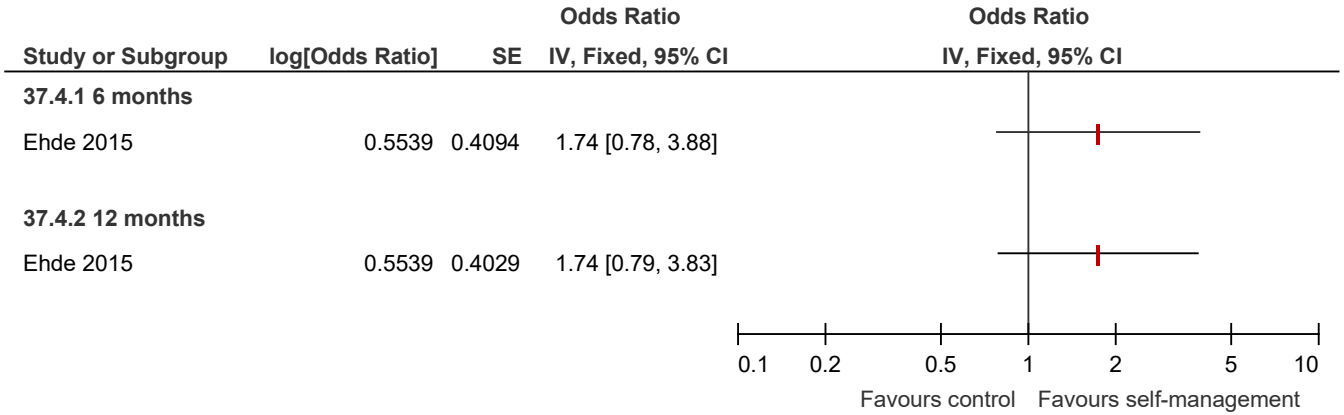


Figure 250: SF-8 physical domain (0-100; higher better)

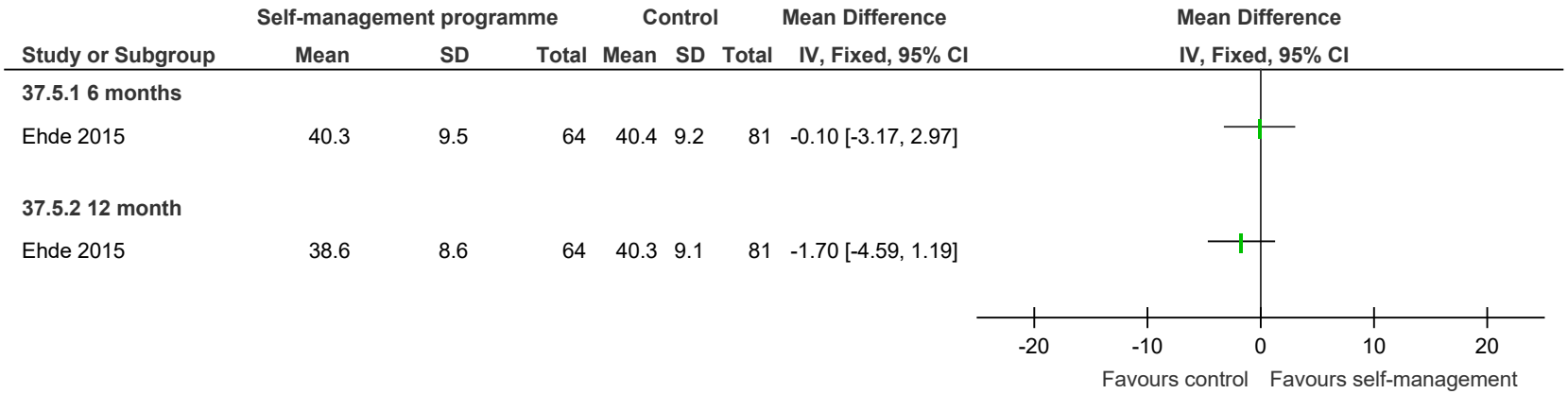


Figure 251: SF-8 mental health domain (0-100; higher better)

	Self-management programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
37.6.1 6 months								
Ehde 2015	48.2	9.8	64	47	9.5	81	1.20 [-1.97, 4.37]	
37.6.2 12 month								
Ehde 2015	47.7	9.2	64	47.2	10	81	0.50 [-2.63, 3.63]	

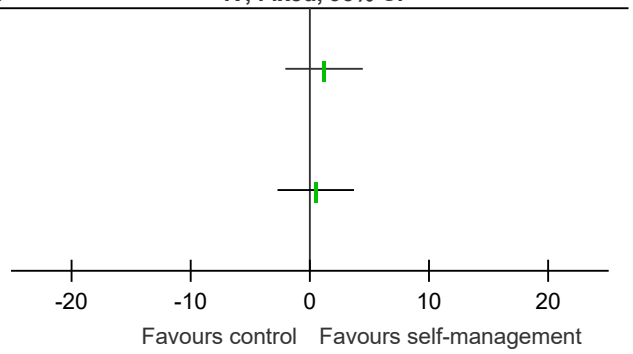


Figure 252: MSIS-29 (0-100; lower better)

	Self-management programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
37.7.1 Physical								
Barlow 2009	-3.3	17.7411	78	3.3	17.6146	64	-6.60 [-12.44, -0.76]	
37.7.2 Psychological								
Barlow 2009	-5.9	27.9422	78	-2.3	26.8223	64	-3.60 [-12.64, 5.44]	

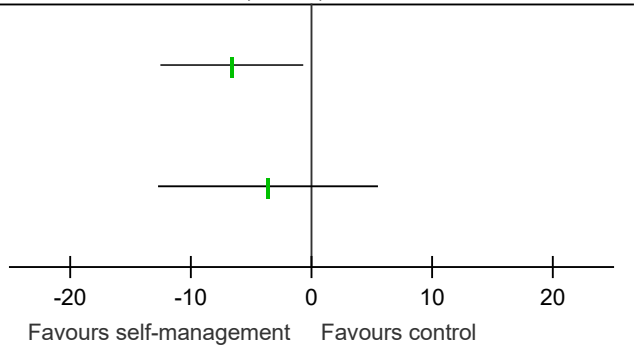


Figure 253: HADS – anxiety (0-21; lower better)

	Self-management programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Barlow 2009	-0.7	3.9917	78	-0.2	4.0033	64	-0.50 [-1.82, 0.82]	

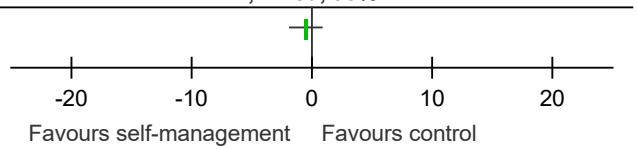


Figure 254: HADS – depression (0-21; lower better)

	Self-management programme			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Barlow 2009	-0.9	3.3438	78	0	2.4095	64	-0.90 [-1.85, 0.05]	

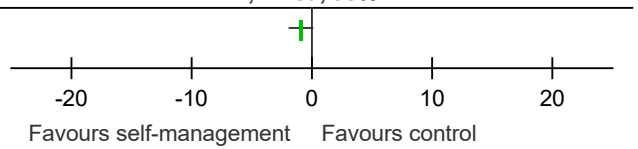


Figure 255: Patient Health Questionnaire-9 (PHQ-9) – depression (0-27; lower better)

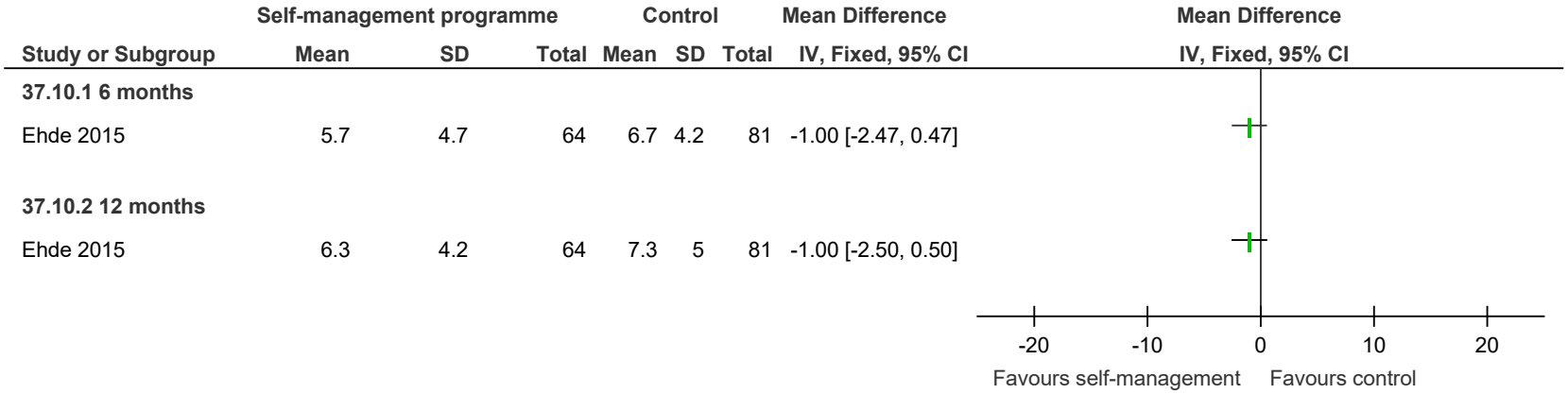


Figure 256: At least 50% reduction in PHQ-9 depression compared to baseline

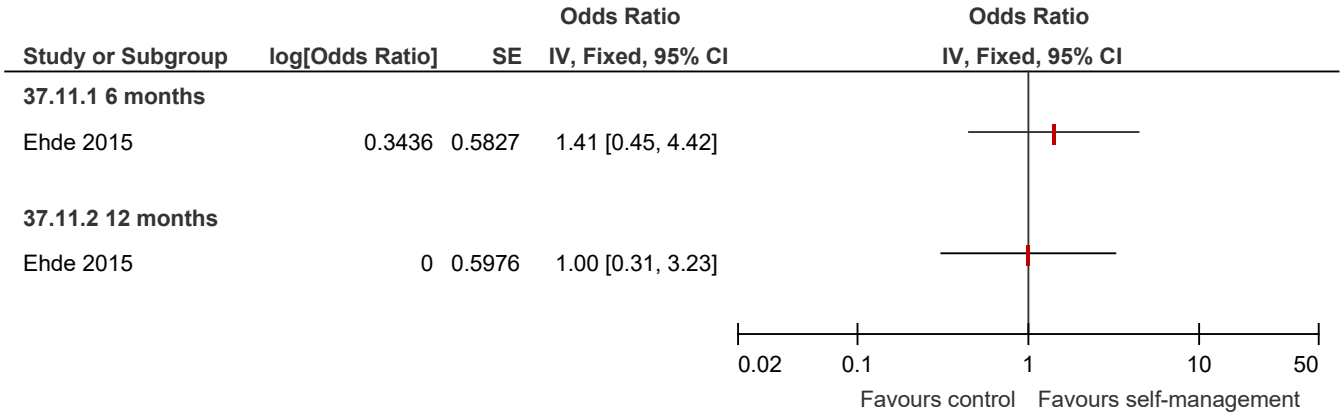


Figure 257: Adverse events leading to withdrawal

Study or Subgroup	Self-management programme Events	Total	Control Events	Total	Risk Difference M-H, Fixed, 95% CI
Afrasiabifar 2016	0	32	0	31	0.00 [-0.06, 0.06]

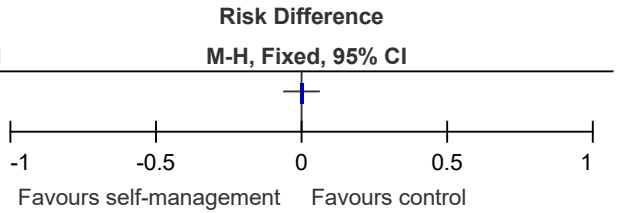


Figure 258: Serious adverse events

Study or Subgroup	Self-management programme Events	Total	Control Events	Total	Risk Difference M-H, Fixed, 95% CI
37.13.1 6 months					
Ehde 2015	0	62	0	79	0.00 [-0.03, 0.03]
37.13.2 12 months					
Ehde 2015	0	60	0	80	0.00 [-0.03, 0.03]

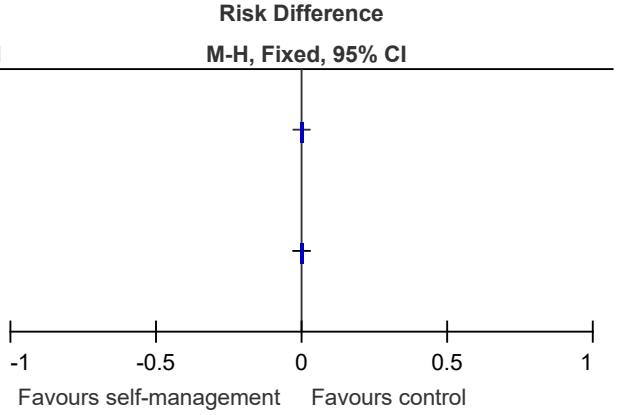
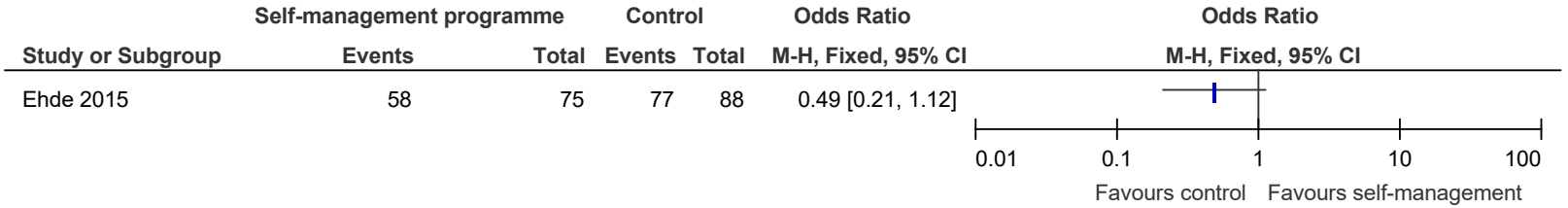


Figure 259: Treatment adherence – attending all 8 sessions



E.33 Self-management programme + exercise vs. control (waitlist) – up to 6 months outcomes

Figure 260: WEIMuS Fatigue Scale (0-68, 0-36 or 0-32; lower better)

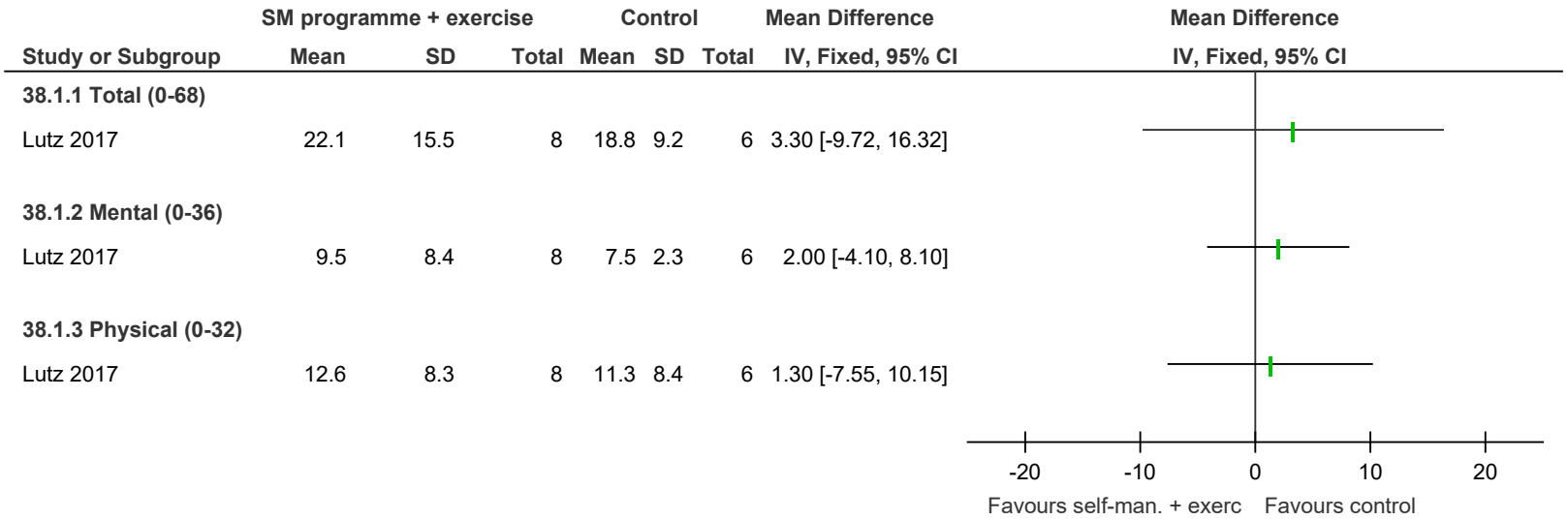


Figure 261: Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) score (0-100; higher better)

	Self-management + exercis			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lutz 2017	77.2	11.4	8	74.6	11.5	6	2.60 [-9.53, 14.73]	

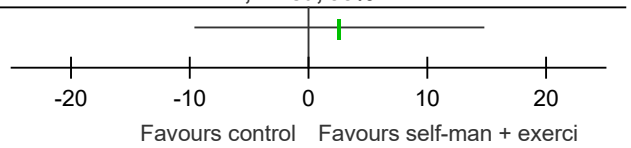
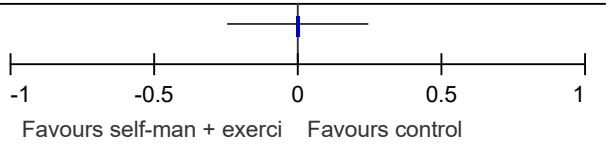


Figure 262: Adverse events

	Self-management + exercis		Control		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Lutz 2017	0	8	0	6	0.00 [-0.24, 0.24]	



E.34 CBT vs. control - up to 6 months and >6 months outcomes (<6 months unless otherwise indicated in plot)

Figure 263: Checklist Individual Strength (CIS)20r – fatigue subscale (8-56; lower better)

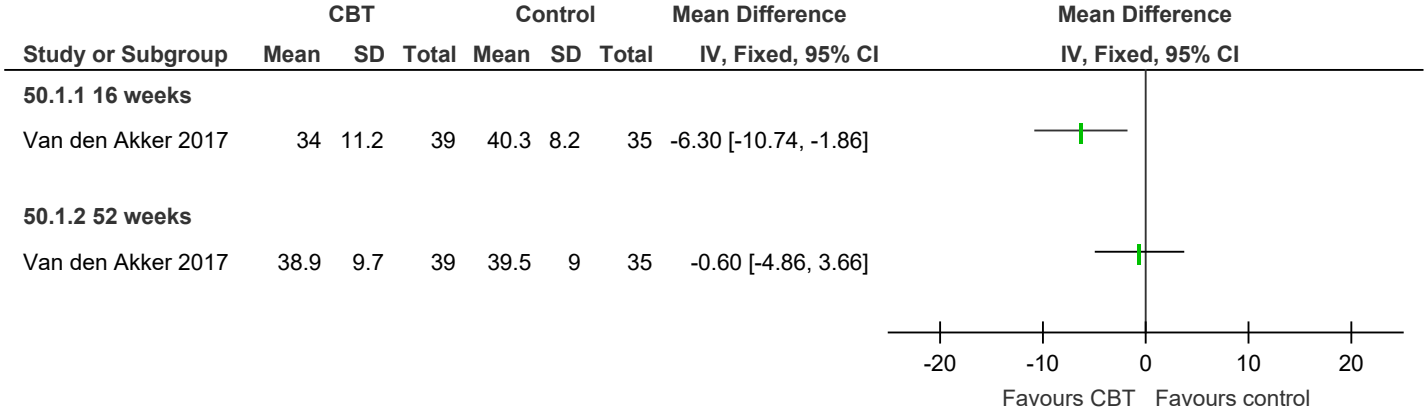


Figure 264: At least 8-point improvement in CIS20r-fatigue from baseline

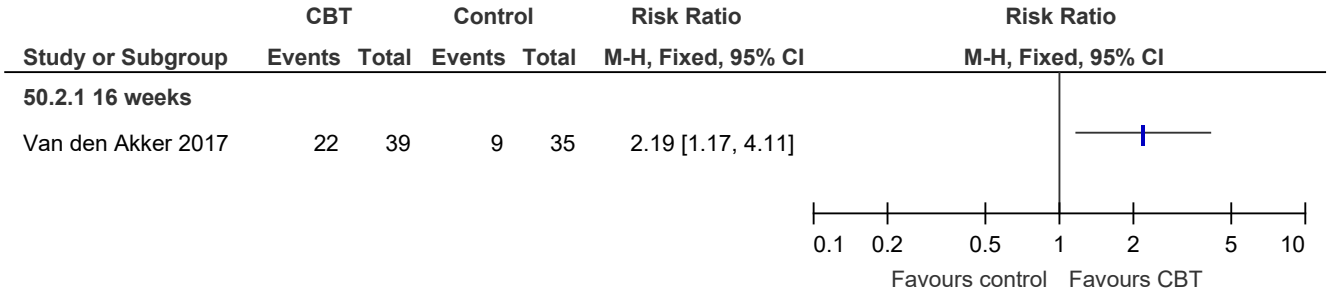


Figure 265: Fatigue Severity Score (1-7; lower better)

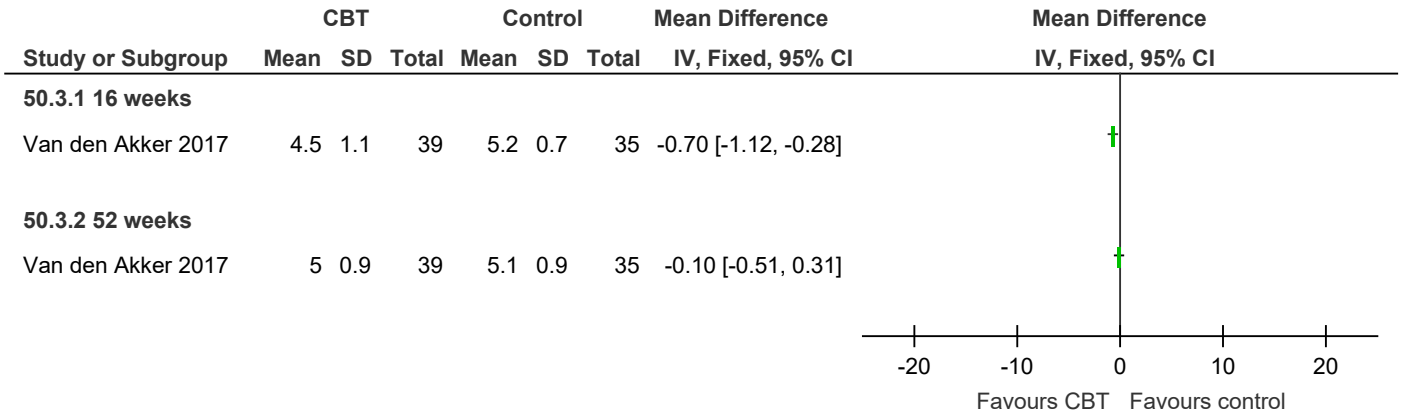


Figure 266: Modified Fatigue Impact Scale – total (0-84; lower better)

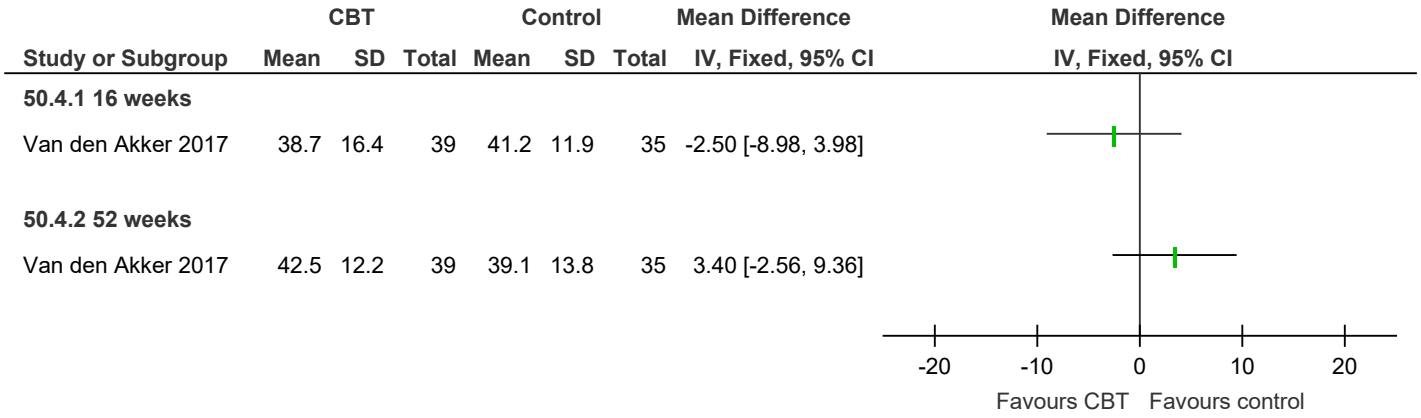


Figure 267: Modified Fatigue Impact Scale – physical (0-36; lower better)

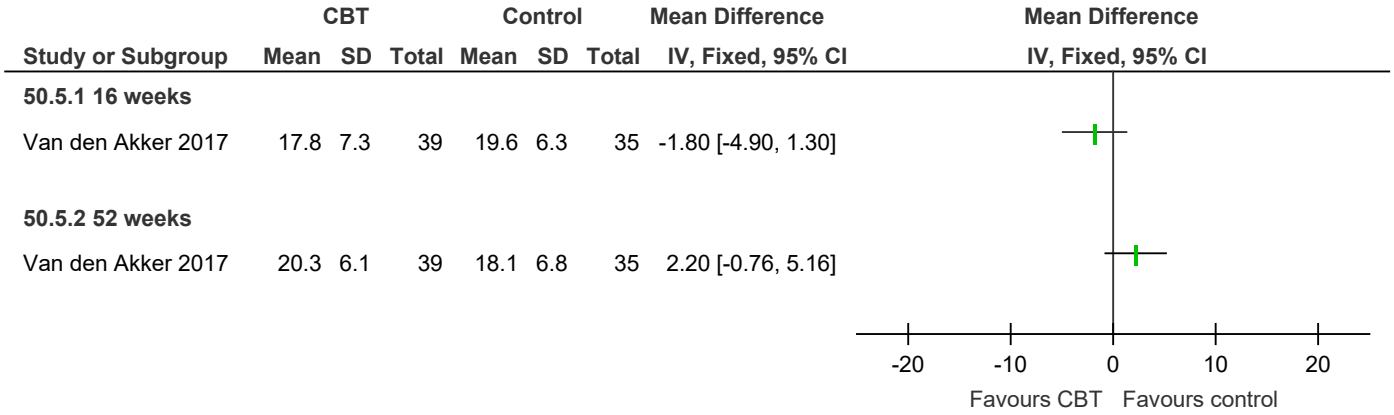


Figure 268: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

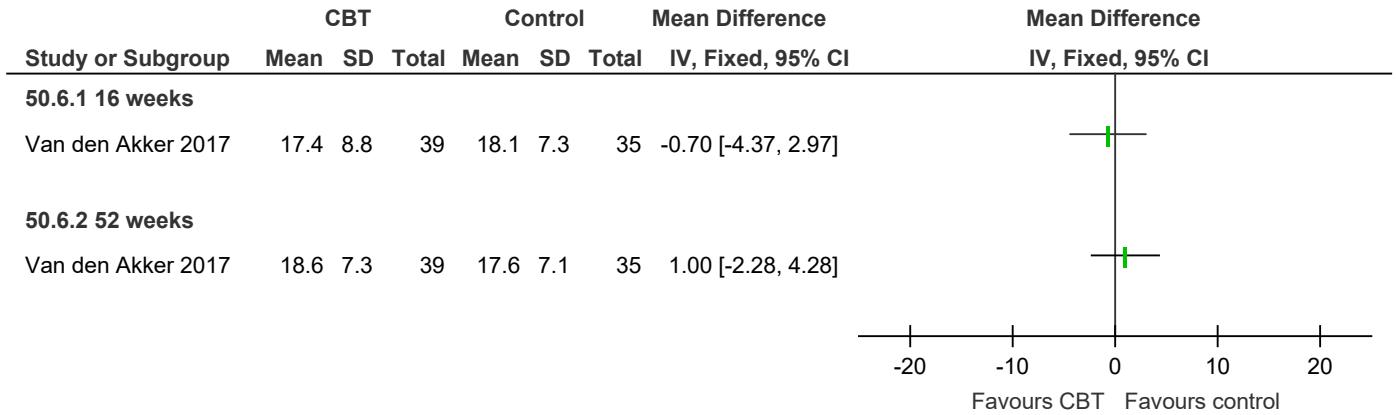


Figure 269: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

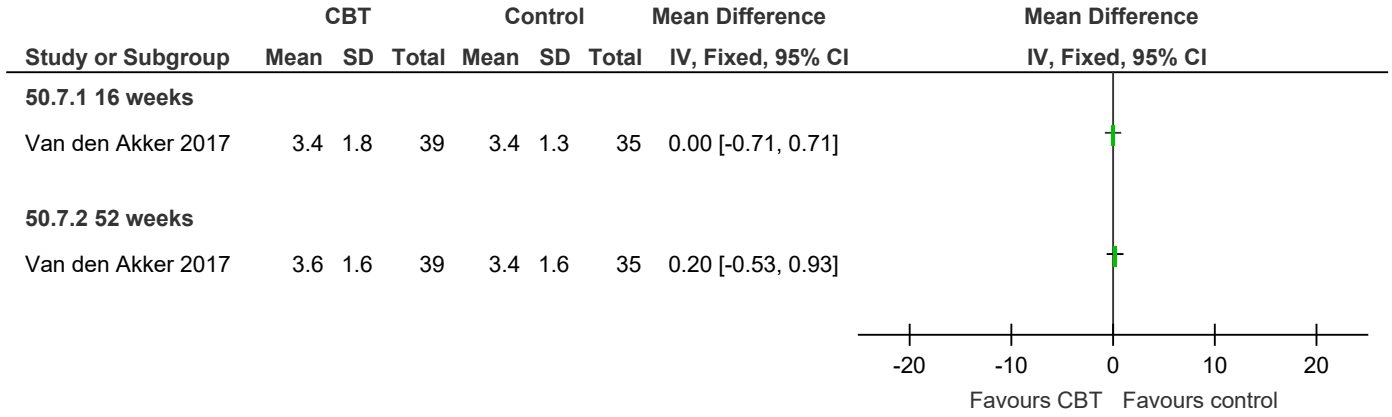


Figure 270: Piper Fatigue Scale (0-10l; lower better)

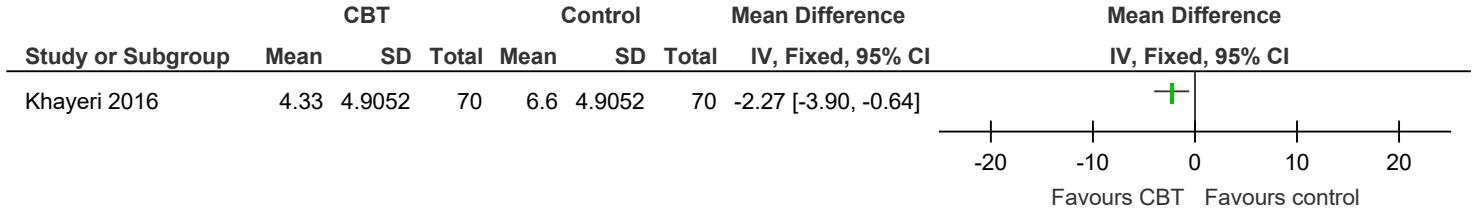


Figure 271: SF-36 vitality (0-100; higher better)

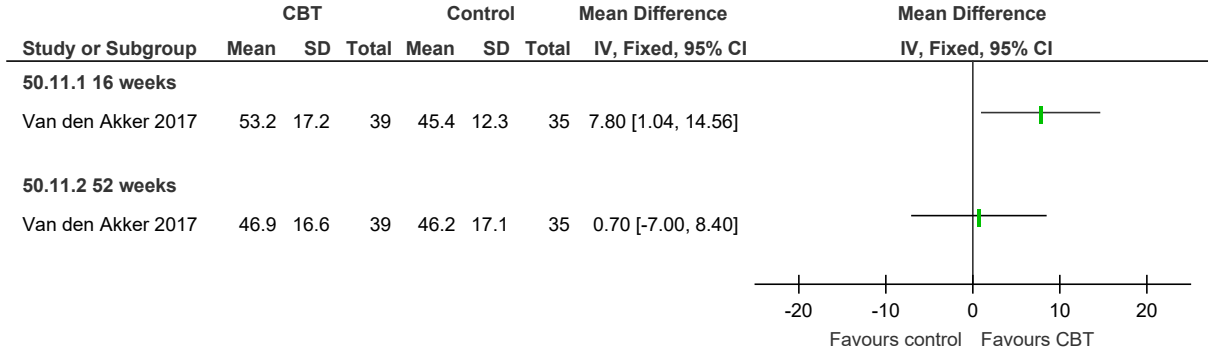


Figure 272: SF-36 physical functioning (0-100; higher better)

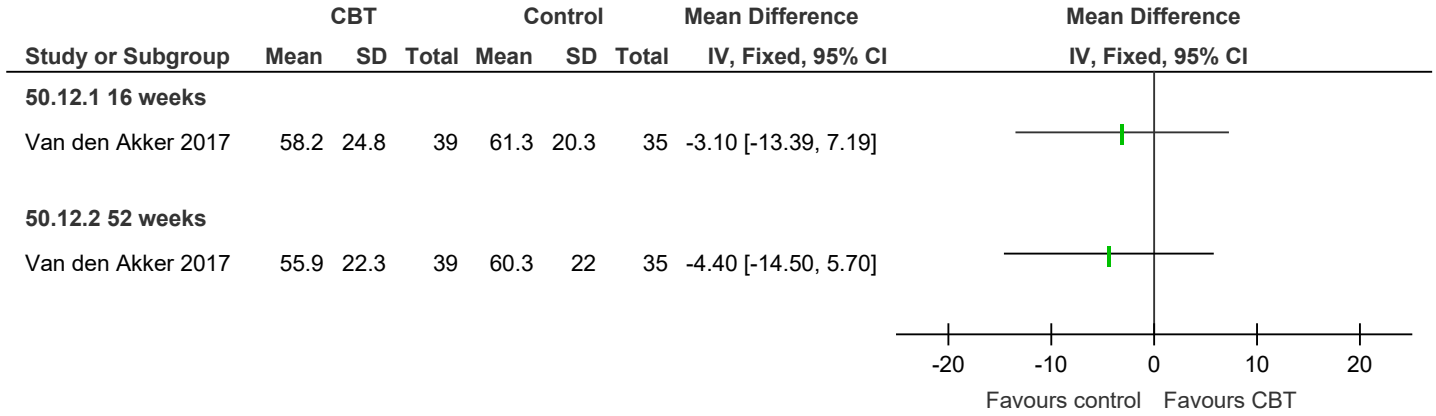


Figure 273: SF-36 physical role functioning (0-100; higher better)

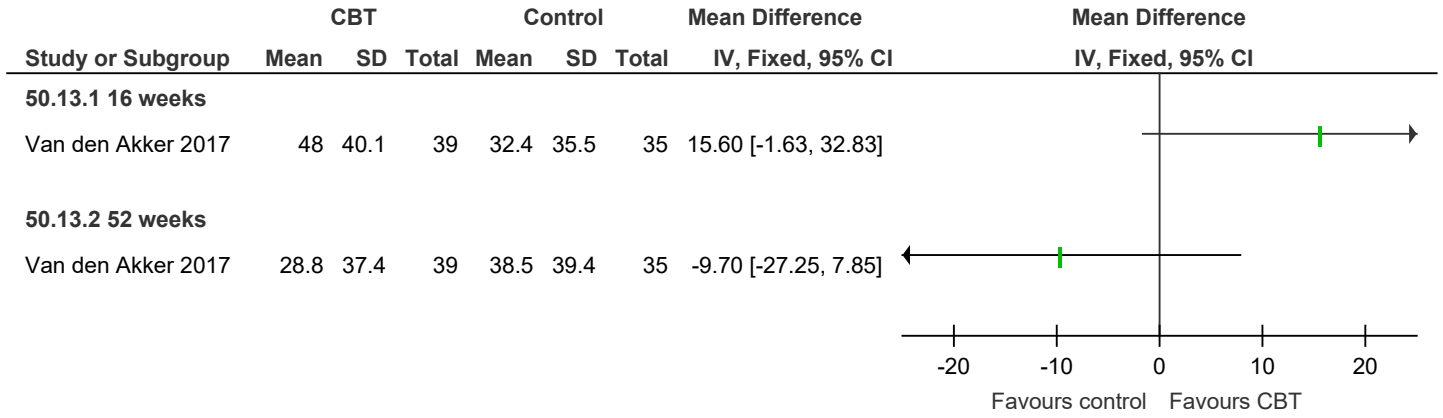


Figure 274: SF-36 emotional role functioning (0-100; higher better)

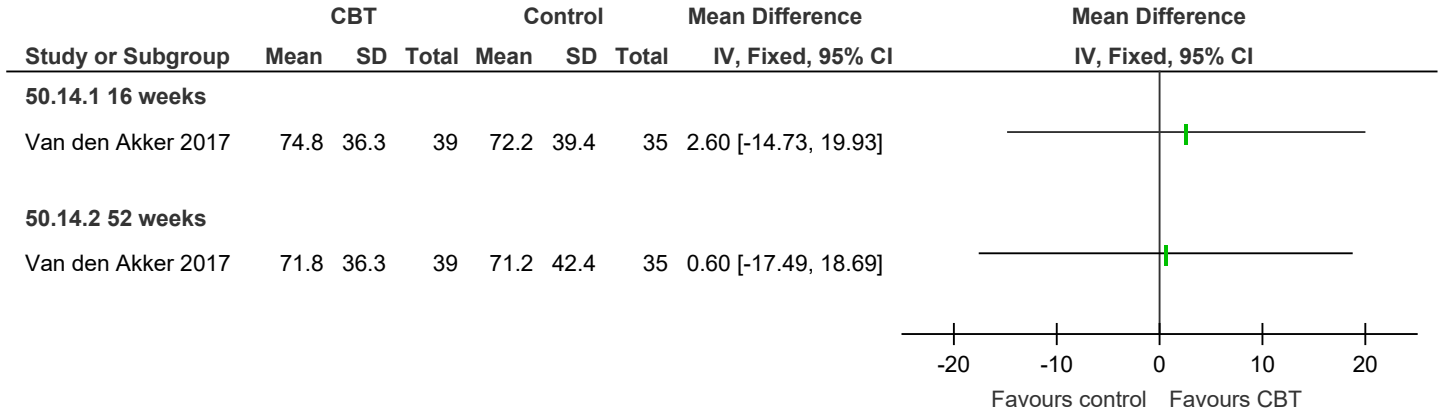


Figure 275: SF-36 social functioning (0-100; higher better)

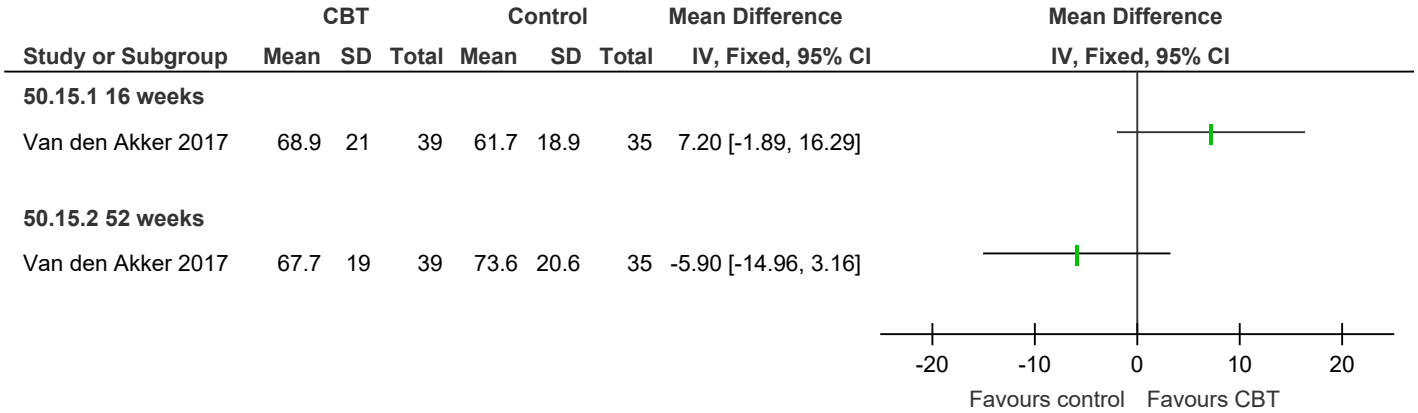


Figure 276: SF-36 mental health (0-100; higher better)

	CBT			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
50.16.1 16 weeks								
Van den Akker 2017	71.7	12.4	39	71.7	13.9	35	0.00 [-6.03, 6.03]	
50.16.2 52 weeks								
Van den Akker 2017	68.3	15.4	39	71.1	16.1	35	-2.80 [-10.00, 4.40]	

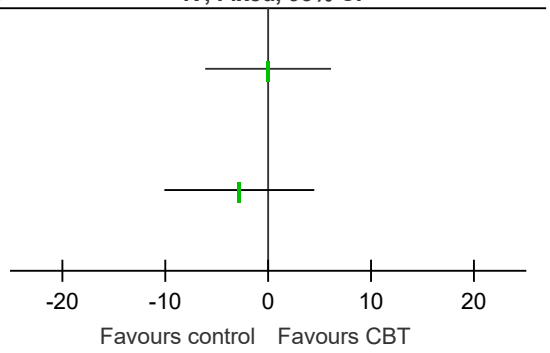


Figure 277: SF-36 general health (0-100; higher better)

	CBT			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
50.17.1 16 weeks								
Van den Akker 2017	46.5	16.2	39	48.2	13.4	35	-1.70 [-8.45, 5.05]	
50.17.2 52 weeks								
Van den Akker 2017	48.6	15.3	39	50.3	15.3	35	-1.70 [-8.68, 5.28]	

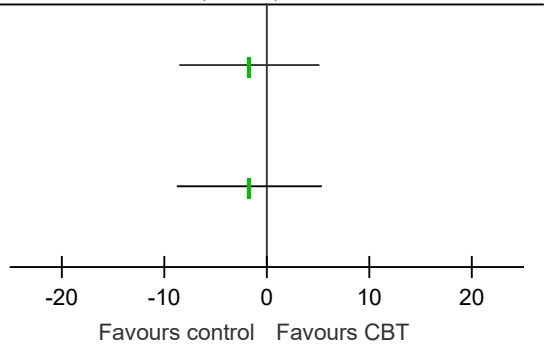


Figure 278: SF-36 body pain (0-100; higher better)

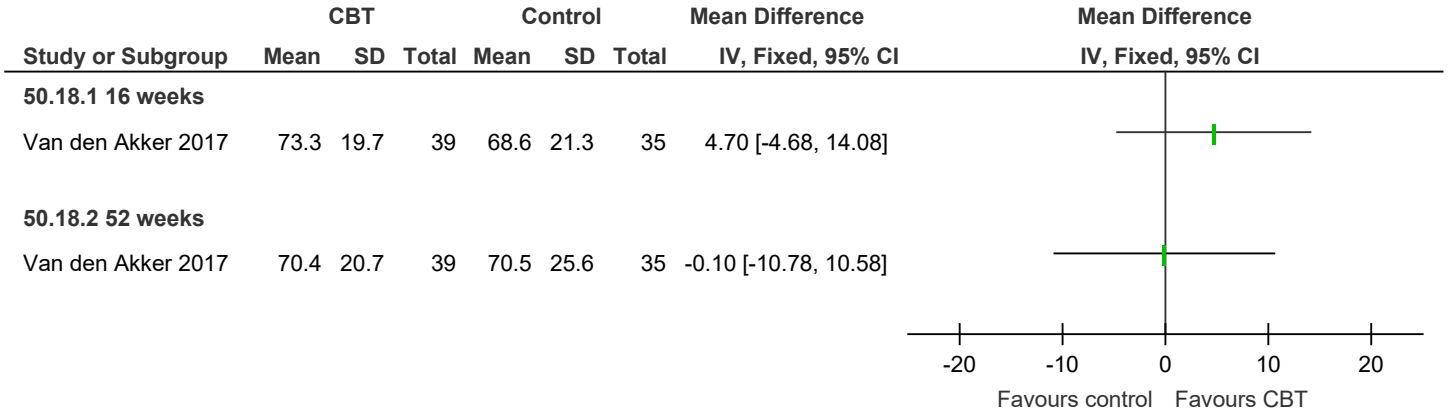


Figure 279: DASS-21 anxiety (0-21; lower better)

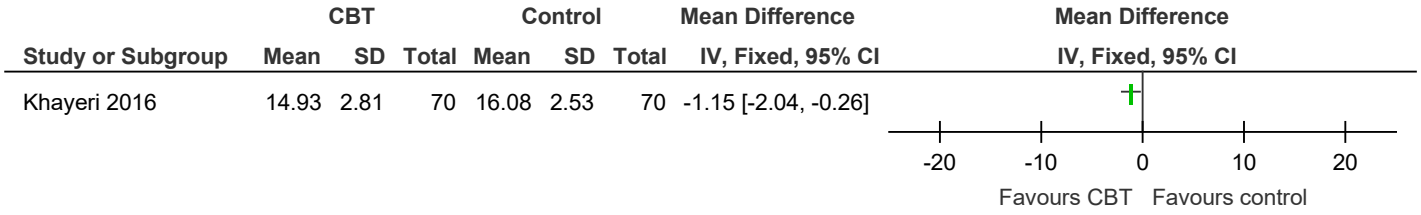


Figure 280: DASS-21 depression (0-21; lower better)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Khayeri 2016	12.66	2.59	70	14.06	1.98	70	-1.40 [-2.16, -0.64]

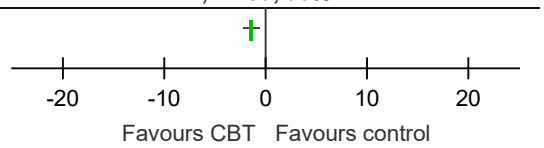


Figure 281: Cognitive – Checklist Individual Strength (CIS)20r – concentration (5-35; lower better)

Study or Subgroup	CBT Mean	CBT SD	CBT Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
50.19.1 16 weeks							
Van den Akker 2017	20.1	7.6	39	21.3	7.3	35	-1.20 [-4.60, 2.20]
50.19.2 52 weeks							
Van den Akker 2017	20.8	7	39	20.4	8	35	0.40 [-3.04, 3.84]

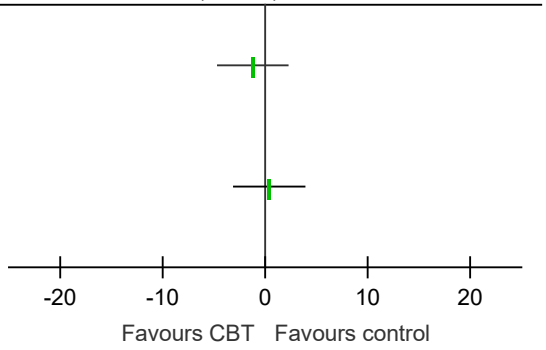
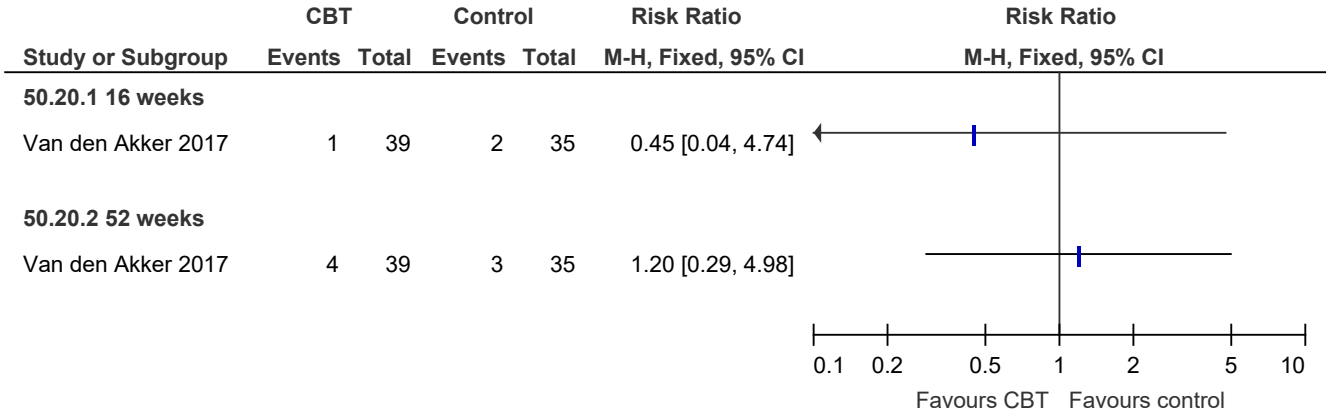


Figure 282: Serious adverse events



E.35 CBT vs. relaxation – up to 6 months and >6 months outcomes (<6 months unless otherwise indicated in plot)

Figure 283: Chalder Fatigue Scale (0-33; lower better)

	CBT			Relaxation			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
51.1.1 5 months								
Van Kessel 2008	8.99	5.31	35	11.11	4.57	37	-2.12 [-4.41, 0.17]	
51.1.2 8 months								
Van Kessel 2008	10.37	6.37	35	12.49	5.24	37	-2.12 [-4.82, 0.58]	

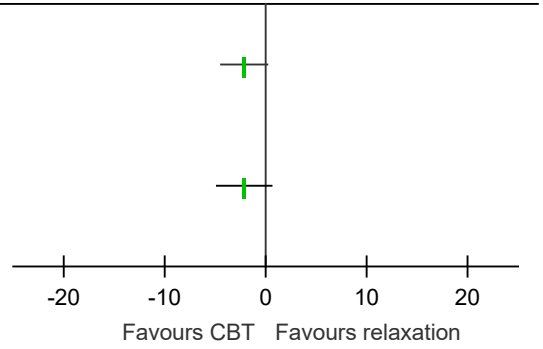


Figure 284: Fatigue-related impairment, work and social adjustment scale (0-40; lower better)

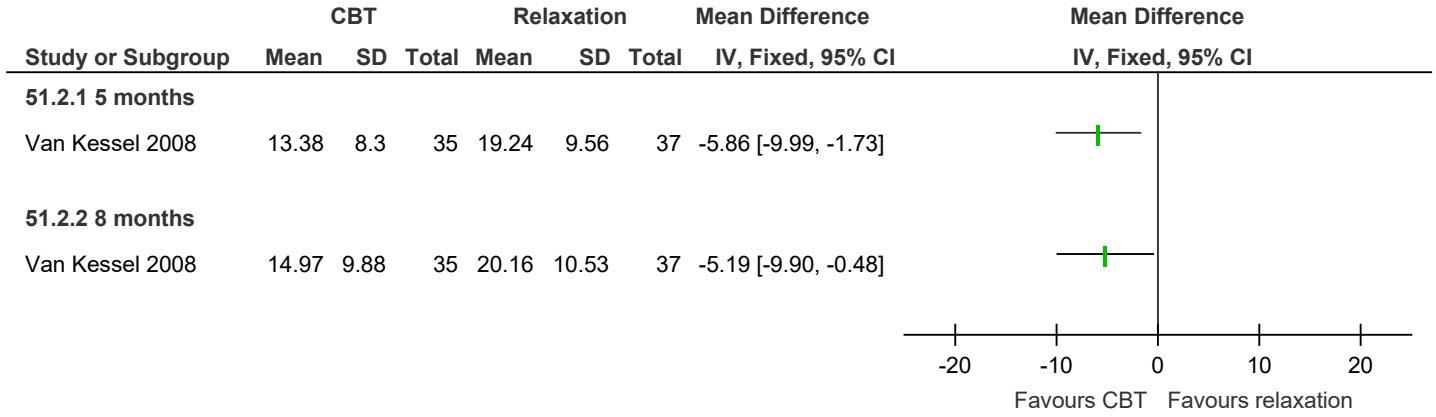


Figure 285: HADS depression (0-21; lower better)

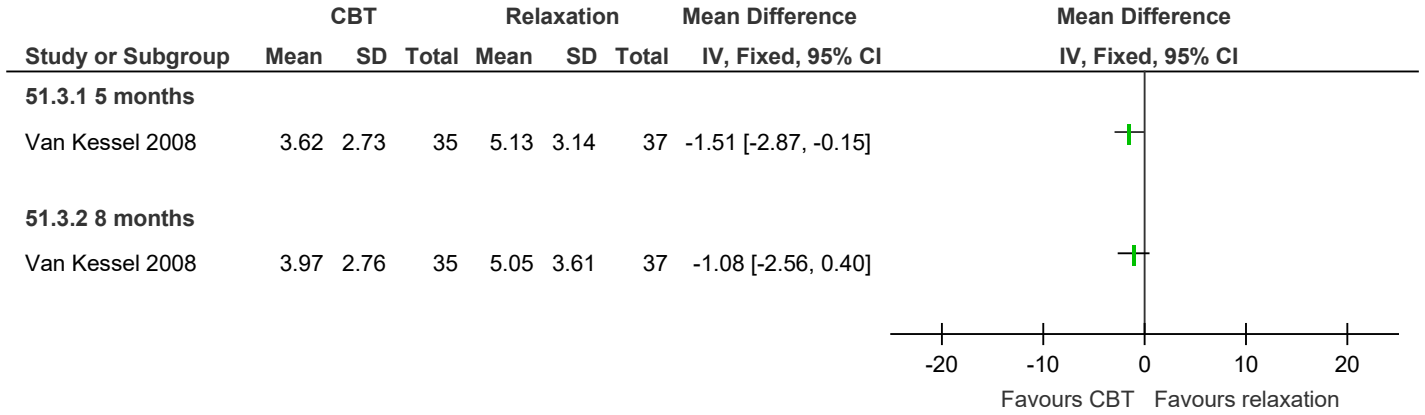


Figure 286: HADS anxiety (0-21; lower better)

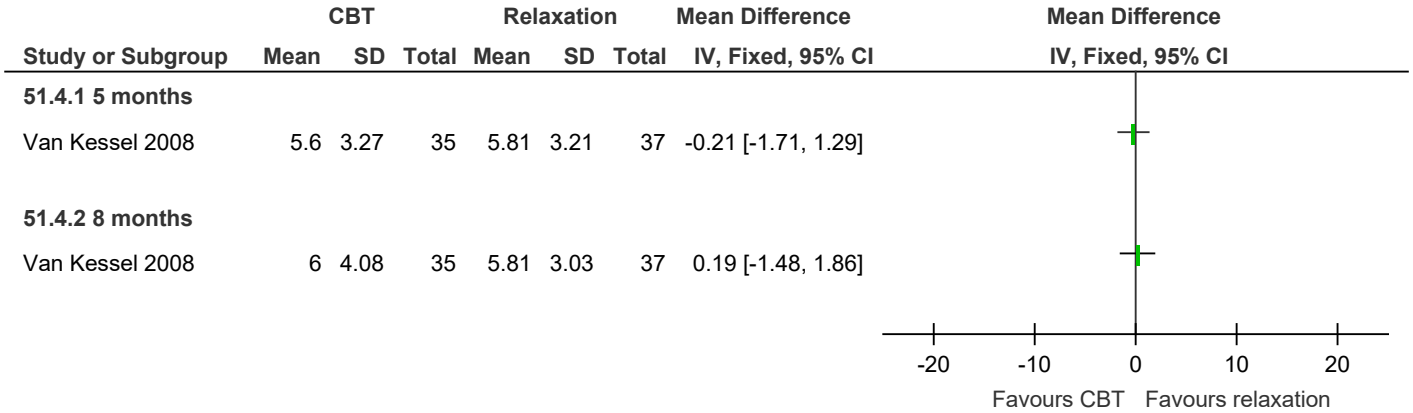
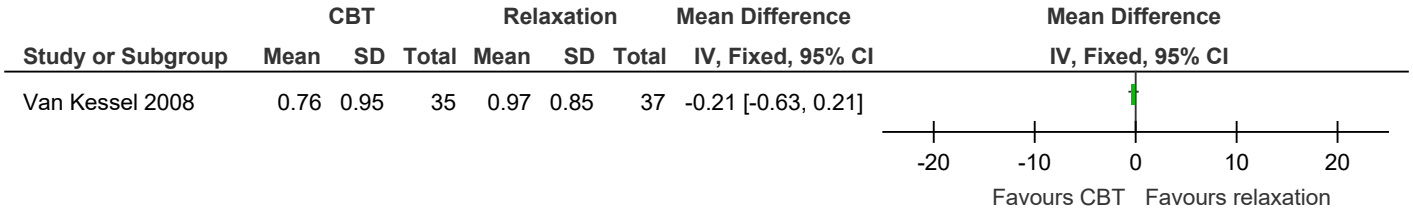
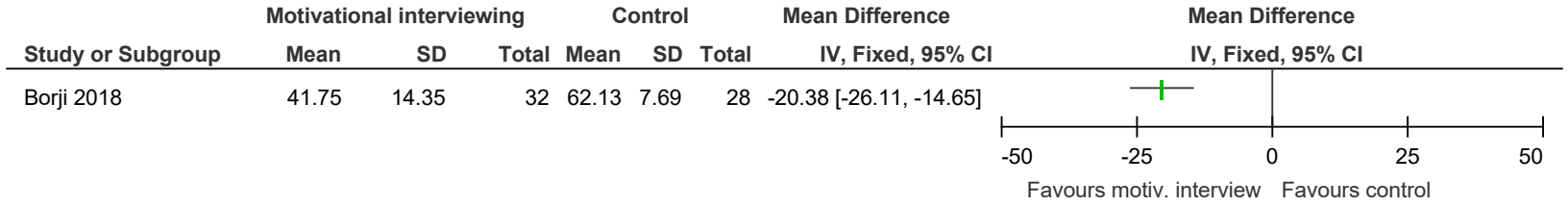


Figure 287: Acceptability – usefulness at end of treatment (1-4; lower better)



E.36 Motivational interviewing vs. control – up to 6 months outcomes

Figure 288: Modified Fatigue Impact Scale – total (0-84; lower better)



E.37 Resistance + aerobic exercise + CBT vs. control (waitlist) – up to 6 months outcomes

Figure 289: Modified Fatigue Impact Scale (lower better)

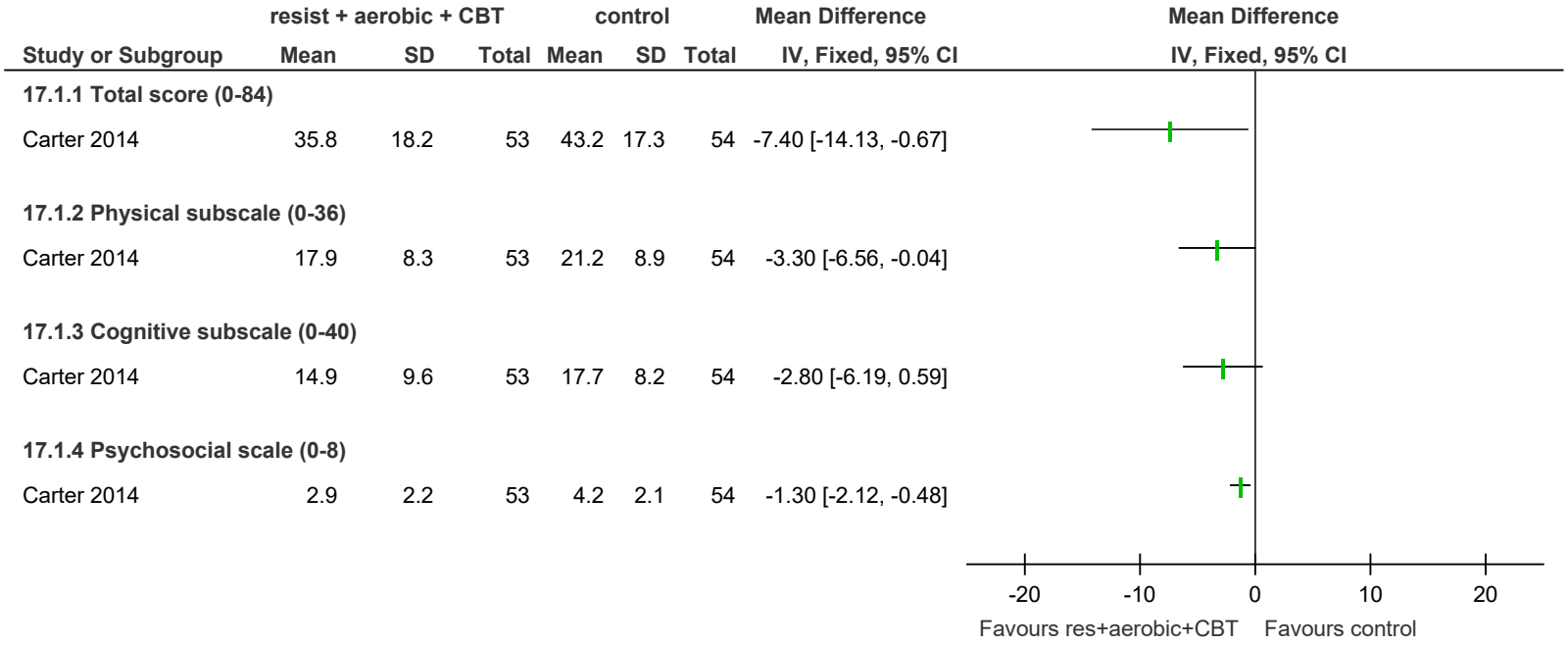


Figure 290: MSQOL-54 score (0-100; higher better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	68.1	20.3	53	60.6	19.2	54	7.50 [0.01, 14.99]

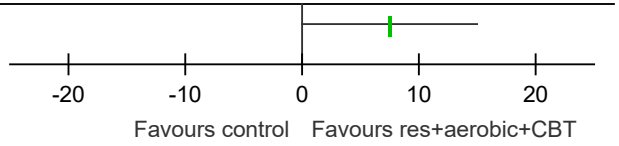


Figure 291: EQ-5D (higher better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	0.744	0.204	53	0.684	0.263	54	0.06 [-0.03, 0.15]

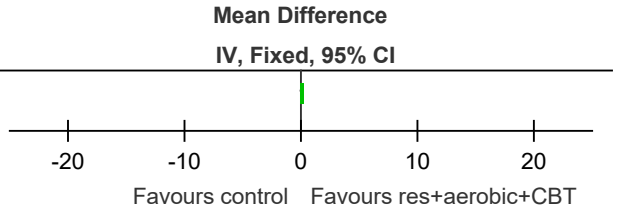


Figure 292: EDSS score (0-10; lower better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	3.5	1.3	53	3.7	1.5	54	-0.20 [-0.73, 0.33]

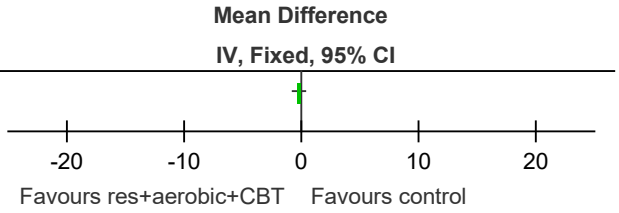


Figure 293: Cognitive – PASAT (higher better)

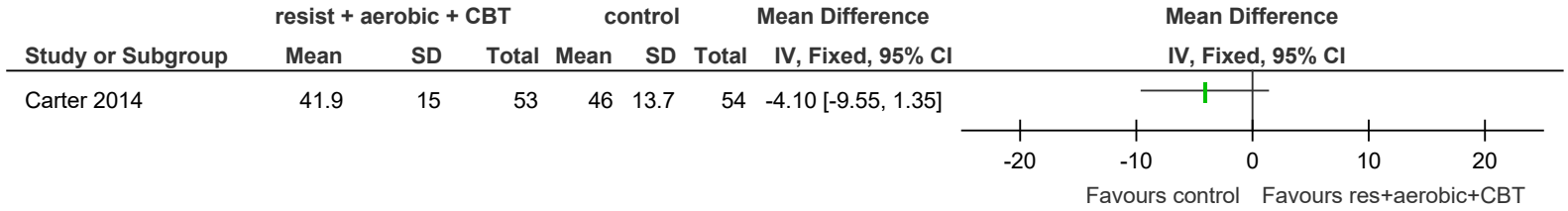
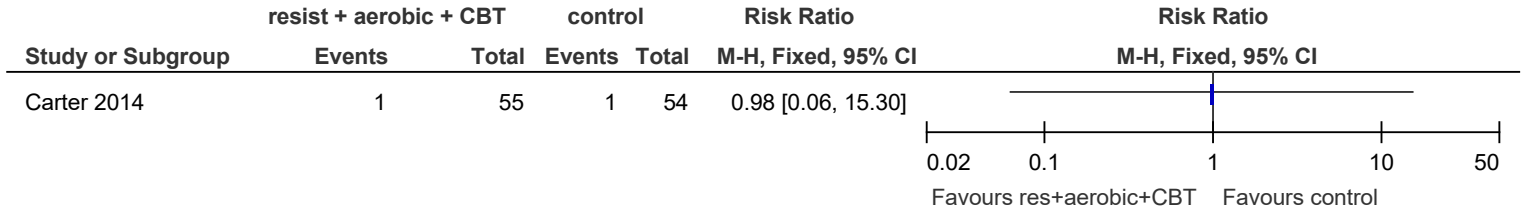


Figure 294: Adverse events (MS relapse) leading to withdrawal



E.38 Resistance + aerobic exercise + CBT vs. control (waitlist) – >6 months outcomes

Figure 295: Modified Fatigue Impact Scale (lower better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
18.1.1 Total score (0-84)							
Carter 2014	39.6	16.6	50	41.3	18.8	49	-1.70 [-8.69, 5.29]
18.1.2 Physical subscale (0-36)							
Carter 2014	20.1	7.8	50	20.7	8.5	49	-0.60 [-3.82, 2.62]
18.1.3 Cognitive subscale (0-40)							
Carter 2014	16	8.8	50	16.7	9.6	49	-0.70 [-4.33, 2.93]
18.1.4 Psychosocial scale (0-8)							
Carter 2014	3.5	1.9	50	4	2.4	49	-0.50 [-1.35, 0.35]

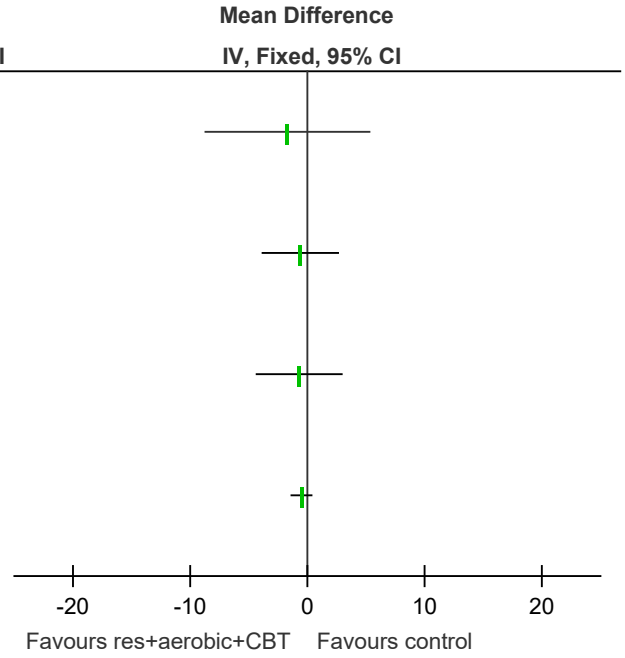


Figure 296: MSQoL-54 score (0-100; higher better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	65.9	20.1	50	60.4	21.1	49	5.50 [-2.62, 13.62]

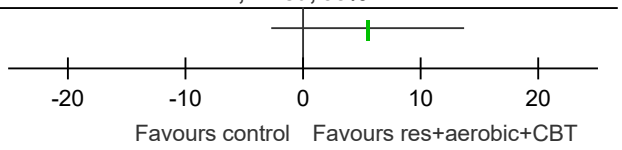


Figure 297: EQ-5D score (0-1; higher better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	0.739	0.249	50	0.734	0.252	49	0.01 [-0.09, 0.10]

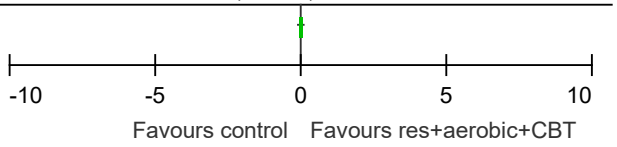


Figure 298: EDSS score (0-10; lower better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	3.7	1.5	50	3.9	1.7	49	-0.20 [-0.83, 0.43]

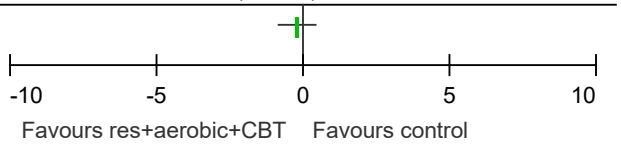


Figure 299: Cognitive – PASAT (higher better)

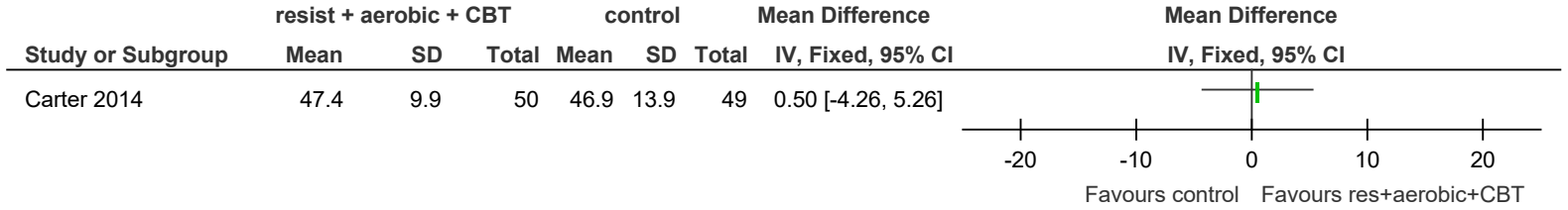


Figure 300: Adverse events (relapse)

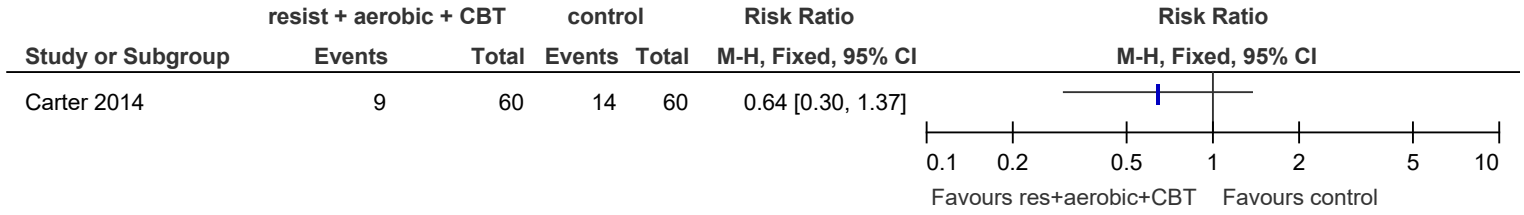
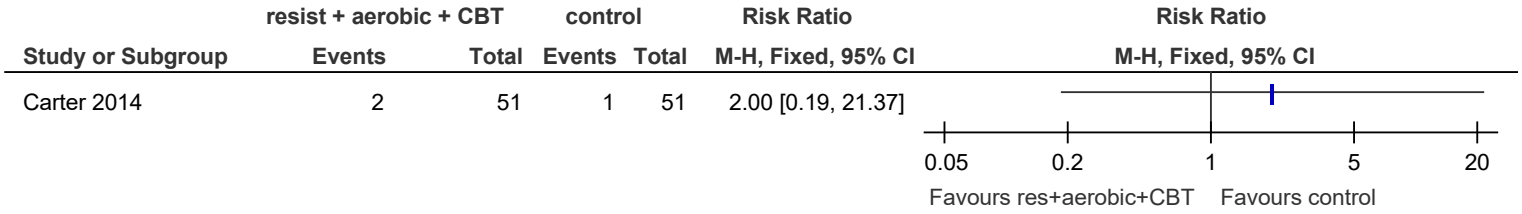


Figure 301: Adverse events (MS relapse) leading to withdrawal



E.39 Motivational interviewing vs. control – >6 months outcomes

Figure 302: Modified Fatigue Impact Scale (lower better)

	resist + aerobic + CBT			control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
18.1.1 Total score (0-84)								
Carter 2014	39.6	16.6	50	41.3	18.8	49	-1.70 [-8.69, 5.29]	
18.1.2 Physical subscale (0-36)								
Carter 2014	20.1	7.8	50	20.7	8.5	49	-0.60 [-3.82, 2.62]	
18.1.3 Cognitive subscale (0-40)								
Carter 2014	16	8.8	50	16.7	9.6	49	-0.70 [-4.33, 2.93]	
18.1.4 Psychosocial scale (0-8)								
Carter 2014	3.5	1.9	50	4	2.4	49	-0.50 [-1.35, 0.35]	

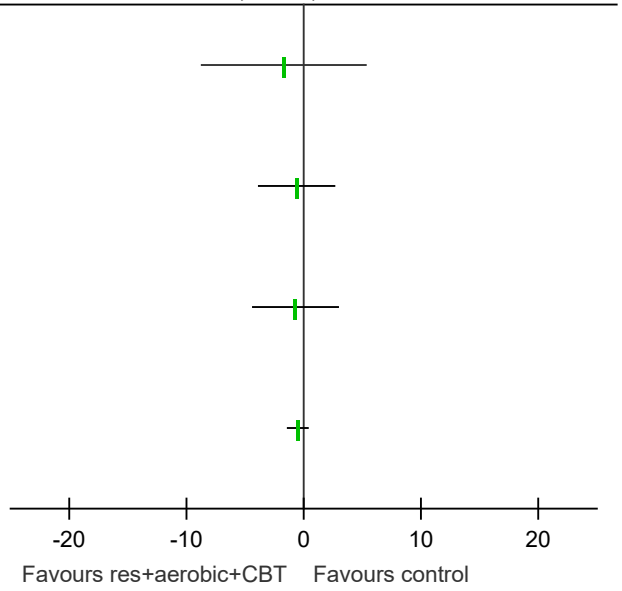


Figure 303: MSQOL-54 score (0-100; higher better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	65.9	20.1	50	60.4	21.1	49	5.50 [-2.62, 13.62]

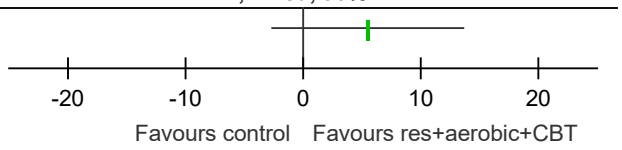


Figure 304: EQ-5D (higher better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	0.739	0.249	50	0.734	0.252	49	0.01 [-0.09, 0.10]

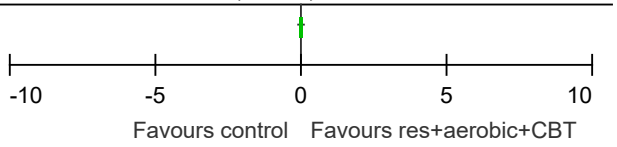


Figure 305: EDSS score (0-10; lower better)

Study or Subgroup	resist + aerobic + CBT Mean	SD	Total	control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Carter 2014	3.7	1.5	50	3.9	1.7	49	-0.20 [-0.83, 0.43]

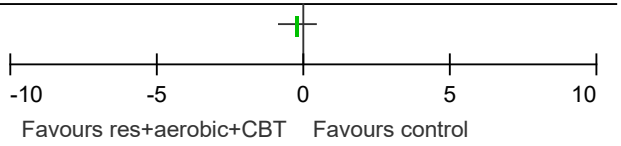


Figure 306: Cognitive – PASAT (higher better)

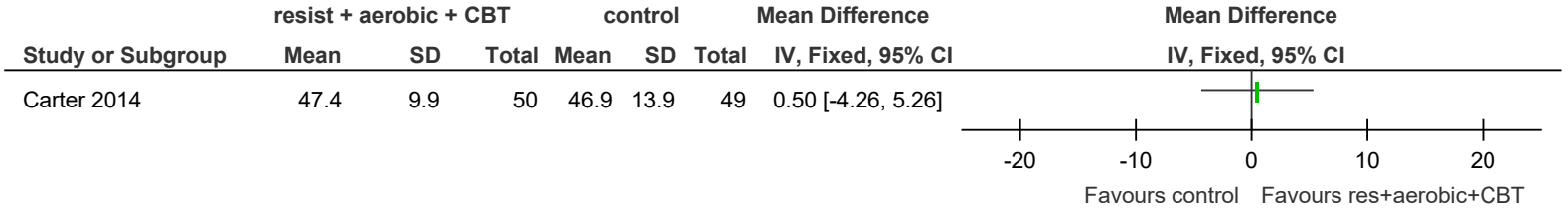


Figure 307: Adverse events (relapse)

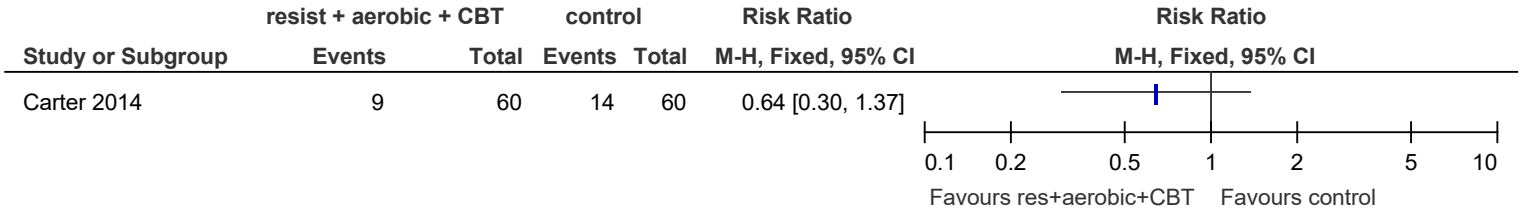
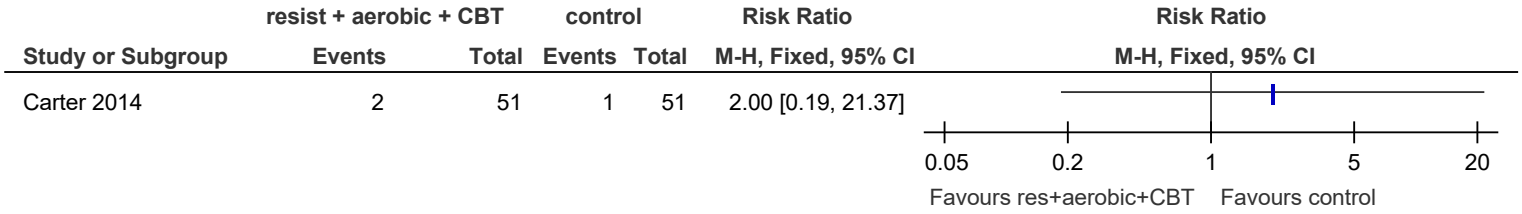


Figure 308: Adverse events (MS relapse) leading to withdrawal



E.40 Diet vs. control – up to 6 months outcomes

Figure 309: Fatigue Severity Scale (1-9; lower better)

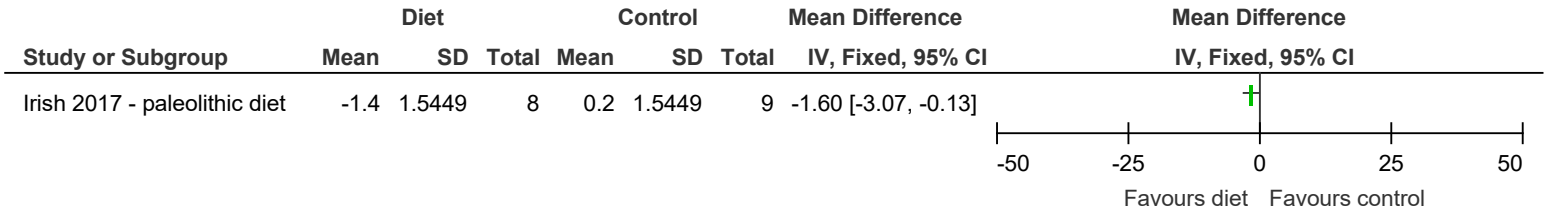


Figure 310: >1-point reduction on Fatigue Severity Scale compared to baseline

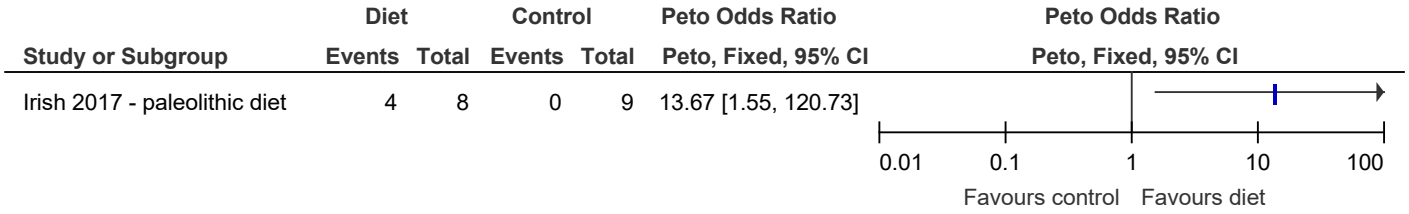


Figure 311: Modified Fatigue Impact Scale – total score (0-84; lower better)

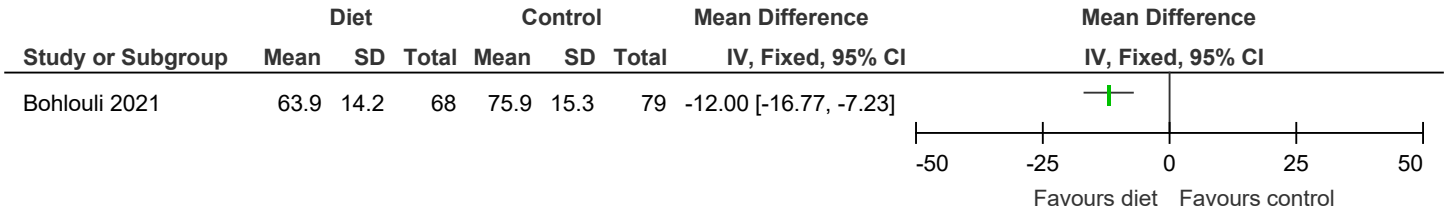


Figure 312: Modified Fatigue Impact Scale – physical subscore (0-36; lower better)

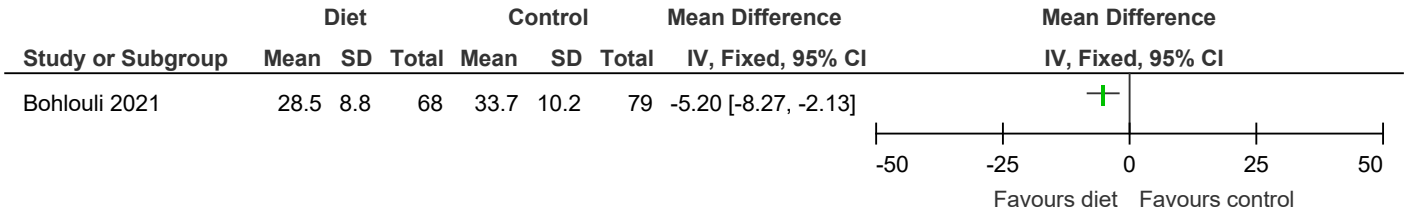


Figure 313: Modified Fatigue Impact Scale – cognitive subscore (0-40; lower better)

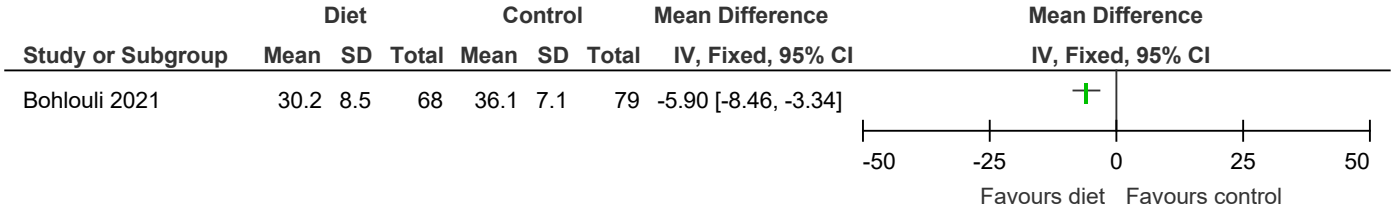


Figure 314: Modified Fatigue Impact Scale – psychosocial subscore (0-8; lower better)

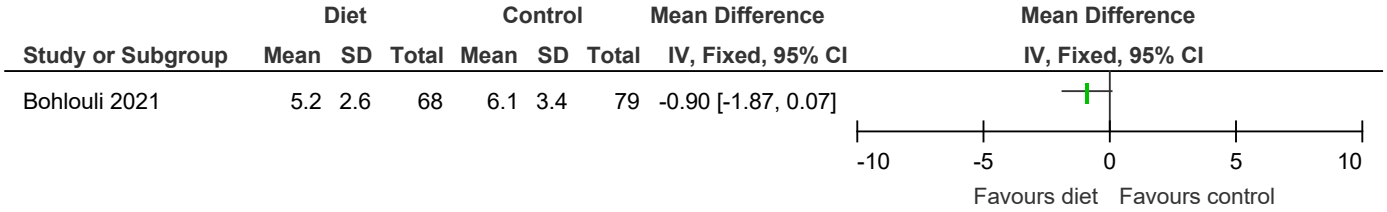


Figure 315: Neurological Fatigue Index (scale unclear but likely 0-30; lower better)

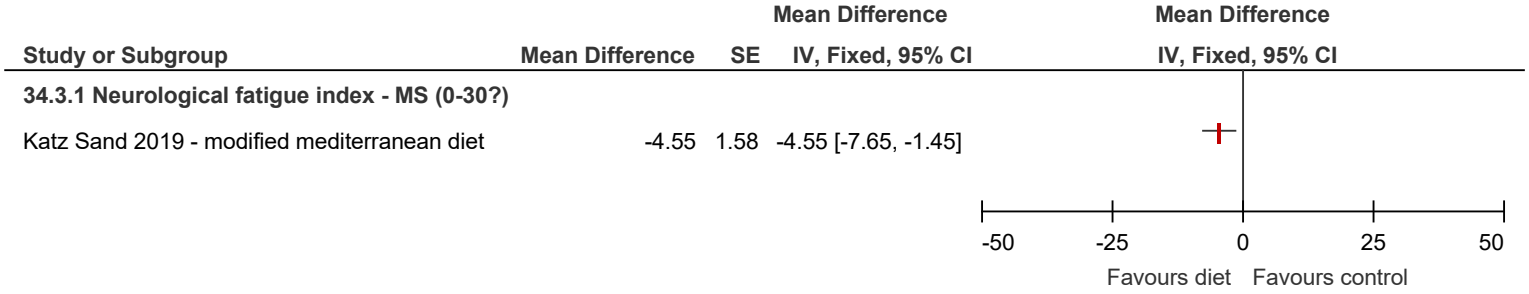


Figure 316: At least 5-point reduction on MSQOL-54 mental health composite compared to baseline

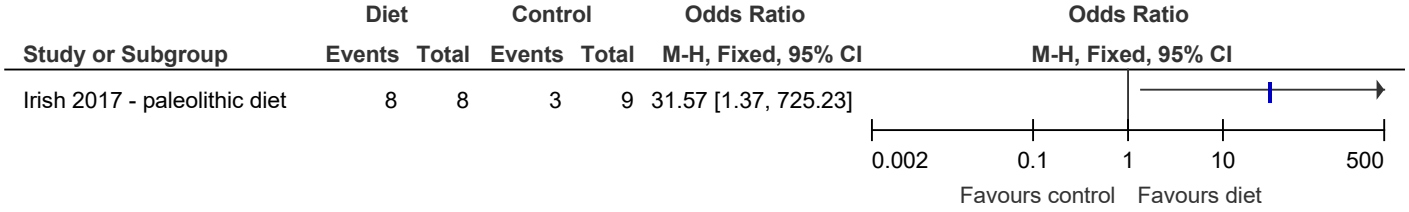


Figure 317: Improvement (no threshold) on MSQOL-54 physical health composite compared to baseline

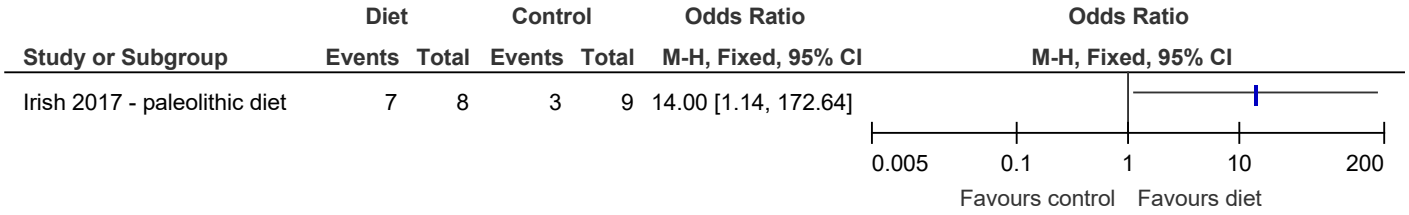


Figure 318: MSIS-29 (0-100; lower better)

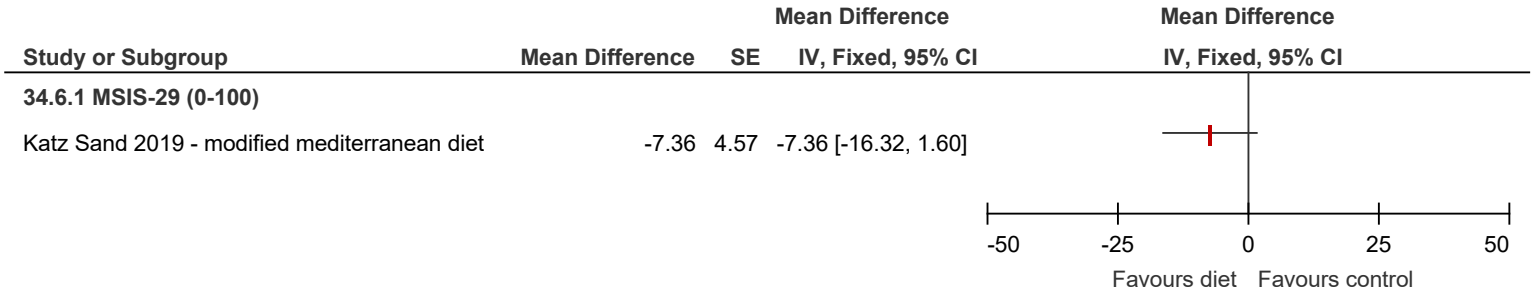


Figure 319: EDSS score (0-10; lower better)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
34.11.1 EDSS score (0-10)				
Bohlouli 2021	-0.4	0.1157	67.3%	-0.40 [-0.63, -0.17]
Katz Sand 2019 - modified mediterranean diet	-0.98	0.36	32.7%	-0.98 [-1.69, -0.27]
Subtotal (95% CI)			**100.0%**	**-0.59 [-1.12, -0.06]**

Heterogeneity: Tau² = 0.10; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%

Test for overall effect: Z = 2.17 (P = 0.03)

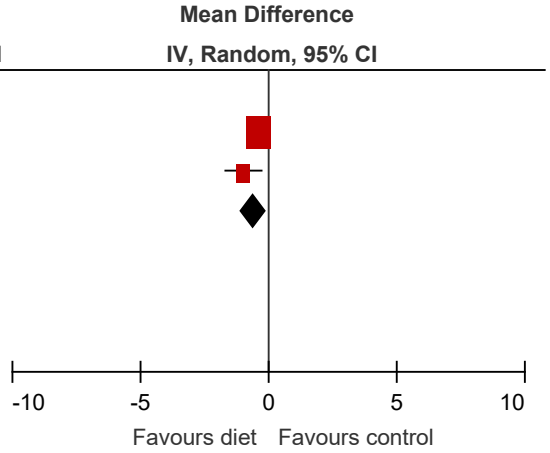


Figure 320: Adverse events

Study or Subgroup	Diet Events	Diet Total	Control Events	Control Total	Weight	Risk Difference M-H, Fixed, 95% CI
Bohlouli 2021	0	68	0	79	88.1%	0.00 [-0.03, 0.03]
Irish 2017 - paleolithic diet	1	9	2	11	11.9%	-0.07 [-0.38, 0.24]
Total (95% CI)		**77**		**90**	**100.0%**	**-0.01 [-0.05, 0.04]**
Total events	1		2			

Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%

Test for overall effect: Z = 0.38 (P = 0.70)

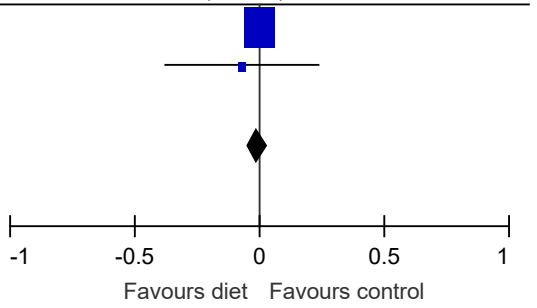


Figure 321: Adverse events leading to withdrawal

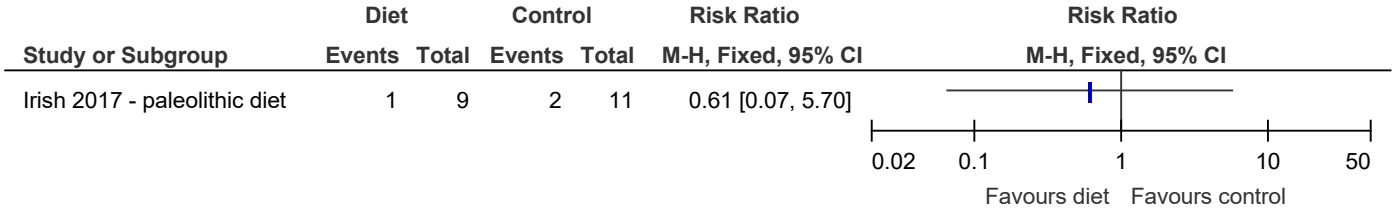
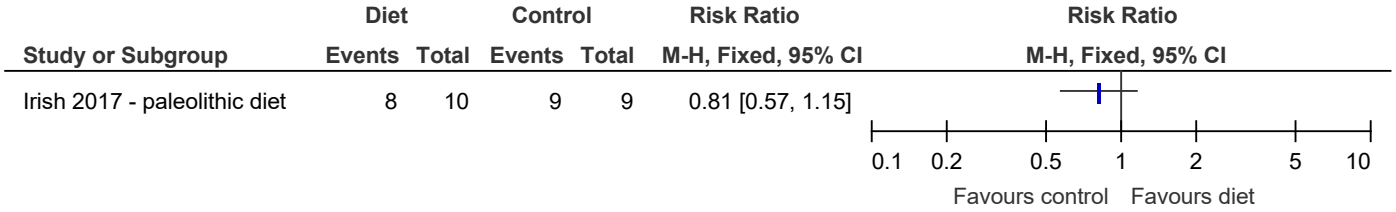


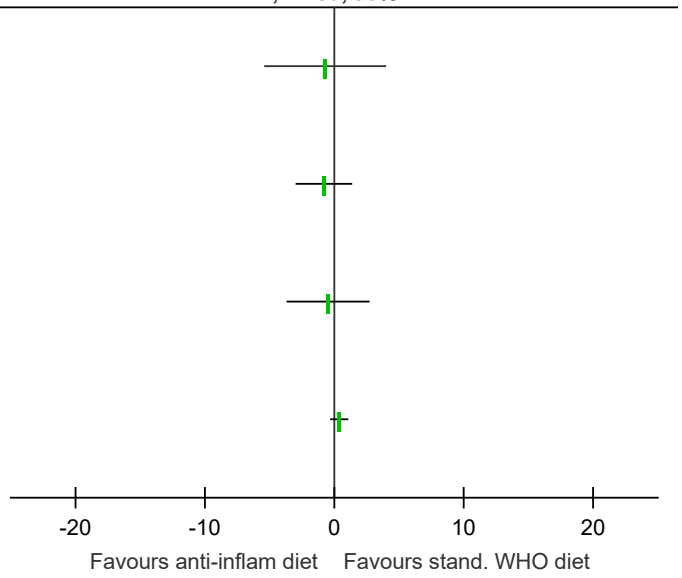
Figure 322: Adherence to intervention or control



E.41 Diet (individualised) vs. standard healthy diet recommendations – up to 6 months outcomes

Figure 323: Modified Fatigue Impact Scale (lower better)

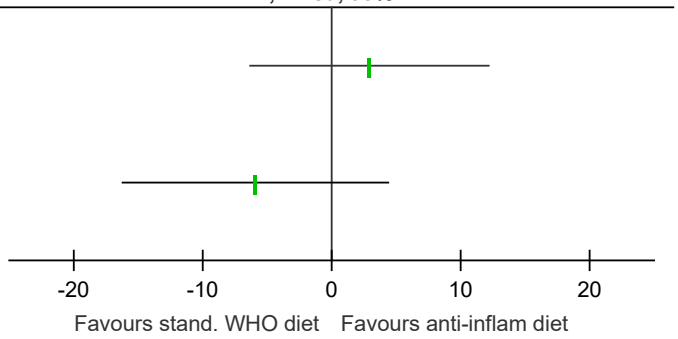
Study or Subgroup	Anti-inflammatory diet Mean	SD	Total	Standard WHO diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
35.1.1 Total score (0-84)							
Mousavi-Shirazi 2020 - anti-inflammatory diet	47.22	12.54	50	47.92	11.11	50	-0.70 [-5.34, 3.94]
35.1.2 Physical subscale (0-36)							
Mousavi-Shirazi 2020 - anti-inflammatory diet	22.18	6.37	50	22.98	4.21	50	-0.80 [-2.92, 1.32]
35.1.3 Cognitive subscale (0-40)							
Mousavi-Shirazi 2020 - anti-inflammatory diet	22.24	7.8	50	22.72	8.2	50	-0.48 [-3.62, 2.66]
35.1.4 Psychosocial scale (0-8)							
Mousavi-Shirazi 2020 - anti-inflammatory diet	2.66	1.81	50	2.28	1.4	50	0.38 [-0.25, 1.01]



Note: for the psychosocial subscale, there is a larger baseline difference between groups for this outcome - scores improved from baseline in the intervention group and worsened slightly in the control group.

Figure 324: MSQOL-54 (0-100; higher better)

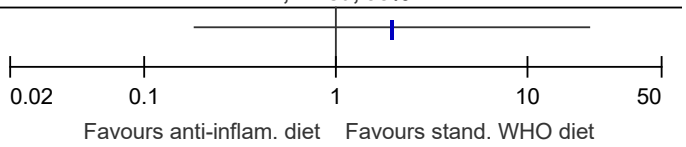
Study or Subgroup	Anti-inflammatory diet Mean	SD	Total	Standard WHO diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
35.2.1 Physical composite							
Mousavi-Shirazi 2020 - anti-inflammatory diet	49.5	23.25	50	46.57	23.92	50	2.93 [-6.32, 12.18]
35.2.2 Mental health composite							
Mousavi-Shirazi 2020 - anti-inflammatory diet	58.52	24.14	50	64.43	28.25	50	-5.91 [-16.21, 4.39]



Note: there is a larger baseline difference between groups for these outcomes, which may mislead interpretation. For both subscales, scores changed very little in both groups from baseline but were higher at baseline in the intervention group for physical composite and lower at baseline in the intervention group for mental health composite.

Figure 325: Adverse events leading to withdrawal (relapse)

Study or Subgroup	Anti-inflammatory diet Events	Total	Standard WHO diet Events	Total	Risk Ratio M-H, Fixed, 95% CI
Mousavi-Shirazi 2020 - anti-inflammatory diet	2	52	1	51	1.96 [0.18, 20.97]



E.42 Diet (individualised) vs. standard healthy diet recommendations – up to 6 months outcomes

Figure 326: Modified Fatigue Impact Scale – total (0-84; lower better)

Study or Subgroup	Mediterranean diet Mean	SD	Total	Standard healthy diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
36.1.1 Total score (0-84)							
Razeghi-Jahromi 2020 - mediterranean-based diet	33.93	2.7514	34	37.98	3.0119	38	-4.05 [-5.38, -2.72]

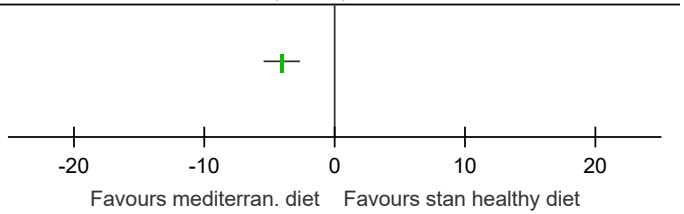


Figure 327: Cognitive – PASAT (higher better)

Study or Subgroup	Mediterranean diet Mean	SD	Total	Standard healthy diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Razeghi-Jahromi 2020 - mediterranean-based diet	42.68	7.0528	27	42.37	6.9404	29	0.31 [-3.36, 3.98]

Figure 328: Cognitive – SDMT (higher better)

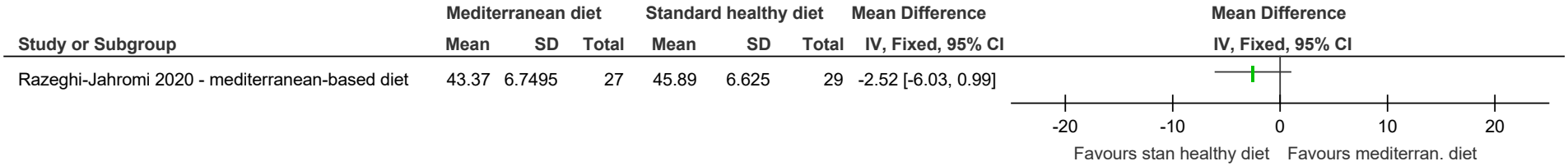


Figure 329: Cognitive – California Verbal Learning Test II - delayed recall (higher better)

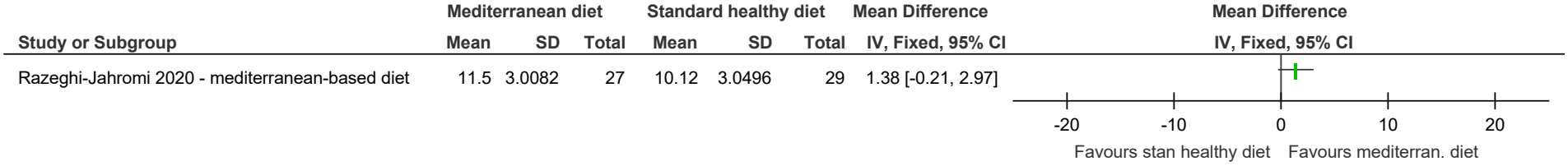


Figure 330: Cognitive – California Verbal Learning Test II - total learning (higher better)

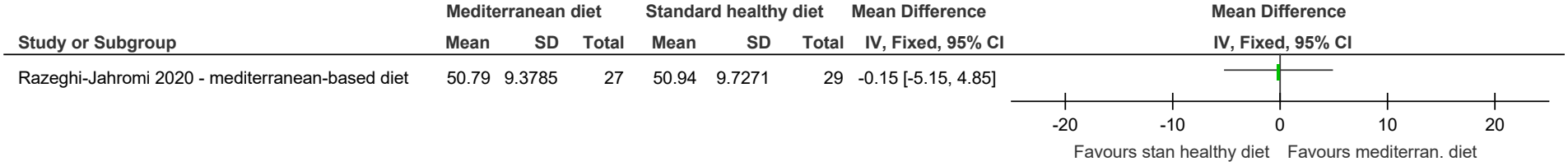


Figure 331: Cognitive – Judgement of line orientation test (higher better)

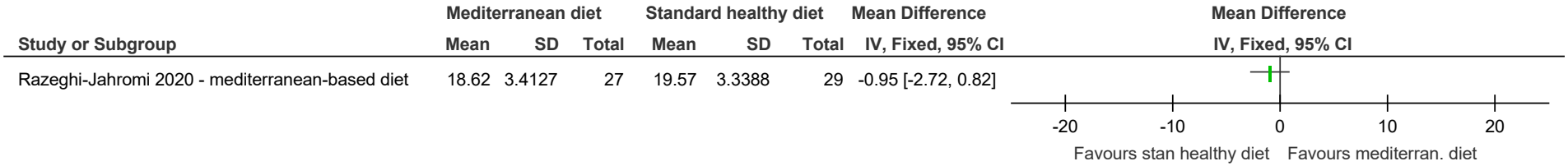


Figure 332: Cognitive – Brief Visuospatial Memory Test-Revised (higher better)

Figure 333: Cognitive – North American Adult Reading Test (higher better)

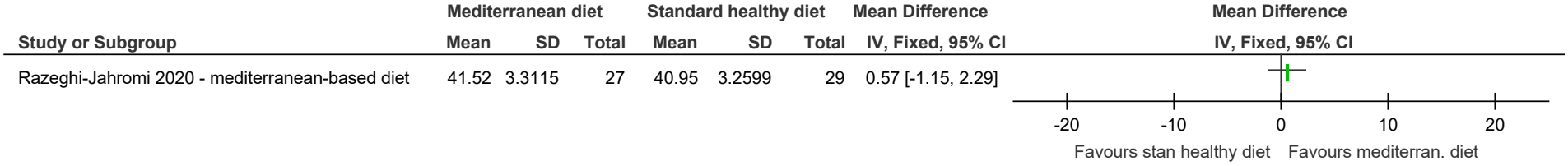


Figure 334: Cognitive – Controlled Oral Word Association Test (higher better)

Study or Subgroup	Mediterranean diet Mean	SD	Total	Standard healthy diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Razeghi-Jahromi 2020 - mediterranean-based diet	8.82	2.0223	27	8.63	1.9454	29	0.19 [-0.85, 1.23]

Figure 335: Cognitive – Delis-Kaplan Executive Function System description (higher better)

Study or Subgroup	Mediterranean diet Mean	SD	Total	Standard healthy diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Razeghi-Jahromi 2020 - mediterranean-based diet	10.97	3.8424	27	11.69	3.7857	29	-0.72 [-2.72, 1.28]

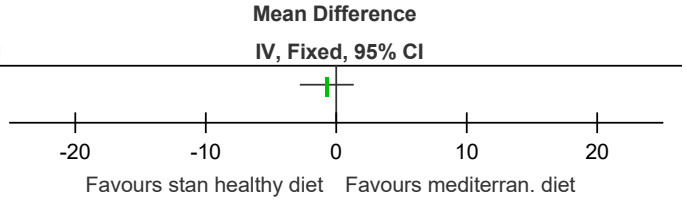


Figure 336: Cognitive – Delis-Kaplan Executive Function System total scoring (higher better)

Study or Subgroup	Mediterranean diet Mean	SD	Total	Standard healthy diet Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Razeghi-Jahromi 2020 - mediterranean-based diet	2.92	1.1123	27	3.39	1.0779	29	-0.47 [-1.04, 0.10]

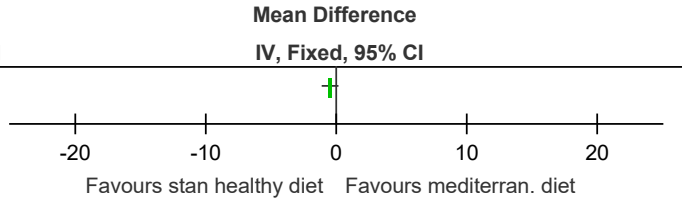
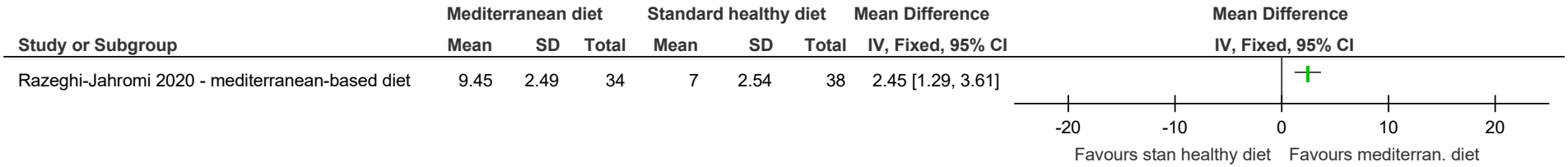


Figure 337: Adherence to intervention (scale 0-14; higher better)



E.43 Wahls diet (modified Palaeolithic elimination diet) vs. Swank diet (low-saturated fat diet) – up to 6 months outcomes

Figure 338: Fatigue Severity Score (scale said to be 1-9; lower better)

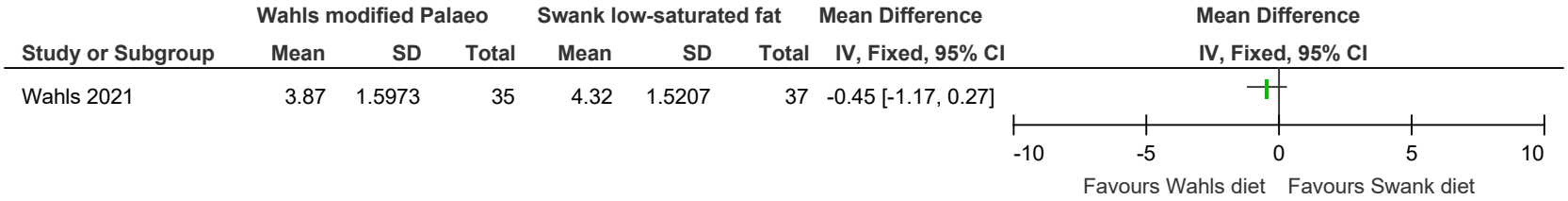


Figure 339: Modified Fatigue Impact Scale (0-84, 0-36, 0-40 or 0-8; lower better)

	Wahls modified Palaeo			Swank low-saturated fat			Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**IV, Fixed, 95% CI**
37.2.1 Total score (0-84)							
Wahls 2021	26.5	17.7482	35	30.2	15.9977	37	-3.70 [-11.52, 4.12]
37.2.2 Physical subscore (0-36)							
Wahls 2021	11.3	6.9218	35	14.7	8.5159	37	-3.40 [-6.98, 0.18]
37.2.3 Cognitive subscore (0-40)							
Wahls 2021	12.8	10.2348	35	13.5	8.3334	37	-0.70 [-5.03, 3.63]
37.2.4 Psychosocial subscore (0-8)							
Wahls 2021	2.37	2.0706	35	3.03	2.0681	37	-0.66 [-1.62, 0.30]

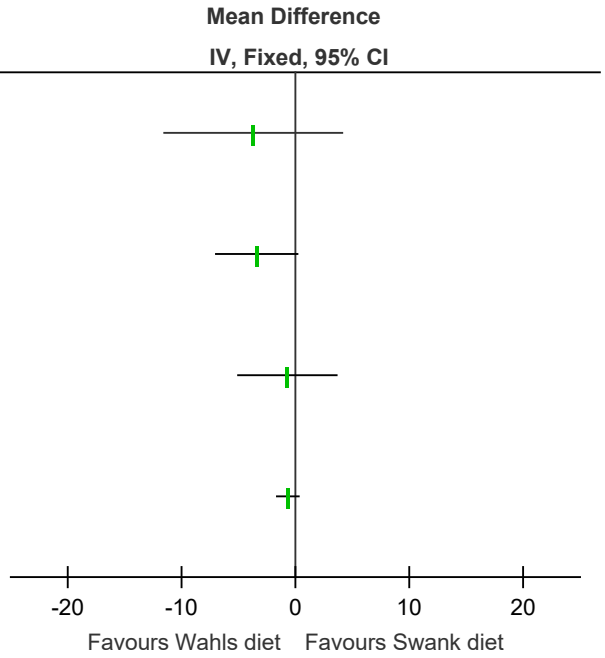


Figure 340: MSQoL-54 (0-100; lower better)

Study or Subgroup	Wahls modified Palaeo Mean	SD	Total	Swank low-saturated fat Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
37.3.1 Physical composite							
Wahls 2021	71	18.9315	35	64.9	19.1607	37	6.10 [-2.70, 14.90]
37.3.2 Mental composite							
Wahls 2021	76.3	21.2387	35	73.6	17.0926	37	2.70 [-6.24, 11.64]

Figure 341: Serious adverse events

Study or Subgroup	Wahls modified Palaeo Events	Total	Swank low-saturated fat Events	Total	Risk Difference M-H, Fixed, 95% CI
Wahls 2021	0	35	0	37	0.00 [-0.05, 0.05]

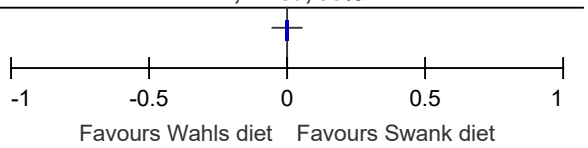
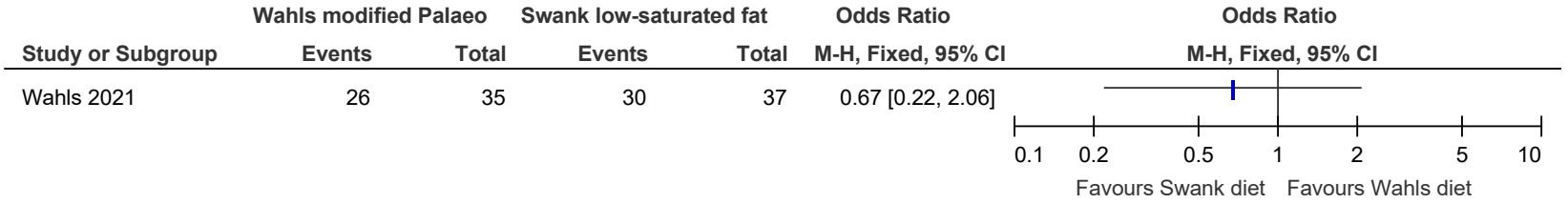


Figure 342: Proportion adherent to diet



E.44 Mindfulness vs. control (usual care)– up to 6 months outcomes

Figure 343: Modified Fatigue Impact Scale – total (0-84; lower better)

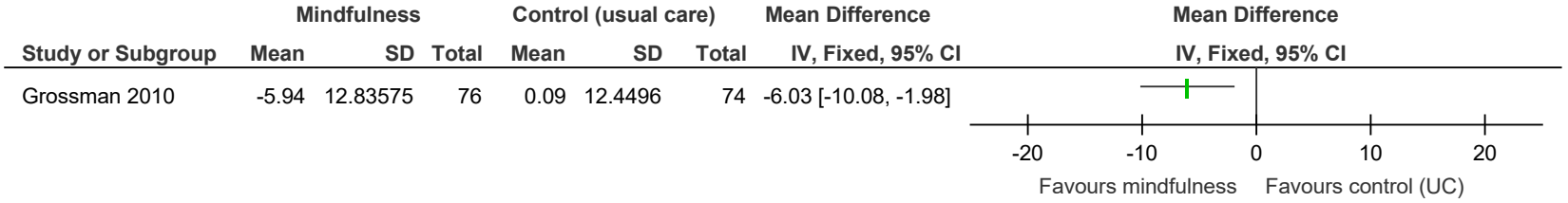


Figure 344: Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS; 1-5; lower better)

	Mindfulness			Control (usual care)			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Grossman 2010	-0.13	0.525696	76	0.05	0.518733	74	-0.18 [-0.35, -0.01]	

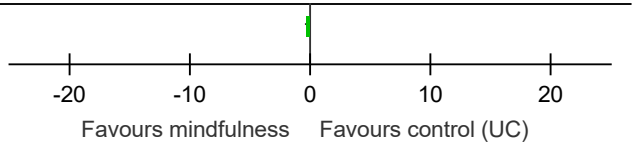
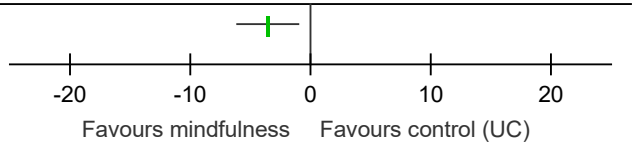


Figure 345: CES-D depression (0-60; lower better)

	Mindfulness			Control (usual care)			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Grossman 2010	-4.63	9.42945	76	-0.86	8.44871	74	-3.77 [-6.63, -0.91]	

Figure 346: STAI anxiety (20-80; lower better)

	Mindfulness			Control (usual care)			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Grossman 2010	-3.68	8.18406	76	-0.13	7.68065	74	-3.55 [-6.09, -1.01]	



E.45 Yoga vs. control – up to 6 months outcomes

Figure 347: Fatigue Severity Scale (1-7; lower better)

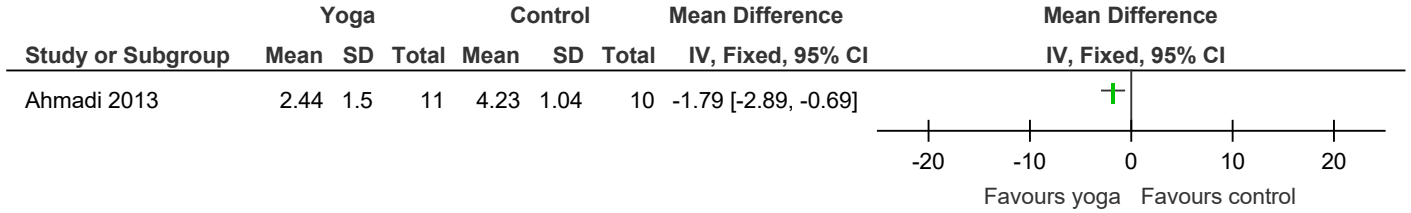


Figure 348: Modified Fatigue Impact Scale – total (0-84; lower better)

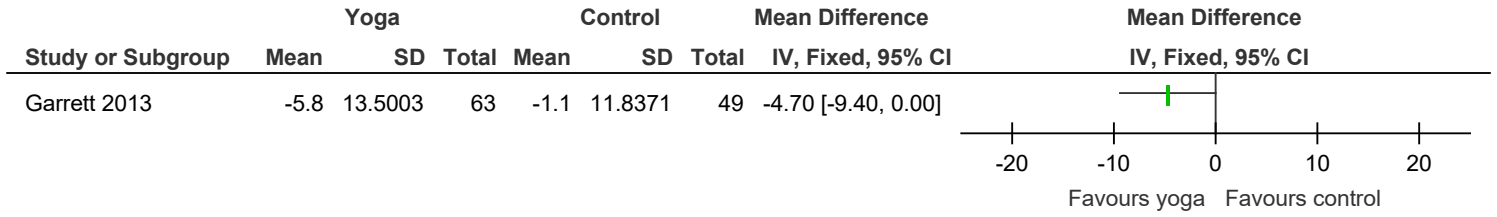


Figure 349: Modified Fatigue Impact Scale – physical (0-36; lower better)

	Yoga			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Garrett 2013	-2.1	6.3531	63	0.4	4.7	49	-2.50 [-4.55, -0.45]	

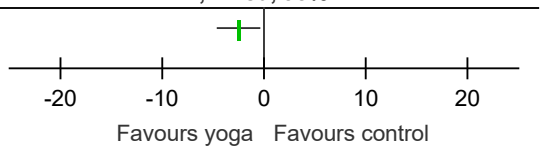


Figure 350: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

	Yoga			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Garrett 2013	-0.96	3.57	63	-0.51	4.18	49	-0.45 [-1.92, 1.02]	

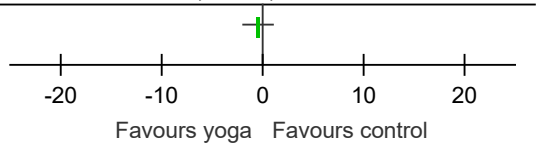


Figure 351: Multidimensional Fatigue Inventory – general fatigue (4-20; lower better)

	Yoga			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	13	2.9	22	14.9	3	20	-1.90 [-3.69, -0.11]	

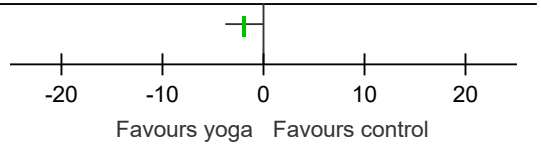


Figure 352: Multidimensional Fatigue Inventory – physical fatigue (4-20; lower better)

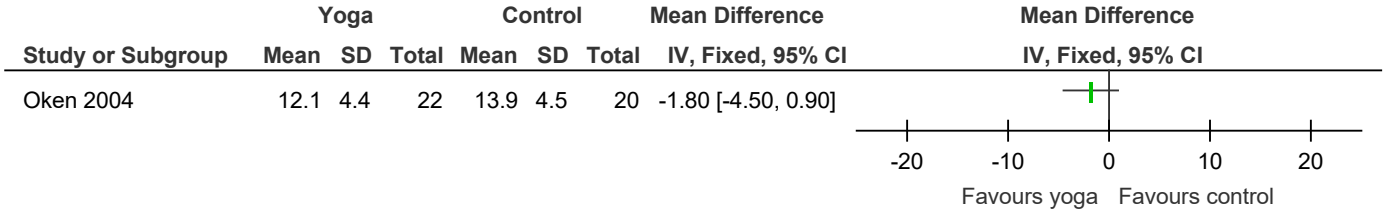


Figure 353: Multidimensional Fatigue Inventory – reduced activity (4-20; lower better)

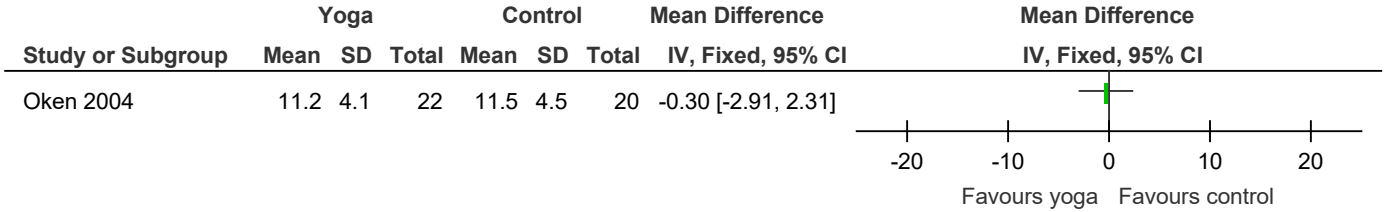


Figure 354: Multidimensional Fatigue Inventory – reduced motivation (4-20; lower better)

	Yoga			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	9.2	3	22	9.8	3	20	-0.60 [-2.42, 1.22]	

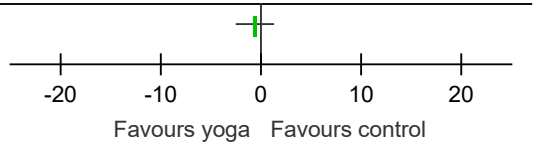


Figure 355: Multidimensional Fatigue Inventory – mental fatigue (4-20; lower better)

	Yoga			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	10.7	4	22	11.2	3.9	20	-0.50 [-2.89, 1.89]	

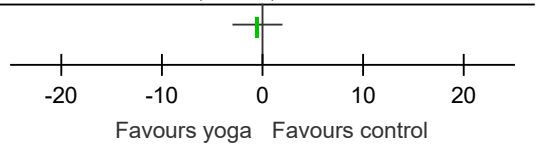


Figure 356: Rhoten Fatigue Scale (0-10; lower better)

	Yoga			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	3.35	0.81	20	3.55	1.23	21	-0.20 [-0.83, 0.43]	

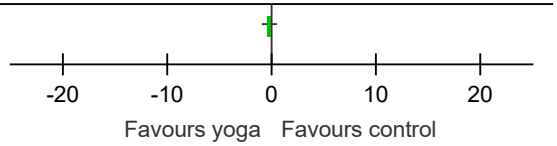


Figure 357: MSQOL-54 physical health composite (0-100; higher better)

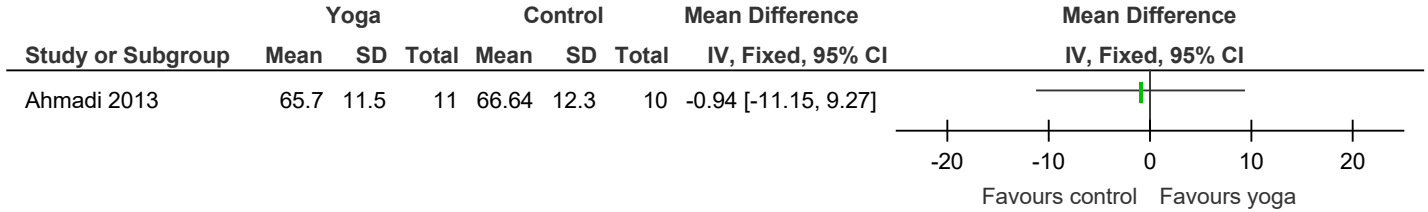


Figure 358: MSQOL-54 mental health composite (0-100; higher better)

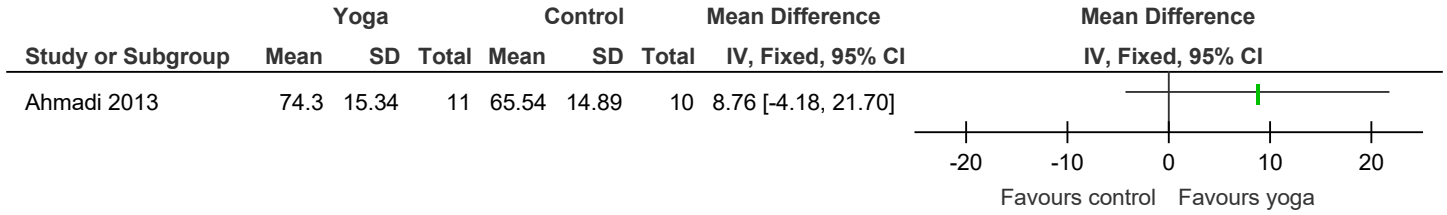


Figure 359: MSQOL-54 change in health domain (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Ahmadi 2013	52.27	23.59	11	52.5	27.51	10	-0.23 [-22.25, 21.79]

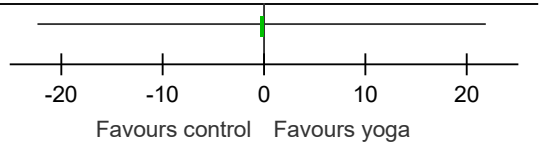


Figure 360: MSIS-29 physical component (0-100; lower better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Garrett 2013	-4	13.8973	63	0.3	14.9704	49	-4.30 [-9.72, 1.12]

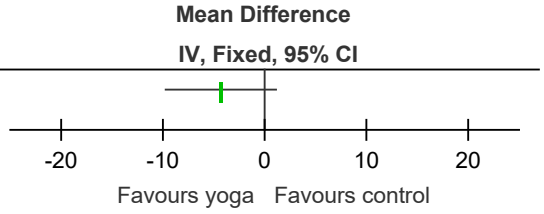


Figure 361: SF-36 physical functioning (0-100; higher better)

	Yoga			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	50.14	11.15	20	38.12	7.88	21	88.8%	12.02 [6.08, 17.96]	
Oken 2004	61	31.6	22	58.1	23.3	20	11.2%	2.90 [-13.79, 19.59]	
Total (95% CI)			**42**			**41**	**100.0%**	**11.00 [5.40, 16.59]**	

Heterogeneity: Chi² = 1.02, df = 1 (P = 0.31); I² = 2%

Test for overall effect: Z = 3.85 (P = 0.0001)

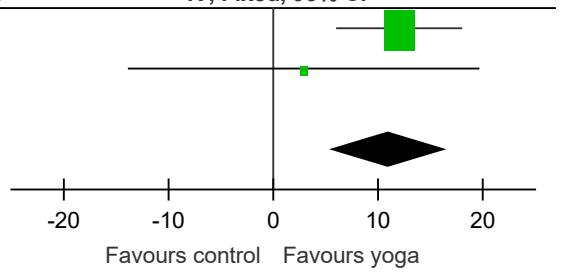


Figure 362: SF-36 emotional limitations (0-100; higher better)

	Yoga			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Hasanpour Dehkordi 2016	35.65	12.3	20	47.15	11.65	21	53.5%	-11.50 [-18.84, -4.16]	
Oken 2004	87.3	24.7	22	72.2	26.6	20	46.5%	15.10 [-0.47, 30.67]	
Total (95% CI)			**42**			**41**	**100.0%**	**0.88 [-25.13, 26.88]**	

Heterogeneity: Tau² = 315.21; Chi² = 9.17, df = 1 (P = 0.002); I² = 89%

Test for overall effect: Z = 0.07 (P = 0.95)

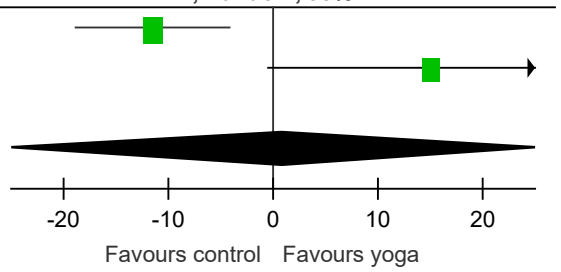


Figure 363: SF-36 physical role limitations (0-100; higher better)

	Yoga			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	45.45	10.32	20	52.14	12.4	21	92.9%	-6.69 [-13.66, 0.28]	
Oken 2004	48.8	39.1	22	52.8	43.6	20	7.1%	-4.00 [-29.14, 21.14]	
Total (95% CI)			**42**			**41**	**100.0%**	**-6.50 [-13.21, 0.22]**	

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 1.90 (P = 0.06)

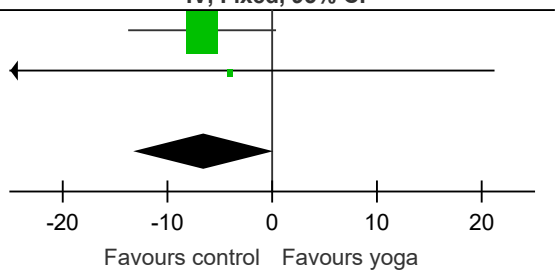


Figure 364: SF-36 energy/vitality (0-100; higher better)

	Yoga			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	52.65	11.87	20	43.32	8.45	21	73.6%	9.33 [3.00, 15.66]	
Oken 2004	51.2	16.7	22	36.7	18.1	20	26.4%	14.50 [3.93, 25.07]	
Total (95% CI)			**42**			**41**	**100.0%**	**10.70 [5.26, 16.13]**	

Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%

Test for overall effect: Z = 3.86 (P = 0.0001)

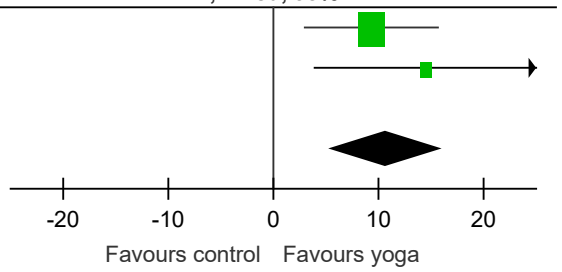


Figure 365: SF-36 mental health (0-100; higher better)

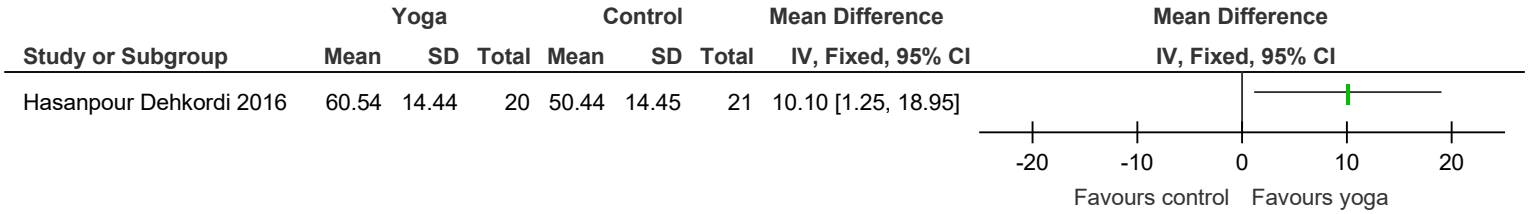


Figure 366: SF-36 social functioning (0-100; higher better)

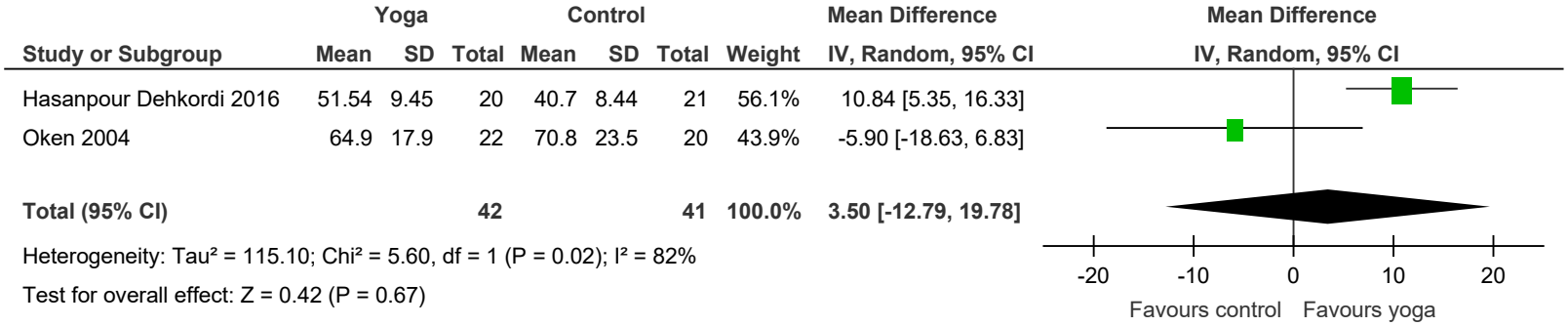


Figure 367: SF-36 body pain (0-100; higher better)

	Yoga			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Hasanpour Dehkordi 2016	38.54	9.25	20	55.71	9.47	21	55.8%	-17.17 [-22.90, -11.44]	
Oken 2004	69.6	17.3	22	68.9	25.3	20	44.2%	0.70 [-12.54, 13.94]	
Total (95% CI)			**42**			**41**	**100.0%**	**-9.27 [-26.67, 8.12]**	

Heterogeneity: Tau² = 132.59; Chi² = 5.90, df = 1 (P = 0.02); I² = 83%

Test for overall effect: Z = 1.04 (P = 0.30)

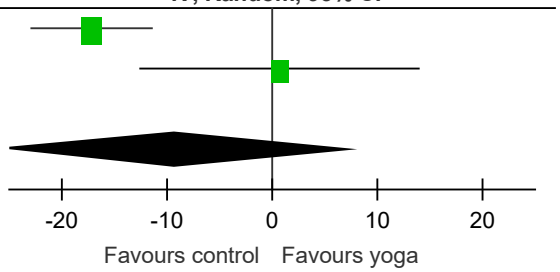


Figure 368: SF-36 general health (0-100; higher better)

	Yoga			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Hasanpour Dehkordi 2016	51.22	8.65	20	42.65	9.25	21	78.8%	8.57 [3.09, 14.05]	
Oken 2004	60.3	18.4	22	55.4	16.5	20	21.2%	4.90 [-5.66, 15.46]	
Total (95% CI)			**42**			**41**	**100.0%**	**7.79 [2.93, 12.65]**	

Heterogeneity: Chi² = 0.37, df = 1 (P = 0.55); I² = 0%

Test for overall effect: Z = 3.14 (P = 0.002)

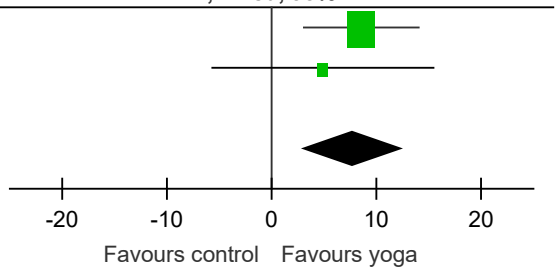


Figure 369: SF-36 health transition (0-100; higher better)

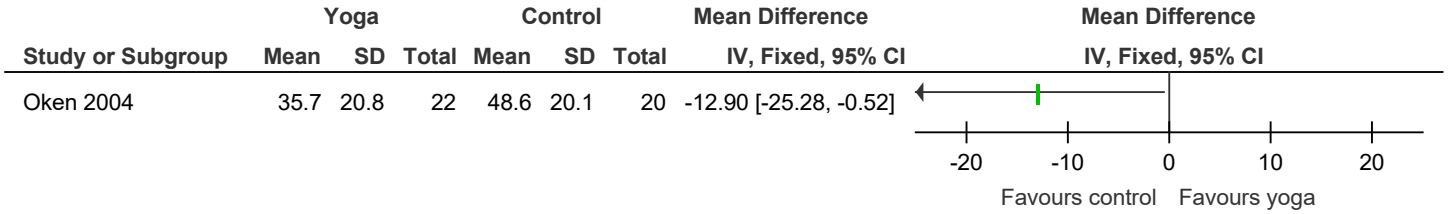


Figure 370: Cognitive – Stroop Colour Word Interference – attention/concentration (higher better)

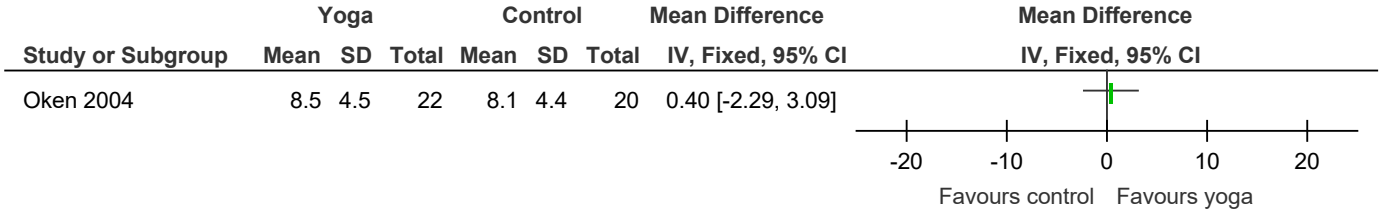


Figure 371: Beck Depression Inventory (0-63; lower better)

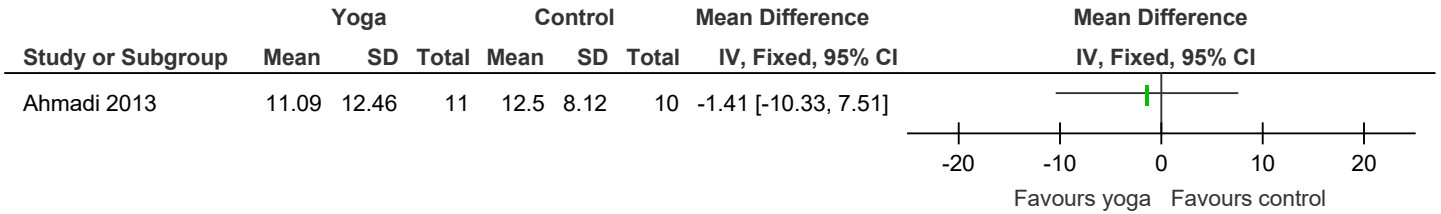


Figure 372: Beck Anxiety Inventory (0-63; lower better)

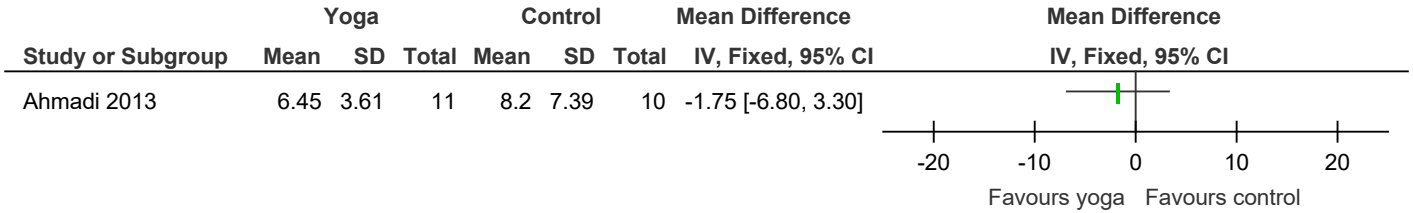


Figure 373: Adverse events leading to withdrawal

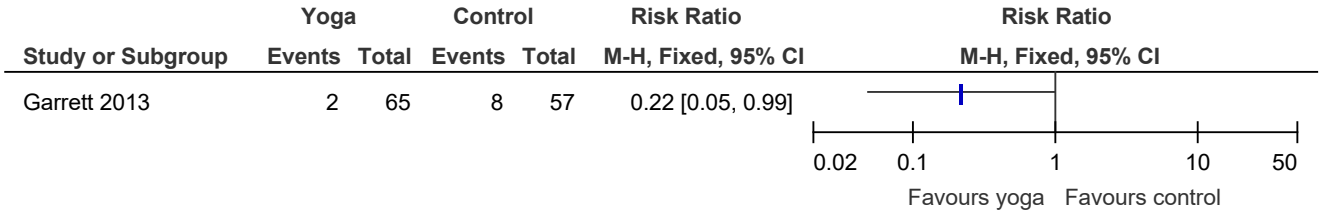
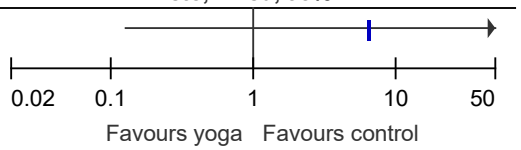


Figure 374: Adverse events (MS exacerbation)

Study or Subgroup	Yoga Events	Yoga Total	Control Events	Control Total	Peto Odds Ratio Peto, Fixed, 95% CI
Oken 2004	1	23	0	20	6.49 [0.13, 329.99]



E.46 Yoga vs. aerobic exercise – up to 6 months outcomes

Figure 375: Fatigue Severity Scale (1-7; lower better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Ahmadi 2013	2.44	1.5	11	1.9	0.73	10	0.54 [-0.46, 1.54]

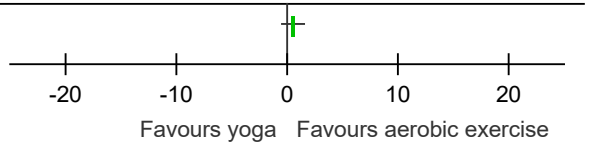


Figure 376: Fatigue Severity Scale (9-63; lower better)

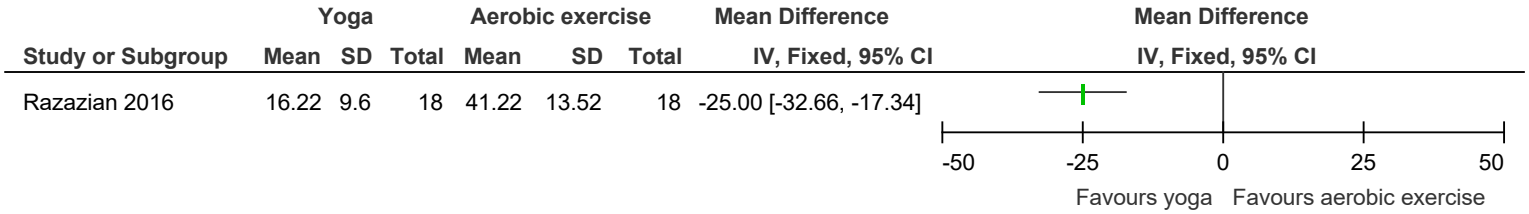


Figure 377: Multidimensional Fatigue Inventory – general fatigue (4-20; lower better)

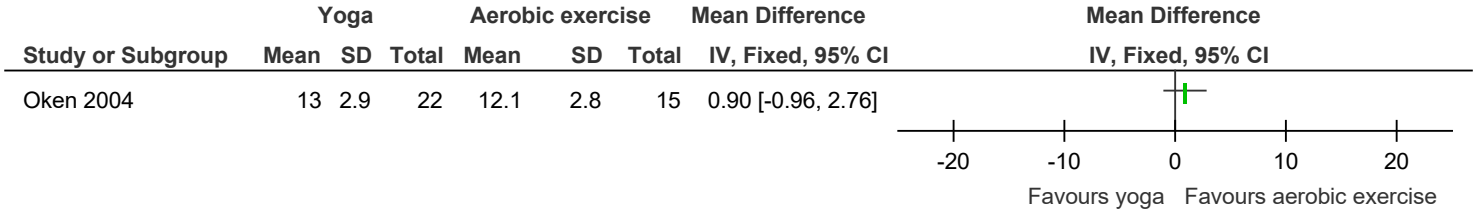


Figure 378: Multidimensional Fatigue Inventory – physical fatigue (4-20; lower better)

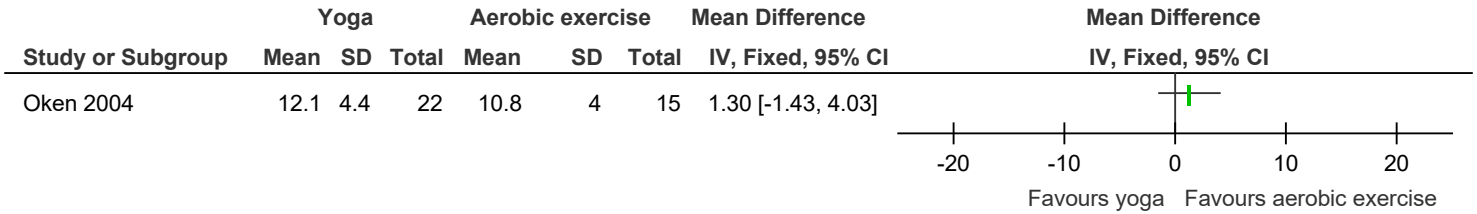


Figure 379: Multidimensional Fatigue Inventory – reduced activity (4-20; lower better)

	Yoga			Aerobic exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	11.2	4.1	22	9.9	3.9	15	1.30 [-1.31, 3.91]	

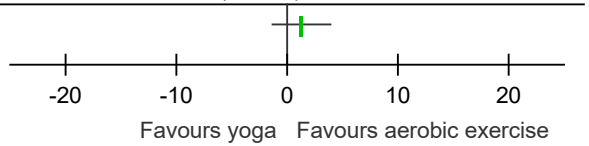


Figure 380: Multidimensional Fatigue Inventory – reduced motivation (4-20; lower better)

	Yoga			Aerobic exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	9.2	3	22	7.7	3.4	15	1.50 [-0.63, 3.63]	

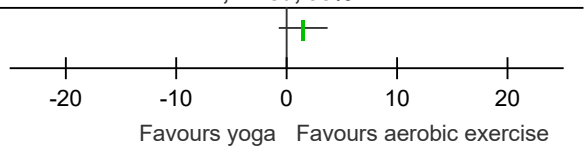


Figure 381: Multidimensional Fatigue Inventory – mental fatigue (4-20; lower better)

	Yoga			Aerobic exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Oken 2004	10.7	4	22	7.8	4.4	15	2.90 [0.12, 5.68]	

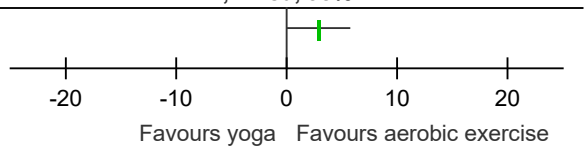


Figure 382: Rhoten Fatigue Scale (0-10; lower better)

	Yoga			Aerobic exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	3.35	0.81	20	2.55	0.94	20	0.80 [0.26, 1.34]	

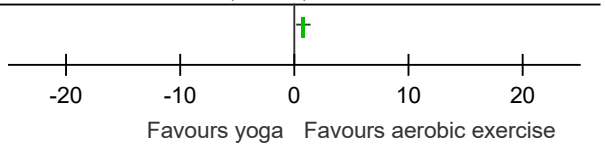


Figure 383: MSQOL-54 physical health composite (0-100; higher better)

	Yoga			Aerobic exercise			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ahmadi 2013	65.7	11.5	11	71.19	10.1	10	-5.49 [-14.73, 3.75]	

Figure 384: MSQOL-54 mental health composite (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Ahmadi 2013	74.3	15.34	11	64.62	15.12	10	9.68 [-3.36, 22.72]

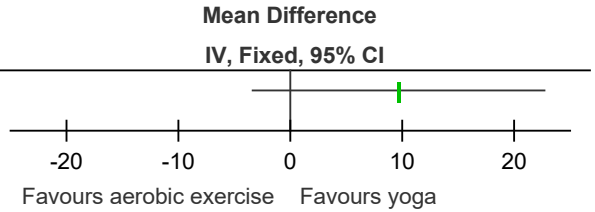


Figure 385: MSQOL-54 change in health domain (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Ahmadi 2013	52.27	23.59	11	52.5	27.51	10	-0.23 [-22.25, 21.79]

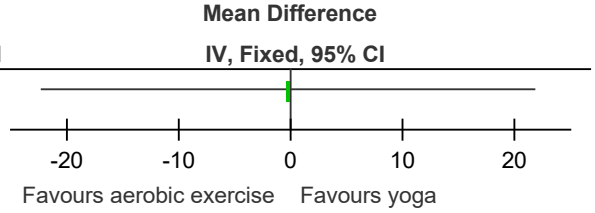


Figure 386: SF-36 physical functioning (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	50.14	11.15	20	52.12	9.87	20	89.8%	-1.98 [-8.51, 4.55]
Oken 2004	61	31.6	22	60	27.9	15	10.2%	1.00 [-18.33, 20.33]
Total (95% CI)			**42**			**35**	**100.0%**	**-1.68 [-7.86, 4.51]**

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%

Test for overall effect: Z = 0.53 (P = 0.60)

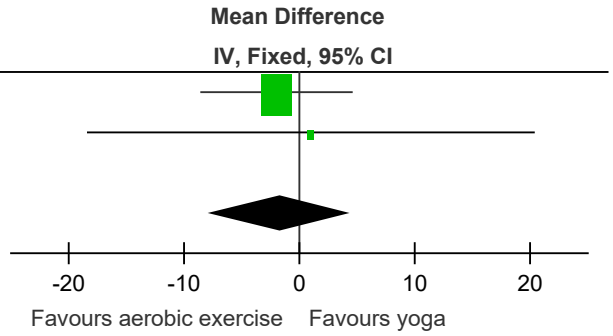


Figure 387: SF-36 emotional limitations (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	35.65	12.3	20	36.23	12.65	20	84.9%	-0.58 [-8.31, 7.15]
Oken 2004	87.3	24.7	22	88.9	30	15	15.1%	-1.60 [-19.96, 16.76]
Total (95% CI)			**42**			**35**	**100.0%**	**-0.73 [-7.86, 6.39]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%

Test for overall effect: Z = 0.20 (P = 0.84)

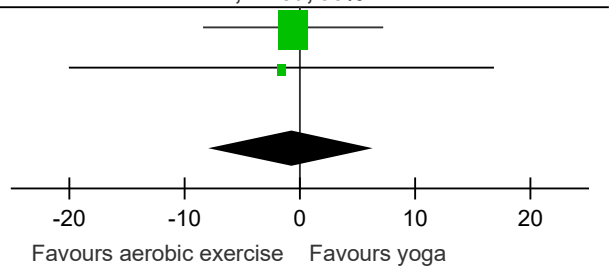


Figure 388: SF-36 physical role limitations (0-100; higher better)

	Yoga			Aerobic exercise				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Hasanpour Dehkordi 2016	45.45	10.32	20	46.14	13.45	20	92.7%	-0.69 [-8.12, 6.74]
Oken 2004	48.8	39.1	22	61.7	41	15	7.3%	-12.90 [-39.31, 13.51]
Total (95% CI)			**42**			**35**	**100.0%**	**-1.59 [-8.74, 5.57]**

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.66)

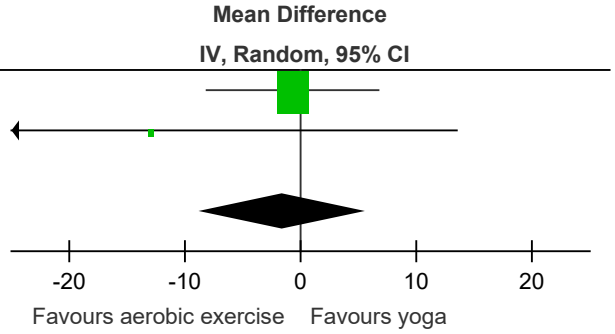


Figure 389: SF-36 energy/vitality (0-100; higher better)

	Yoga			Aerobic exercise				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Hasanpour Dehkordi 2016	52.65	11.87	20	55.24	11.54	20	72.6%	-2.59 [-9.85, 4.67]
Oken 2004	51.2	16.7	22	52.8	18.8	15	27.4%	-1.60 [-13.40, 10.20]
Total (95% CI)			**42**			**35**	**100.0%**	**-2.32 [-8.50, 3.86]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%

Test for overall effect: Z = 0.74 (P = 0.46)

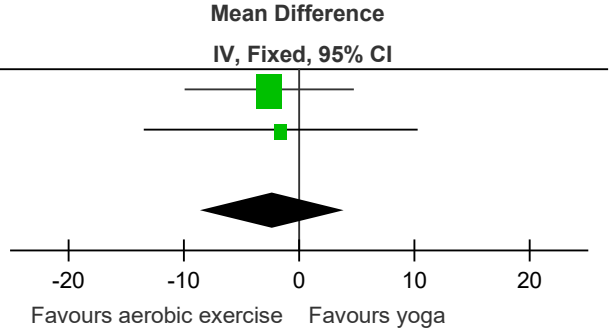


Figure 390: SF-36 mental health (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	60.54	14.44	20	61.78	10.87	20	-1.24 [-9.16, 6.68]

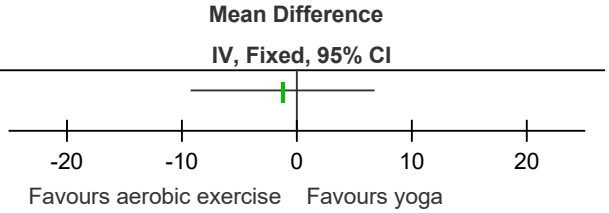


Figure 391: SF-36 social functioning (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Weight	Mean Difference IV, Random, 95% CI
Hasanpour Dehkordi 2016	51.54	9.45	20	47.22	8.78	20	55.0%	4.32 [-1.33, 9.97]
Oken 2004	64.9	17.9	22	81.7	24	15	45.0%	-16.80 [-31.06, -2.54]
Total (95% CI)			**42**			**35**	**100.0%**	**-5.18 [-25.78, 15.41]**

Heterogeneity: Tau² = 192.39; Chi² = 7.28, df = 1 (P = 0.007); I² = 86%

Test for overall effect: Z = 0.49 (P = 0.62)

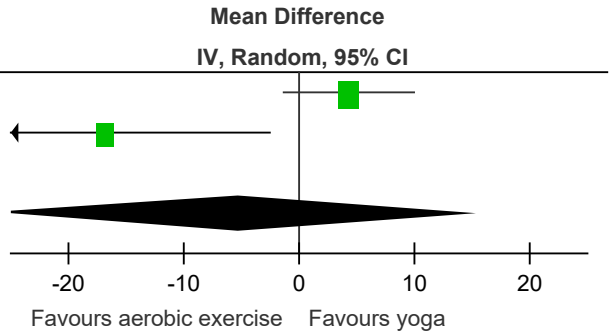


Figure 392: SF-36 body pain (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	38.54	9.25	20	39.65	11.19	20	76.2%	-1.11 [-7.47, 5.25]
Oken 2004	69.6	17.3	22	70.8	17.4	15	23.8%	-1.20 [-12.59, 10.19]
Total (95% CI)			**42**			**35**	**100.0%**	**-1.13 [-6.69, 4.42]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%

Test for overall effect: Z = 0.40 (P = 0.69)

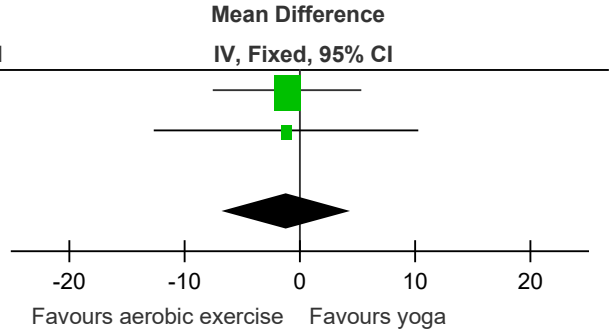


Figure 393: SF-36 general health (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Weight	Mean Difference IV, Fixed, 95% CI
Hasanpour Dehkordi 2016	51.22	8.65	20	55.23	10.96	20	76.9%	-4.01 [-10.13, 2.11]
Oken 2004	60.3	18.4	22	61	16	15	23.1%	-0.70 [-11.87, 10.47]
Total (95% CI)			**42**			**35**	**100.0%**	**-3.25 [-8.61, 2.12]**

Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%

Test for overall effect: Z = 1.19 (P = 0.24)

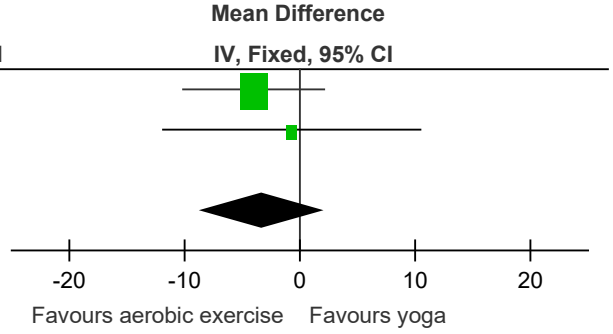


Figure 394: SF-36 health transition (0-100; higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Oken 2004	35.7	20.8	22	36.7	28.1	15	-1.00 [-17.67, 15.67]

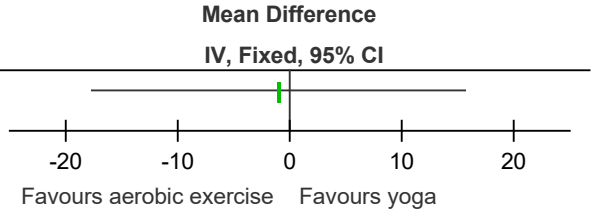


Figure 395: Beck Depression Inventory (0-63; lower better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Weight	Mean Difference IV, Random, 95% CI
Ahmadi 2013	11.09	12.46	11	5.6	3.4	10	48.7%	5.49 [-2.17, 13.15]
Razazian 2016	5.06	2.92	18	21.33	6.88	18	51.3%	-16.27 [-19.72, -12.82]
Total (95% CI)			**29**			**28**	**100.0%**	**-5.67 [-26.99, 15.65]**

Heterogeneity: Tau² = 227.56; Chi² = 25.77, df = 1 (P < 0.00001); I² = 96%

Test for overall effect: Z = 0.52 (P = 0.60)

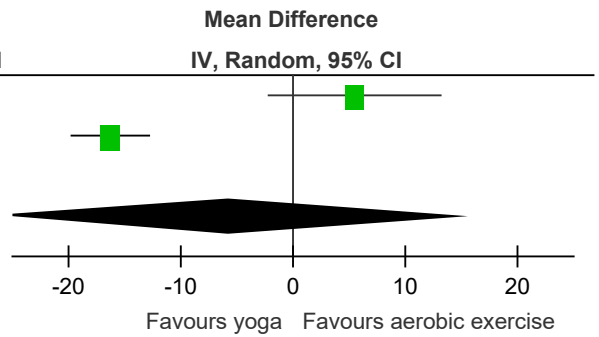


Figure 396: Beck Anxiety Inventory (0-63; lower better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Ahmadi 2013	6.45	3.61	11	6.1	4.95	10	0.35 [-3.39, 4.09]

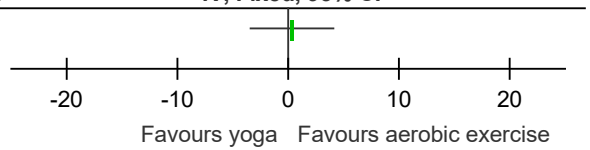


Figure 397: Cognitive – Stroop Colour Word Interference (higher better)

Study or Subgroup	Yoga Mean	Yoga SD	Yoga Total	Aerobic exercise Mean	Aerobic exercise SD	Aerobic exercise Total	Mean Difference IV, Fixed, 95% CI
Oken 2004	8.5	4.5	22	9.9	6.2	20	-1.40 [-4.70, 1.90]

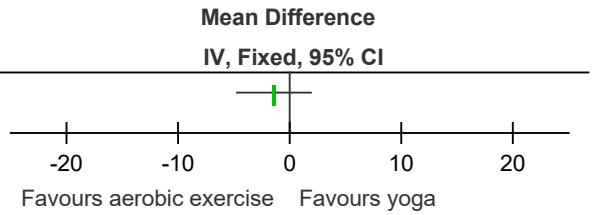
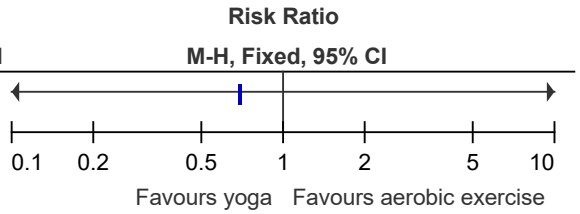


Figure 398: Adverse events (MS exacerbation)

Study or Subgroup	Yoga Events	Yoga Total	Aerobic exercise Events	Aerobic exercise Total	Risk Ratio M-H, Fixed, 95% CI
Oken 2004	1	23	1	16	0.70 [0.05, 10.32]



E.47 Pilates vs. control (waitlist, no intervention) – up to 6 months outcomes

Figure 399: Modified Fatigue Impact Scale – total (0-84; lower better)

	Pilates			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Eftekhari 2018	6.46	3.55	13	10.5	4.18	12	42.1%	-4.04 [-7.09, -0.99]	
Fleming 2019	24.4	10.3	9	48.3	13.7	6	22.3%	-23.90 [-36.76, -11.04]	
Fleming 2021	31	13.5	39	40.5	15.8	41	35.6%	-9.50 [-15.93, -3.07]	
Total (95% CI)			**61**			**59**	**100.0%**	**-10.40 [-18.98, -1.82]**	

Heterogeneity: Tau² = 43.05; Chi² = 10.15, df = 2 (P = 0.006); I² = 80%

Test for overall effect: Z = 2.38 (P = 0.02)

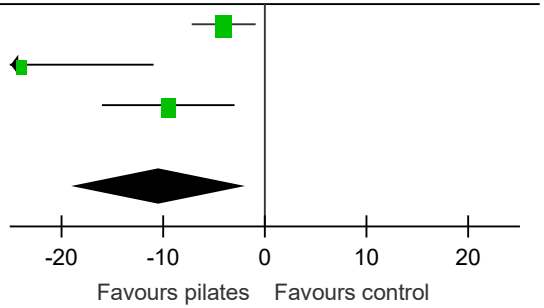


Figure 400: Modified Fatigue Impact Scale – physical (0-36; lower better)

	Pilates			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fleming 2019	13.1	4.2	9	22.8	6.7	6	21.0%	-9.70 [-15.72, -3.68]	
Fleming 2021	16.1	6.2	39	21.3	7.9	41	79.0%	-5.20 [-8.30, -2.10]	
Total (95% CI)			**48**			**47**	**100.0%**	**-6.14 [-8.90, -3.39]**	

Heterogeneity: Chi² = 1.69, df = 1 (P = 0.19); I² = 41%

Test for overall effect: Z = 4.36 (P < 0.0001)

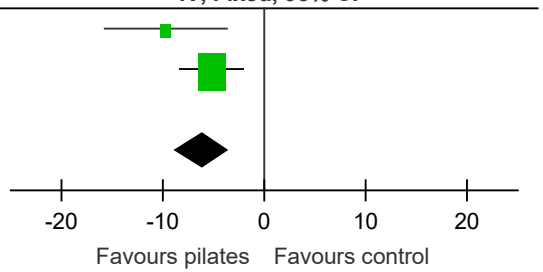


Figure 401: Modified Fatigue Impact Scale – cognitive (0-40; lower better)

	Pilates			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fleming 2019	8.9	7.3	9	20.8	9.4	6	37.7%	-11.90 [-20.81, -2.99]	
Fleming 2021	11.7	8.3	39	15.3	9	41	62.3%	-3.60 [-7.39, 0.19]	
Total (95% CI)			**48**			**47**	**100.0%**	**-6.73 [-14.62, 1.15]**	

Heterogeneity: Tau² = 22.25; Chi² = 2.82, df = 1 (P = 0.09); I² = 65%

Test for overall effect: Z = 1.67 (P = 0.09)

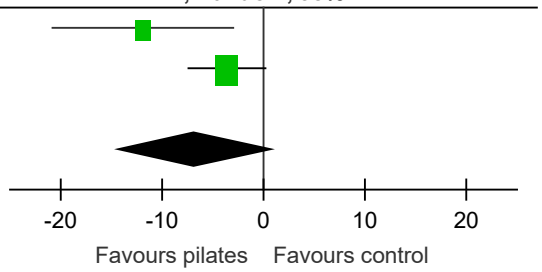


Figure 402: Modified Fatigue Impact Scale – psychosocial (0-8; lower better)

	Pilates			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fleming 2019	2.3	1.3	9	4.7	0.8	6	48.2%	-2.40 [-3.46, -1.34]	
Fleming 2021	3.2	1.8	39	4	2.2	41	51.8%	-0.80 [-1.68, 0.08]	
Total (95% CI)			**48**			**47**	**100.0%**	**-1.57 [-3.14, -0.00]**	

Heterogeneity: Tau² = 1.03; Chi² = 5.17, df = 1 (P = 0.02); I² = 81%

Test for overall effect: Z = 1.96 (P = 0.05)

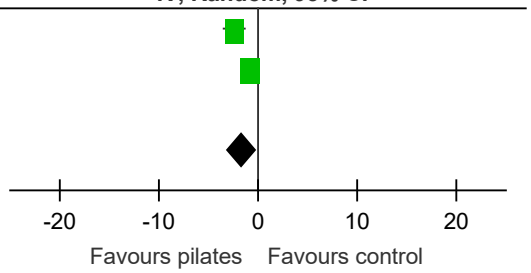


Figure 403: STAY-Y1 anxiety (20-80; lower better)

	Pilates			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fleming 2019	24.5	3.8	9	43	7.3	6	-18.50 [-24.85, -12.15]	

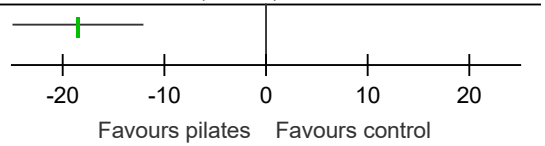


Figure 404: STAY-Y2 anxiety (20-80; lower better)

	Pilates			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fleming 2019	32.6	8.7	9	48.5	14.2	6	40.9%	-15.90 [-28.60, -3.20]	
Fleming 2021	37.1	9.1	39	38.7	10.2	41	59.1%	-1.60 [-5.83, 2.63]	
Total (95% CI)			**48**			**47**	**100.0%**	**-7.44 [-21.22, 6.33]**	

Heterogeneity: Tau² = 78.91; Chi² = 4.38, df = 1 (P = 0.04); I² = 77%

Test for overall effect: Z = 1.06 (P = 0.29)

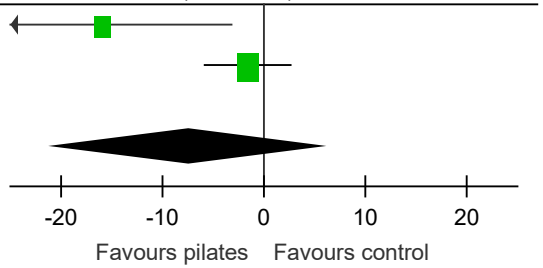


Figure 405: HADS – anxiety (0-21; lower better)

	Pilates			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Fleming 2019	13	2	9	10.7	2.7	6	44.6%	2.30 [-0.22, 4.82]	
Fleming 2021	5.1	3	39	5.8	4.3	41	55.4%	-0.70 [-2.32, 0.92]	
Total (95% CI)			**48**			**47**	**100.0%**	**0.64 [-2.29, 3.56]**	

Heterogeneity: Tau² = 3.33; Chi² = 3.84, df = 1 (P = 0.05); I² = 74%

Test for overall effect: Z = 0.43 (P = 0.67)

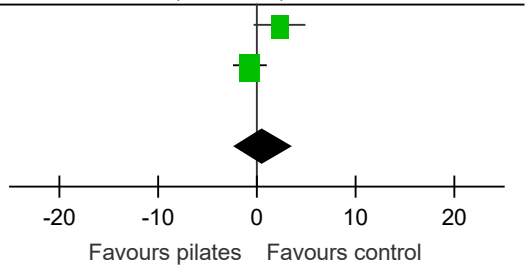


Figure 406: HADS depression (0-21; lower better)

Study or Subgroup	Pilates Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fleming 2019	4	5.9	9	9.3	2.7	6	35.6%	-5.30 [-9.72, -0.88]
Fleming 2021	4	3.1	39	5.3	3	41	64.4%	-1.30 [-2.64, 0.04]
Total (95% CI)			**48**			**47**	**100.0%**	**-2.72 [-6.48, 1.03]**

Heterogeneity: Tau² = 5.23; Chi² = 2.88, df = 1 (P = 0.09); I² = 65%

Test for overall effect: Z = 1.42 (P = 0.16)

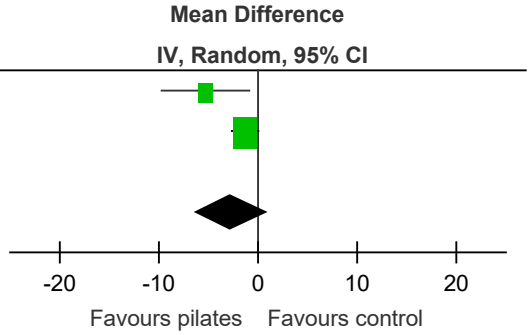


Figure 407: QIDS depression (0-27; lower better)

Study or Subgroup	Pilates Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fleming 2019	4.3	3.2	9	9.5	7.1	6	5.2%	-5.20 [-11.25, 0.85]
Fleming 2021	5.1	2.7	39	7.4	3.7	41	94.8%	-2.30 [-3.71, -0.89]
Total (95% CI)			**48**			**47**	**100.0%**	**-2.45 [-3.83, -1.07]**

Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%

Test for overall effect: Z = 3.49 (P = 0.0005)

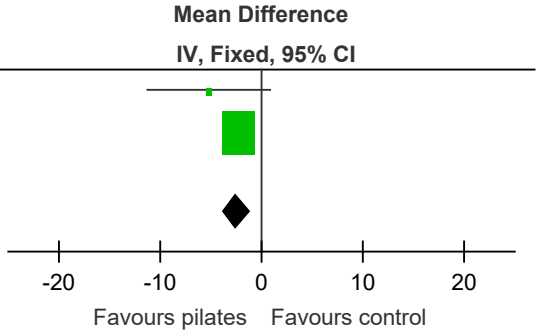


Figure 408: POMS-B total mood (scale unclear; lower better)

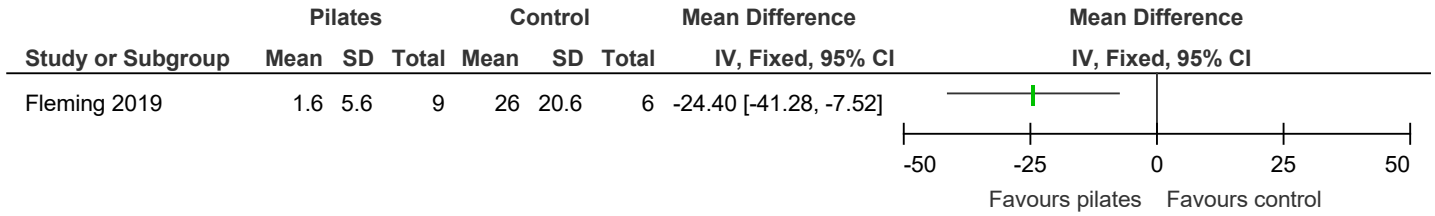


Figure 409: POMS-B depression (scale unclear; lower better)

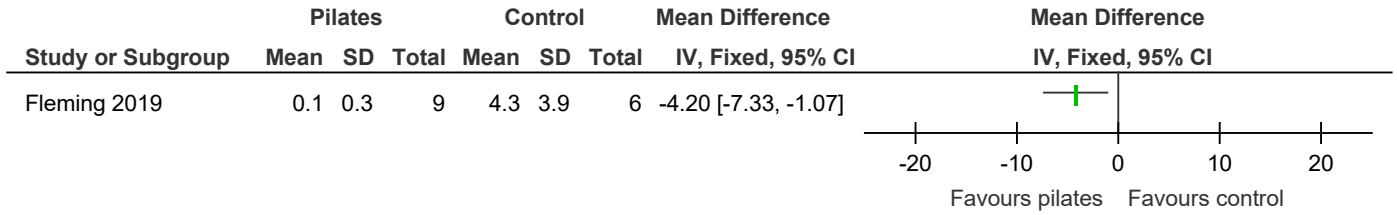


Figure 410: POMS-B fatigue (scale unclear; lower better)

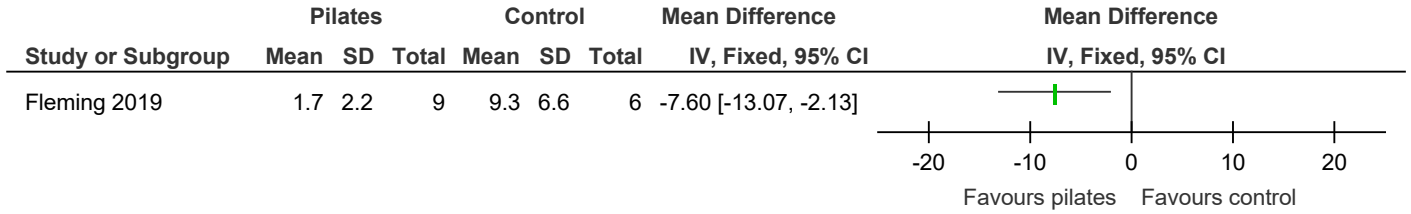


Figure 411: Adverse events

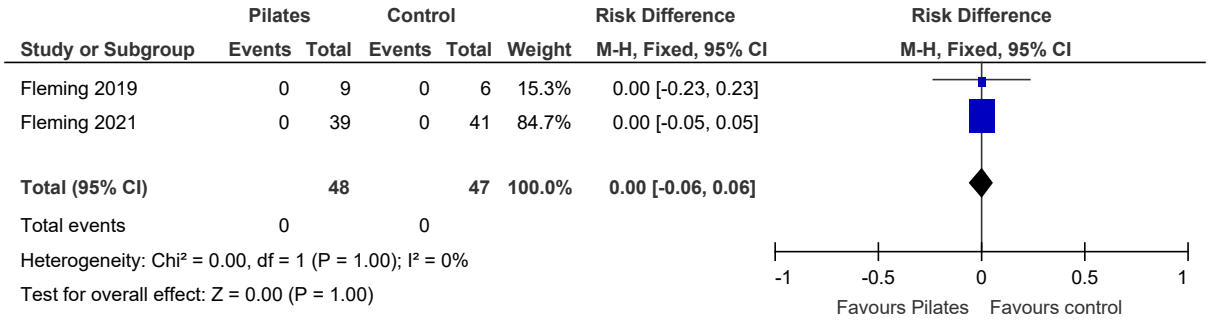
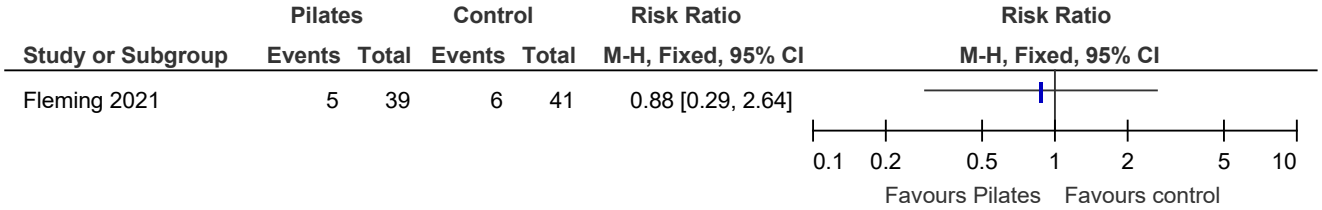


Figure 412: Discontinuation possibly related to intervention



E.48 Pilates vs. resistance + balance exercises – up to 6 months outcomes

Figure 413: Modified Fatigue Impact Scale physical (0-36; lower better)

	Pilates			Resist. + balance exercis			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Kucuk 2016	7.18	3.63	11	7.44	5.27	9	-0.26 [-4.32, 3.80]	

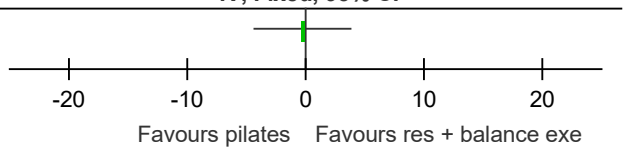


Figure 414: Modified Fatigue Impact Scale cognitive (0-40; lower better)

	Pilates			Resist. + balance exercis			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Kucuk 2016	5.82	5.04	11	7.33	6.6	9	-1.51 [-6.75, 3.73]	

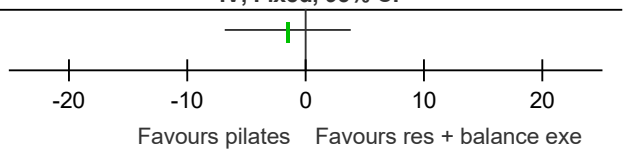


Figure 415: Modified Fatigue Impact Scale cognitive (0-8; lower better)

	Pilates			Resist. + balance exercis			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Kucuk 2016	7.64	9.6	11	13.11	10.24	9	-5.47 [-14.24, 3.30]

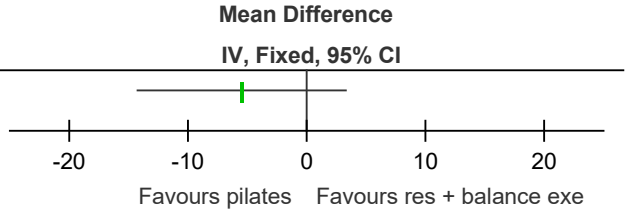


Figure 416: Multiple Sclerosis International Quality of Life questionnaire (MusiQoL; 0-100; higher better)

	Pilates			Resist. + balance exercis			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Kucuk 2016	23.82	7.53	11	40.05	17.96	9	-16.23 [-28.78, -3.68]

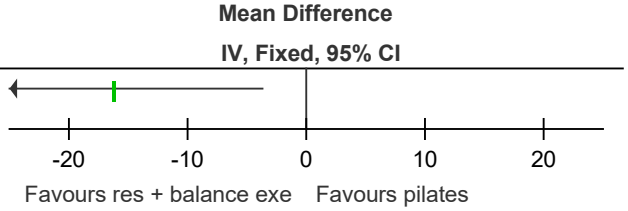


Figure 417: Cognitive – PASAT (higher better)

	Pilates			Resist. + balance exercis			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Kucuk 2016	47.82	11.21	11	27.89	13.17	9	19.93 [9.07, 30.79]

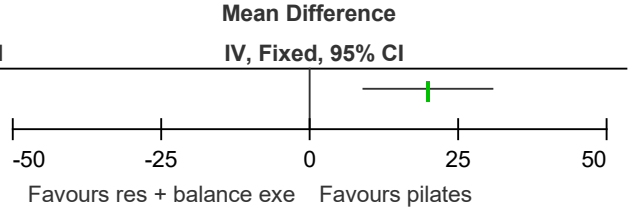
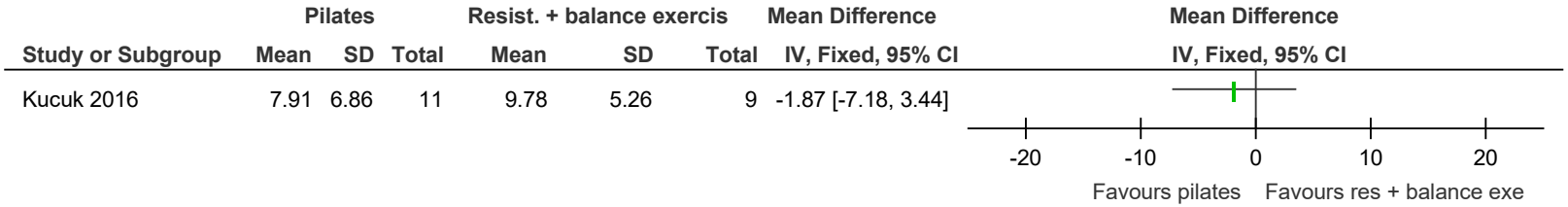


Figure 418: Beck Depression Inventory (0-63; lower better)



E.49 Pilates + balance training vs. relaxation – up to 6 months outcomes

Note other outcomes for this study were median values only and are reported in the results section of the report.

Figure 419: Adverse or harmful events

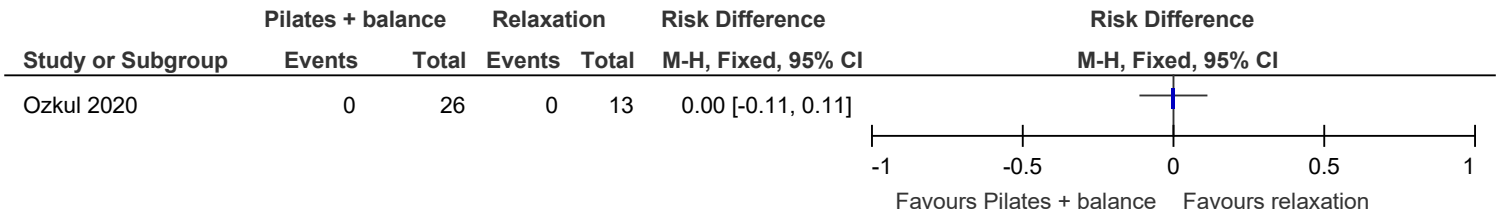
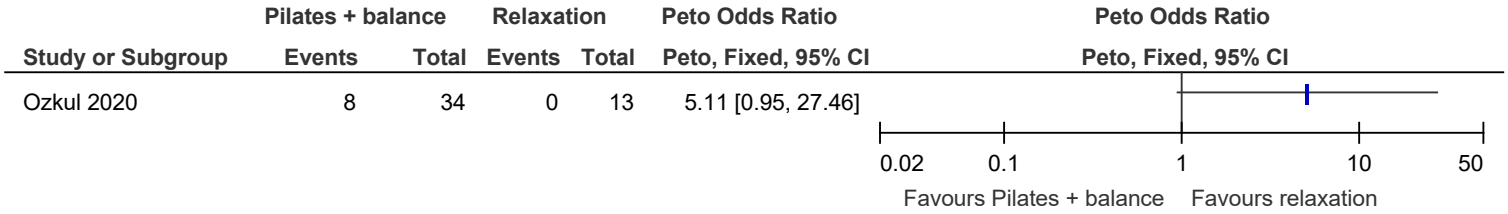
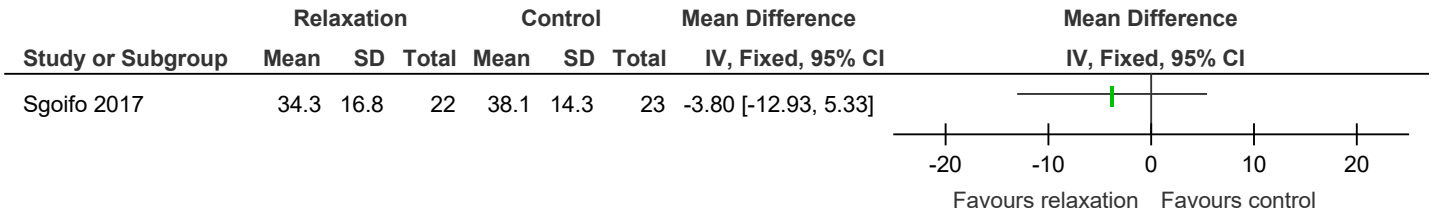


Figure 420: Adherence – discontinuation due to work intensity



E.50 Relaxation vs. control (waitlist) – up to 6 months outcomes

Figure 421: Modified Fatigue Impact Scale – total (0-84; lower better)



E.51 Acupressure vs. control (touching only/sham) – up to 6 months outcomes

Figure 422: Fatigue Severity Scale (scale used unclear; lower better)

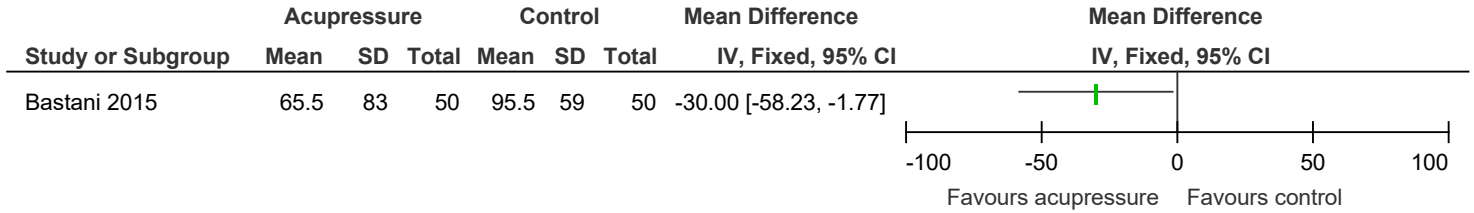


Figure 423: Fatigue Severity Scale (scale 1-7; lower better)

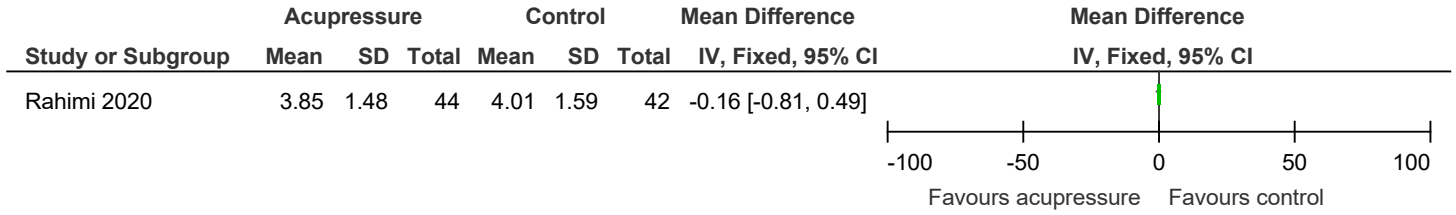
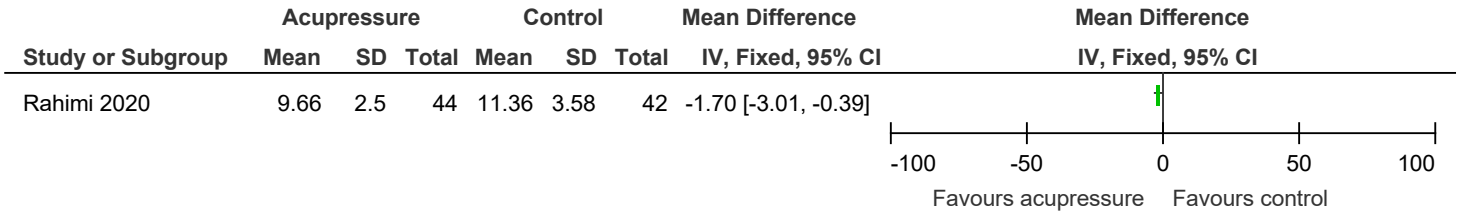


Figure 424: Depression - DASS-42 (scale 0-42; lower better)



E.52 Reflexology/relaxation vs. control (usual care) – up to 6 months outcomes

Figure 425: Fatigue Severity Scale (1-7; lower better)

	Reflexology/relaxation			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
46.1.1 Foot reflexology vs. control								
Dilek Dogan 2021	2.62	1.35	30	4.97	1.8	30	27.8%	-2.35 [-3.16, -1.54]
Nazari 2015	2.89	0.94	25	4.74	0.86	25	72.2%	-1.85 [-2.35, -1.35]
Subtotal (95% CI)			**55**			**55**	**100.0%**	**-1.99 [-2.41, -1.56]**
Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² = 7%								
Test for overall effect: Z = 9.19 (P < 0.00001)								
46.1.2 Relaxation vs. control								
Nazari 2015	4.27	0.78	25	4.74	0.86	25	100.0%	-0.47 [-0.93, -0.01]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-0.47 [-0.93, -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.02 (P = 0.04)								

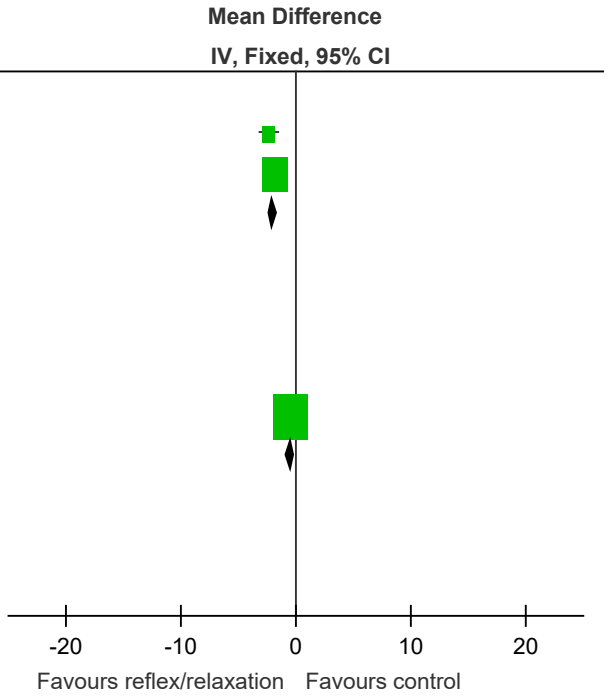


Figure 426: MSQoL-54 physical composite (0-100 usually; higher better)

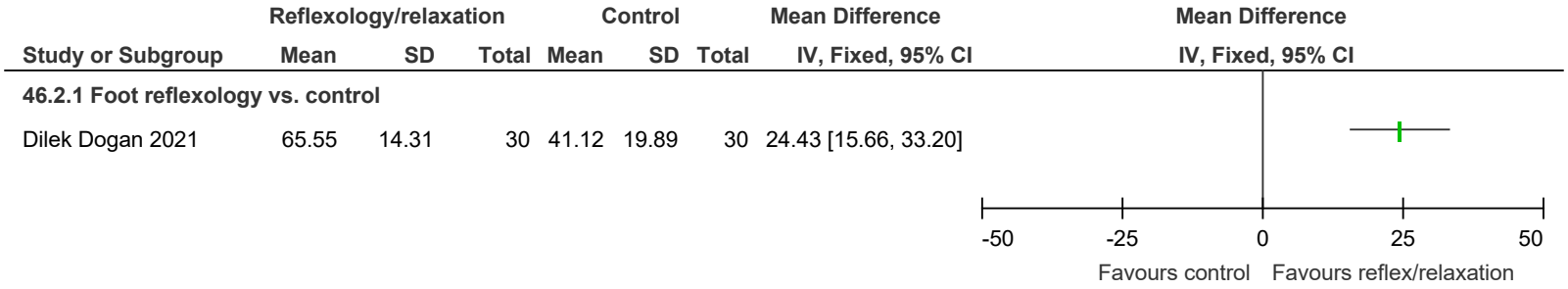


Figure 427: MSQoL-54 mental composite (0-100 usually; higher better)

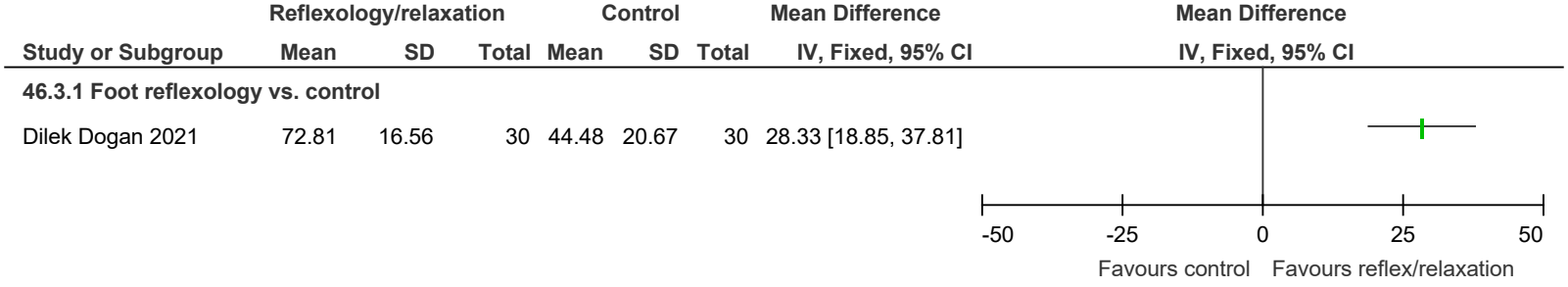
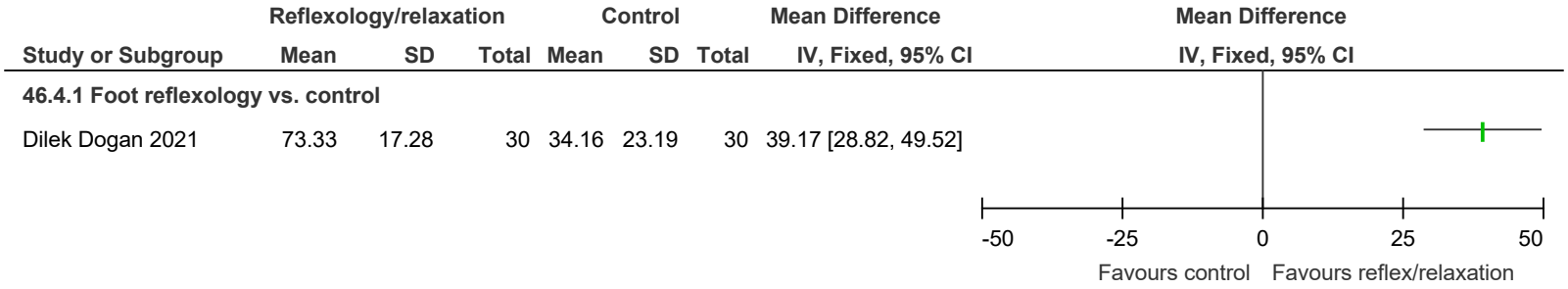


Figure 428: MSQoL-54 health change (0-100 usually; higher better)



E.53 Massage vs. control (usual care) – up to 6 months outcomes

Figure 429: Fatigue Severity Scale (9-63; lower better)

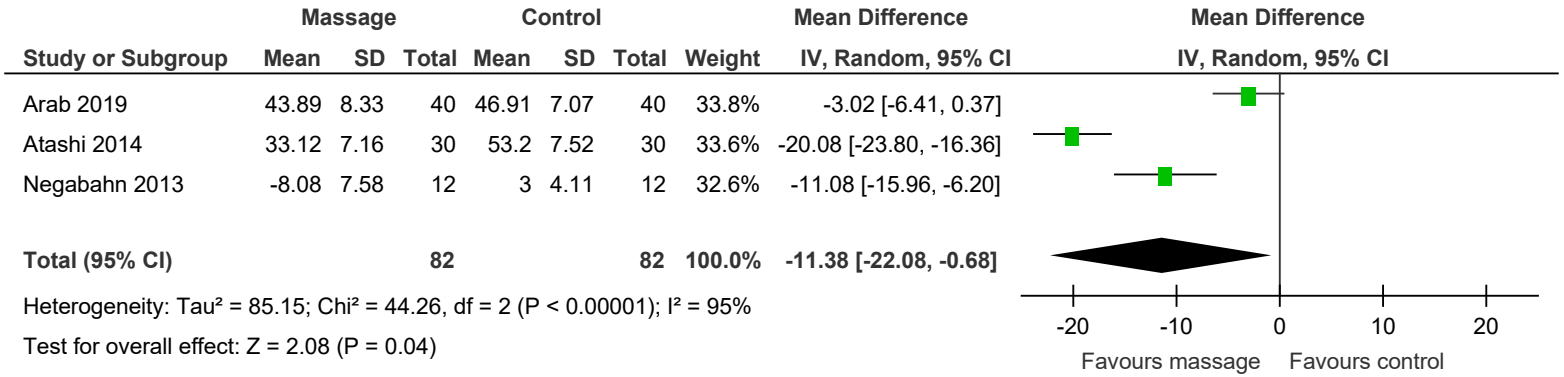


Figure 430: Fatigue relief and effectiveness of fatigue reduction VAS (scale 0-10; higher better)

	Massage			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Arab 2019	6.85	2.33	40	5.55	3.07	40	1.30 [0.11, 2.49]	

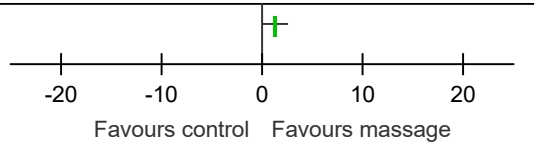
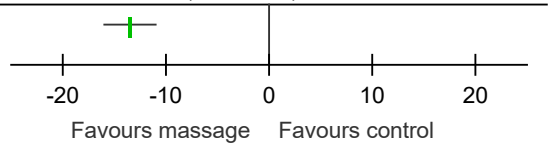


Figure 431: Anxiety – Spielberger Overt Anxiety Questionnaire (scale 20-80; lower better)

	Massage			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Atashi 2014	38.65	5.11	30	52.13	4.71	30	-13.48 [-15.97, -10.99]	



E.54 Reflexology vs. non-specialised foot massage – up to 6 months outcomes

Figure 432: Fatigue Impact Scale (lower better)

Study or Subgroup	Reflexology Mean	SD	Total	Non-speciali foot massage Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
47.1.1 Total score (0-160)							
Sajadi 2020	67.76	32.24	33	81.33	38.56	30	-13.57 [-31.22, 4.08]
47.1.2 Physical subscale (0-40)							
Sajadi 2020	17.24	8.12	33	22.3	11.06	30	-5.06 [-9.89, -0.23]
47.1.3 Cognitive subscale (0-40)							
Sajadi 2020	17.55	9.23	33	19.53	11.09	30	-1.98 [-7.05, 3.09]
47.1.4 Psychosocial scale (0-80)							
Sajadi 2020	33.27	17.08	33	40.1	20.59	30	-6.83 [-16.22, 2.56]

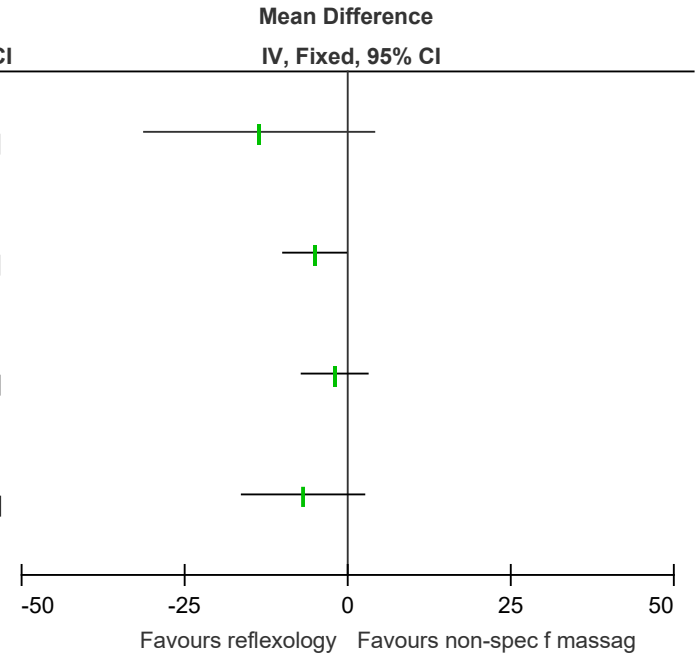
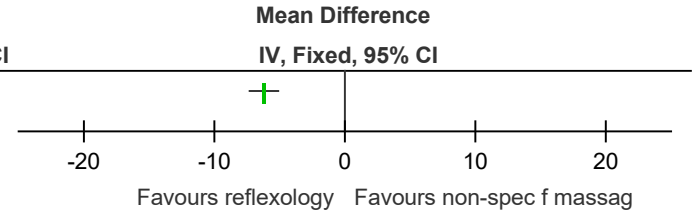


Figure 433: State Anxiety Inventory (20-80; lower better)

Study or Subgroup	Reflexology Mean	SD	Total	Non-speciali foot massage Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Sajadi 2020	43.3	2.06	33	49.5	2.35	30	-6.20 [-7.30, -5.10]



Appendix F – GRADE tables

Table 33: Clinical evidence profile: Aerobic exercise vs. control – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-7) (follow up: range 4 weeks to 26 weeks; Scale from: 1 to 7)												
4	randomised trials	very serious [a]	very serious [b]	not serious	serious [c,d]	none	68	61	-	MD **0.71 lower** (1.87 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: range 7 weeks to 12 weeks; Scale from: 9 to 63)												
3	randomised trials	very serious [a]	very serious [b]	serious [e]	serious [c,f]	none	114	69	-	MD **7.59 lower** (17.64 lower to 2.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - total (0-84) (follow up: range 8 weeks to 26 weeks; Scale from: 0 to 84)												
3	randomised trials	very serious [a]	very serious [b]	serious [e]	serious [c,g]	none	65	60	-	MD **3.21 lower** (12.34 lower to 5.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - physical (0-36) (follow up: 8 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [c,h]	none	15	13	-	MD **4.8 lower** (9.69 lower to 0.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - cognitive (0-40) (follow up: 8 weeks; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [e]	serious [c,i]	none	15	13	-	MD **4.3 lower** (9.38 lower to 0.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - psychosocial (0-8) (follow up: 8 weeks; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	serious [e]	very serious [c,j]	none	15	13	-	MD **0.1 lower** (1.3 lower to 1.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue subscale of Checklist Individual Strength-20 (8-56) (follow up: 26 weeks; Scale from: 8 to 56)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,k]	none	37	34	-	MD **0.4 lower** (4.82 lower to 4.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale for Motor and Cognitive Challenge (FSMC) - physical (10-50) (follow up: 12 weeks; Scale from: 10 to 50)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,l]	none	21	21	-	MD **3.4 lower** (9 lower to 2.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale for Motor and Cognitive Challenge (FSMC) - cognitive (10-50) (follow up: 12 weeks; Scale from: 10 to 50)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,m]	none	21	21	-	MD **0.9 lower** (7.81 lower to 6.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Rhoten Fatigue Scale (0-10) (follow up: 12 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,n]	none	20	21	-	MD **1 lower** (1.67 lower to 0.33 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact Scale (0-160) (follow up: 24 weeks; Scale from: 0 to 160)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,o]	none	69	69	-	MD **8.21 lower** (19.44 lower to 3.02 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - general fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,p]	none	15	20	-	MD **2.8 lower** (4.73 lower to 0.87 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - physical fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,q]	none	15	20	-	MD **3.1 lower** (5.93 lower to 0.27 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - reduced activity (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,r]	none	15	20	-	MD **1.6 lower** (4.39 lower to 1.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - reduced motivation (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,s]	none	15	20	-	MD **2.1 lower** (4.27 lower to 0.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - mental fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,t]	none	15	20	-	MD **3.4 lower** (6.21 lower to 0.59 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 physical composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [e]	very serious [c,u]	none	10	10	-	MD **5.15 higher** (4.71 lower to 15.01 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MSQOL-54 mental composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	serious [e]	very serious [c,v]	none	10	10	-	MD **1.92 lower** (15.07 lower to 11.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MSQOL-54 change in health domain (0-100) (follow up: 8 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	serious [e]	very serious [c,w]	none	10	10	-	MD **0** (24.11 lower to 24.11 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MSIS-29 - physical (0-100) (follow up: range 12 weeks to 24 weeks; Scale from: 0 to 100)

2	randomised trials	very serious [a]	not serious	not serious	serious [c,x]	none	90	90	-	MD **5.75 lower** (11.5 lower to 0.01 lower)	⨁◯◯◯ VERY LOW	CRITICAL

MSIS-29 - psychological (0-100) (follow up: range 12 weeks to 24 weeks; Scale from: 0 to 100)

2	randomised trials	very serious [a]	not serious	not serious	not serious [y]	none	90	90	-	MD **3.36 lower** (9.18 lower to 2.47 higher)	⨁⨁◯◯ LOW	CRITICAL

SF-36 physical functioning (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)

2	randomised trials	very serious [a]	serious [z]	not serious	serious [aa,c]	none	35	41	-	MD **10.89 higher** (0.53 higher to 21.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 emotional limitations (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	very serious [b]	not serious	very serious [ab,c]	none	35	41	-	MD **0.85 higher** (25.92 lower to 27.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical role limitations (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	serious [z]	not serious	serious [ac,c]	none	35	41	-	MD **4.91 lower** (12.54 lower to 2.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 energy/vitality (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [ad,c]	none	35	41	-	MD **12.76 higher** (7.21 higher to 18.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental health (0-100) (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ae,c]	none	20	21	-	MD **11.34 higher** (3.54 higher to 19.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 social functioning (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [af,c]	none	35	41	-	MD **6.95 higher** (1.94 higher to 11.96 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 body pain (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	very serious [b]	not serious	very serious [ag,c]	none	35	41	-	MD **8.24 lower** (25.69 lower to 9.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 general health (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	serious [ah,c]	none	35	41	-	MD **10.85 higher** (5.45 higher to 16.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 health transition (0-100) (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ai,c]	none	15	20	-	MD **11.9 lower** (28.63 lower to 4.83 higher)	⨁◯◯◯ VERY LOW	CRITICAL
EDSS scale (0-10) (follow up: 8 weeks; Scale from: 0 to 10)												
1	randomised trials	serious [a]	not serious	serious [e]	serious [aj,c]	none	26	21	-	MD **0.29 higher** (0.67 lower to 1.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Guy's neurological disability scale (0-60) (follow up: 7 weeks; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [ak,c]	none	8	8	-	MD **0.62 higher** (1.24 lower to 2.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HAQUAMS - fatigue/thinking (1-5) (follow up: 8 weeks; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [al,c]	none	15	13	-	MD **0.8 lower** (1.51 lower to 0.09 lower)	⨁◯◯◯ VERY LOW	CRITICAL
HAQUAMS - total (1-5) (follow up: 8 weeks; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [am,c]	none	15	13	-	MD **0.4 lower** (0.71 lower to 0.09 lower)	⨁◯◯◯ VERY LOW	CRITICAL
HAQUAMS - mood (1-5) (follow up: 8 weeks; Scale from: 1 to 5)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [e]	serious [an,c]	none	15	13	-	MD **0.4 lower** (0.86 lower to 0.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HAQUAMS - social function (1-5) (follow up: 8 weeks; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [ao,c]	none	15	13	-	MD **0.1 lower** (0.58 lower to 0.38 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Digit Symbol Substitution Test (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ap,c]	none	21	21	-	MD **8.8 higher** (0.23 higher to 17.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Word List Generation (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [aq,c]	none	21	21	-	MD **1.1 higher** (3.5 lower to 5.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Selective reminding test (long-term storage) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ar,c]	none	21	21	-	MD **3.6 lower** (9.23 lower to 2.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Selective reminding test (consistent long-term retrieval) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [as,c]	none	21	21	-	MD **8.8 lower** (14.64 lower to 2.96 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Spatial Recall Test (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [e]	serious [at,c]	none	21	21	-	MD **3.6 higher** (0.09 lower to 7.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Paced Auditory Serial Attention Test (PASAT) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [au,c]	none	21	21	-	MD **2.1 higher** (2.6 lower to 6.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - checklist individual strength concentration (5-35) (follow up: 26 weeks; Scale from: 5 to 35)												
1	randomised trials	very serious [a]	not serious	not serious	serious [av,c]	none	37	34	-	MD **0.9 higher** (2.43 lower to 4.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Stroop Colour Word Interference (attention/concentration) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [aw,c]	none	15	20	-	MD **1.8 higher** (1.88 lower to 5.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: range 8 weeks to 10 weeks; Scale from: 0 to 63)												
2	randomised trials	very serious [a]	not serious	serious [e]	serious [ax,c]	none	23	23	-	MD **5.65 lower** (9.9 lower to 1.39 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory - fast screen (0-21) (follow up: 8 weeks; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	serious [e]	serious [ay,c]	none	26	21	-	MD **1.4 lower** (4.16 lower to 1.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Anxiety Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [e]	very serious [az,c]	none	10	10	-	MD **2.1 lower** (7.61 lower to 3.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of adverse events - only MS exacerbations reported (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	12/69 (17.4%)	24.6%	**RR 0.71** (0.37 to 1.36)	**71 fewer per 1,000** (from 155 fewer to 89 more)	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of adverse events - mixed (follow up: range 6 weeks to 6 months)												
5	randomised trials	very serious [a]	not serious	not serious	serious [ba]	none	10/72 (13.9%)	0/69 (0.0%)	**RD 0.14** (0.04 to 0.24)	**140 more per 1,000** (from 40 more to 240 more) [bb]	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of adverse events - orthopaedic problems reported separately (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	16/69 (23.2%)	34.8%	**RR 0.67** (0.39 to 1.14)	**115 fewer per 1,000** (from 212 fewer to 49 more)	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of adverse events - at least one fall reported separately (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	12/69 (17.4%)	30.4%	**RR 0.57** (0.31 to 1.07)	**131 fewer per 1,000** (from 210 fewer to 21 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - up to 6 month outcomes	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	2/14 (14.3%)	0/12 (0.0%)	**OR 6.92** (0.41 to 118.14)	**143 more per 1,000** (from 73 fewer to 359 more) [bb]	⨁◯◯◯ VERY LOW	CRITICAL

Acceptability - Completed all 1-1 phone calls

1	randomised trials	serious [a]	not serious	not serious	Very serious [c]	none	47/69 (68.1%)	76.8%	**OR 0.64** (0.30 to 1.37)	**89 fewer per 1,000** (from 270 fewer to 51 more)	⨁◯◯◯ VERY LOW	CRITICAL

Acceptability - Completed all teleconference calls with or without at least one makeup session

1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	59/69 (85.5%)	84.1%	**OR 1.12** (0.44 to 2.84)	**15 more per 1,000** (from 142 fewer to 97 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Heterogeneity present that could not be explained by prespecified subgrouping strategies and I2 >75%

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±0.66.

e. Downgraded by 1 increment as the follow-up time was less than the minimum of 3 months specified in the protocol for the majority of the evidence

f. MID used to assess imprecision was ±6.495

g. MID used to assess imprecision was ± 6.1

h. MID used to assess imprecision was ±3.6

i. MID used to assess imprecision was ±3.95

j. MID used to assess imprecision was ±0.83

k. MID used to assess imprecision was ±3.98

l. MID used to assess imprecision was ±4.55

m. MID used to assess imprecision was ±5.0

n. MID used to assess imprecision was ±0.74

o. MID used to assess imprecision was 15.38

p. MID used to assess imprecision was ±1.85

q. MID used to assess imprecision was ±2.15

r. MID used to assess imprecision was ±2.0

s. MID used to assess imprecision was ±1.48

t. MID used to assess imprecision was ±2.08

u. MID used to assess imprecision was ±6.29

v. MID used to assess imprecision was ±7.35

w. MID used to assess imprecision was ±15.3

x. MID used to assess imprecision was ±8.18

y. MID used to assess imprecision was ±10.75

z. Downgraded by 1 increment as point estimates differ widely despite I2 being below 50%

aa. MID used to assess imprecision was ±6.83

ab. MID used to assess imprecision was ±10.15

ac. MID used to assess imprecision was ±10.06

ad. MID used to assess imprecision was ±7.97

ae. MID used to assess imprecision was ±6.28

af. MID used to assess imprecision was ±7.17

ag. MID used to assess imprecision was ±5.96

ah. MID used to assess imprecision was ±6.28

ai. MID used to asses imprecision was ±11.2

aj. MID used to assess imprecision was ±0.84

ak. MID used to assess imprecision was ±2.18

al. MID used to assess imprecision was ±0.85

am. MID used to assess imprecision was ±0.45

an. MID used to assess imprecision was ±0.28

ao. MID used to assess imprecision was ±0.38

ap. MID used to assess imprecision was ±7.2

aq. MID used to assess imprecision was ±3.3

ar. MID used to assess imprecision was ±3.25

as. MID used to assess imprecision was ±3.85

at. MID used to assess imprecision was ±2.95

au. MID used to assess imprecision was ±4.68

av. MID used to assess imprecision was ±3.7

aw. MID used to assess imprecision was ±2.7

ax. MID used to assess imprecision was ±3.95

ay. MID used to assess imprecision was 2.39

az. MID used to assess imprecision was ±3.17

ba. Imprecision assessed using OIS due to zero events in both arms of at least one study. Downgraded by 1 increment if power 80-90% and 2 increments if power <80%.

bb. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 34: Clinical evidence profile: Aerobic exercise vs. control – outcomes >6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	control (no intervention, waitlist control, education only) - >6 months outcomes	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-7) (follow up: 52 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	33	30	-	MD **0.1 higher** (0.44 lower to 0.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - total (0-84) (follow up: 52 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	33	30	-	MD **0.9 lower** (7.15 lower to 5.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue subscale of Checklist Individual Strength-20 (8-56) (follow up: 52 weeks; Scale from: 8 to 56)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	33	30	-	MD **0.5 higher** (4.52 lower to 5.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - checklist individual strength concentration (5-35) (follow up: 52 weeks; Scale from: 5 to 35)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	33	30	-	MD **1.2 higher** (2.4 lower to 4.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Incidence of adverse events - MS relapse (follow up: 52 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	-/31	-/34 [g]	**OR 0.28** (0.10 to 0.81)	**Could not be calculated as no control group risk given** [g]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±0.48

d. MID used to assess imprecision was ±6.1

e. MID used to assess imprecision was ±3.98

f. MID used to assess imprecision was ±3.70

g. Control group risk could not be calculated as number of events not reported - therefore absolute effect could not be calculated.

Table 35: Clinical evidence profile: Aerobic exercise vs. neurological rehabilitation – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise	neurological rehabilitation (respiratory, postural and stretching)	Relative (95% CI)	Absolute (95% CI)		
Average adherence rate												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	11	11	-	MD **3 lower** (8.91 lower to 2.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±3.0

Table 36: Clinical evidence profile: Functional electrical stimulation + aerobic exercise vs. control (waitlist) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Functional electrical stimulation + aerobic exercise	control (waitlist)	Relative (95% CI)	Absolute (95% CI)		
5-item MFIS score (0-20) (follow up: 12 weeks; Scale from: 0 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	6	6	-	MD **2.57 lower** (7.61 lower to 2.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Decrease in fatigue on MFIS 5-item (any decrease) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4/6 (66.7%)	50.0%	**OR 2.00** (0.19 to 20.61)	**167 more per 1,000** (from 340 fewer to 454 more)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale of Motor and Cognitive Functions - Total score (20-100) (follow up: 12 weeks; Scale from: 20 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,d]	none	6	6	-	MD **2.5 lower** (10.09 lower to 5.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale of Motor and Cognitive Functions - Cognitive score (10-50) (follow up: 12 weeks; Scale from: 10 to 50)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	6	6	-	MD **1 lower** (4.84 lower to 2.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Scale of Motor and Cognitive Functions - Motor score (10-50) (follow up: 12 weeks; Scale from: 10 to 50)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,f]	none	6	6	-	MD **1.5 lower** (6.95 lower to 3.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Decrease in fatigue on FSMC total score (any decrease) (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Functional electrical stimulation + aerobic exercise	control (waitlist)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	5/6 (83.3%)	66.7%	**OR 2.50** (0.16 to 38.60)	**167 more per 1,000** (from 434 fewer to 321 more)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 (0-100 for all) - Mental health composite (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,g]	none	6	6	-	MD **0.72 higher** (12.95 lower to 14.39 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 (0-100 for all) - Physical health composite (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	6	6	-	MD **8.95 higher** (2.1 higher to 15.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 (0-100 for all) - Change in health domain (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,i]	none	6	6	-	MD **4.17 lower** (19.23 lower to 10.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PHQ-9 (depression; 0-27) (follow up: 12 weeks; Scale from: 0 to 27)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	6	6	-	MD **2.83 higher** (1.96 lower to 7.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 12 weeks)												
1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	5/11 (45.5%)	14.3%	**RR 3.18** (0.46 to 21.85)	**312 more per 1,000** (from 77 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±0.62

d. MID used to assess imprecision was ±4.27

e. MID used to assess imprecision was ±1.70

f. MID used to assess imprecision was ±2.91

g. MID used to assess imprecision was ±4.82

h. MID used to assess imprecision was ±3.39

i. MID used to assess imprecision was ±7.91

j. MID used to assess imprecision was ±2.74

Table 37: Clinical evidence profile: Resistance training vs. control (waitlist control, no intervention, usual care or education only) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	control (waitlist control, no intevention, usual care or education only)	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact Scale - total (0-84) (follow up: range 4 weeks to 22 weeks; Scale from: 0 to 84)												
3	randomised trials	very serious [a]	very serious [b]	serious [c]	serious [d,e]	none	69	64	-	MD **4.85 lower** (14.33 lower to 4.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - physical (0-36) (follow up: range 4 weeks to 22 weeks; Scale from: 0 to 36)												
2	randomised trials	serious [a]	not serious	not serious	not serious [f]	none	46	44	-	MD **0.81 lower** (3.5 lower to 1.88 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Modified Fatigue Impact Scale - cognitive (0-40) (follow up: range 4 weeks to 22 weeks; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	control (waitlist control, no intevention, usual care or education only)	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	not serious	serious [c,g]	none	46	44	-	MD **1.3 higher** (1.49 lower to 4.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact Scale - psychosocial (0-8) (follow up: range 4 weeks to 22 weeks; Scale from: 0 to 8)												
2	randomised trials	serious [a]	serious [h]	not serious	very serious [d,i]	none	46	34	-	MD **0.32 lower** (2.05 lower to 1.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (1-7) (follow up: 12 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	not serious [c]	very serious [d,j]	none	16	18	-	MD **0.2 lower** (1.2 lower to 0.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory (4-20) - General fatigue (follow up: 12 weeks; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [d,k]	none	16	18	-	MD **0.9 higher** (2.37 lower to 4.17 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory (4-20) - Physical fatigue (follow up: 12 weeks; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,l]	none	16	18	-	MD **1.6 lower** (4.48 lower to 1.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory (4-20) - Reduced activity (follow up: 12 weeks; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [d,m]	none	16	18	-	MD **0.6 lower** (3.54 lower to 2.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory (4-20) - Reduced motivation (follow up: 12 weeks; Scale from: 4 to 20)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	control (waitlist control, no intevention, usual care or education only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [d,n]	none	16	18	-	MD **0.5 lower** (2.2 lower to 1.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory (4-20) - Mental fatigue (follow up: 12 weeks; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [d,o]	none	16	18	-	MD **0** (3.79 lower to 3.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 quality of life (0-100) - Physical summary (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,p]	none	16	18	-	MD **3.8 higher** (0.85 lower to 8.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 quality of life (0-100) - Mental summary (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [d,q]	none	16	18	-	MD **2.4 lower** (9.28 lower to 4.48 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 quality of life (0-100) - General health domain (follow up: 4 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,r]	none	10	9	-	MD **8.4 higher** (8.96 lower to 25.76 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 quality of life (0-100) - Physical functioning domain (follow up: 4 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,s]	none	10	9	-	MD **5.4 lower** (41.29 lower to 30.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 quality of life (0-100) - Physical limitation domain (follow up: 4 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	control (waitlist control, no intevention, usual care or education only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,t]	none	10	9	-	MD **5.6 higher** (28.3 lower to 39.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (0-100) - Emotional limitation domain (follow up: 4 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,u]	none	10	9	-	MD **27.6 higher** (7.32 lower to 62.52 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (0-100) - Emotional wellbeing domain (follow up: 4 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,v]	none	10	9	-	MD **11.6 higher** (4.01 lower to 27.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (0-100) - Pain domain (follow up: 4 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,w]	none	10	9	-	MD **12.1 higher** (17.41 lower to 41.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (0-100) - Energy/fatigue domain (follow up: 4 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,x]	none	10	9	-	MD **11.4 higher** (6.55 lower to 29.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 quality of life (0-100) - Social functioning domain (follow up: 4 weeks; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	control (waitlist control, no intevention, usual care or education only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,y]	none	10	9	-	MD **14.9 higher** (11.14 lower to 40.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL
WHOQOL-BREF (0-100) - Overall score (follow up: 22 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d,z]	none	36	35	-	MD **0** (0.51 lower to 0.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
WHOQOL-BREF (0-100) - Overall health change (follow up: 22 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [aa,d]	none	36	35	-	MD **0.6 lower** (2.11 lower to 0.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
WHOQOL-BREF (0-100) - Overall physical health change (follow up: 22 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious [ab]	none	36	35	-	MD **0.2 lower** (0.65 lower to 0.25 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Functional capacity (% - baseline set at 100%) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [ac,d]	none	16	18	-	MD **12.1 higher** (4.35 higher to 19.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Major Depression Inventory (scale unclear) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [ad,d]	none	16	18	-	MD **0.2 lower** (4.5 lower to 4.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	control (waitlist control, no intevention, usual care or education only)	Relative (95% CI)	Absolute (95% CI)		
Incidence of adverse events (harm) (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [ae]	none	0/10 (0.0%)	0/9 (0.0%)	**RD 0.00** (-0.18 to 0.18)	**0 fewer per 1,000** (from 180 fewer to 180 more) [af]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 10 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious	none	5/23 (21.7%)	0/20 (0.0%)	**OR 7.90** (1.24 to 50.09)	**217 more per 1,000** (from 37 more to 398 more) [af]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Heterogeneity that cannot be explained by prespecified subgrouping strategies and I2 >75%

c. Downgraded by 1 increment as the follow-up duration for the majority of the evidence is less than the 3 month minimum specified in the protocol

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±7.78

f. MID used to assess imprecision was ±3.63

g. MID used to assess imprecision was ±4.05

h. Heterogeneity that cannot be explained by prespecified subgrouping strategies

i. MID used to assess imprecision was ±1.08

j. MID used to assess imprecision was ±0.45

k. MID used to assess imprecision was ±2.05

l. MID used to assess imprecision was ±2.17

m. MID used to assess imprecision was ±2.00

n. MID used to assess imprecision was ±1.42

o. MID used to assess imprecision was ±2.74

p. MID used to assess imprecision was ±4.18

q. MID used to assess imprecision was ±4.43

r. MID used to assess imprecision was ±9.63

s. MID used to assess imprecision was ±18.83

t. MID used to assess imprecision was ±17.53

u. MID used to assess imprecision was ±20.48

v. MID used to assess imprecision was ±10.43

w. MID used to assess imprecision was ±18.0

x. MID used to assess imprecision was ±13.5

y. MID used to assess imprecision was ±14.08

z. MID used to assess imprecision was ±0.48

aa. MID used to assess imprecision ±0.5

ab. MID used to assess imprecision was ±2.33

ac. MID used to assess imprecision was ±6.44

ad. MID used to assess imprecision was ±2.98

ae. Imprecision assessed based on sample size as zero events in both arms of a single study. Downgraded by 2 increments as sample size <70.

af. Absolute effect calculated manually using risk difference as zero events in at least one arm of one or more studies

Table 38: Clinical evidence profile: Vestibular/balance training vs. control (waitlist control, routine care, information only) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	control (waitlist control, routine care, information only)	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact Scale - total (0-84) (follow up: range 10 weeks to 14 weeks; Scale from: 0 to 84)												
3	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	78	71	-	MD **11.13 lower** (15.43 lower to 6.84 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - physical (0-36) (follow up: 14 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,e]	none	38	38	-	MD **4.7 lower** (7.89 lower to 1.51 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - cognitive (0-40) (follow up: 14 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,f]	none	38	38	-	MD **5.1 lower** (8.43 lower to 1.77 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - psychosocial (0-8) (follow up: 14 weeks; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,g]	none	38	38	-	MD **1.17 lower** (2.02 lower to 0.32 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: 8 weeks; Scale from: 9 to 63)												
2	randomised trials	very serious [a]	not serious	serious [b]	serious [d,h]	none	51	36	-	MD **8.51 lower** (14.75 lower to 2.27 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact Scale - total score (0-160) (follow up: 12 weeks; Scale from: 0 to 160)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	control (waitlist control, routine care, information only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	47	25	-	MD **25.7 lower** (34.3 lower to 17.1 lower)	⨁⨁◯◯ LOW [i]	CRITICAL

Fatigue Impact Scale - physical subscale (0-40) (follow up: 12 weeks; Scale from: 0 to 40)

1	randomised trials	very serious [a]	not serious	not serious	not serious	none	47	25	-	MD **9.8 lower** (12.92 lower to 6.68 lower)	⨁⨁◯◯ LOW [i]	CRITICAL

Fatigue Impact Scale - cognitive subscale (0-40) (follow up: 12 weeks; Scale from: 0 to 40)

1	randomised trials	very serious [a]	not serious	not serious	not serious	none	47	25	-	MD **4.9 lower** (6.65 lower to 3.15 lower)	⨁⨁◯◯ LOW [k]	CRITICAL

Fatigue Impact Scale - psychosocial subscale (0-80) (follow up: 12 weeks; Scale from: 0 to 80)

1	randomised trials	very serious [a]	not serious	not serious	not serious	none	47	25	-	MD **13.5 lower** (18.87 lower to 8.13 lower)	⨁⨁◯◯ LOW [i]	CRITICAL

SF-36 physical summary (0-100) (follow up: 14 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	serious [d,m]	none	38	38	-	MD **3.7 higher** (0.18 lower to 7.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL

SF-36 mental summary (0-100) (follow up: 14 weeks; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	serious [d,n]	none	38	38	-	MD **3.6 higher** (0.22 higher to 6.98 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MusiQoL (0-100) (follow up: 8 weeks; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	control (waitlist control, routine care, information only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,o]	none	27	15	-	MD **10 higher** (2.02 higher to 17.98 higher)	⨁◯◯◯ VERY LOW	CRITICAL
EDSS (0-10) (follow up: 8 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,p]	none	24	21	-	MD **1.12 higher** (0.08 higher to 2.16 higher)	⨁◯◯◯ VERY LOW [a]	CRITICAL
Cognitive - perceived deficits questionnaire (0-80) (follow up: 14 weeks; Scale from: 0 to 80)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,q]	none	38	38	-	MD **6.3 lower** (12.54 lower to 0.06 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 10 weeks; Scale from: 0 to 63)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [d,r]	none	12	13	-	MD **5 lower** (13.7 lower to 3.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory - fast screen (0-21) (follow up: 8 weeks; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,s]	none	24	21	-	MD **1.23 lower** (4.34 lower to 1.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (follow up: range 6 weeks to 10 weeks)												
2	randomised trials	very serious [a]	not serious	serious [b]	very serious [t]	none	0/39 (0.0%)	0/27 (0.0%)	**RD 0.00** (-0.09 to 0.09)	**0 fewer per 1,000** (from 90 fewer to 90 more) [u]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: range 10 weeks to 14 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	control (waitlist control, routine care, information only)	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [a]	not serious	not serious	very serious [v]	none	6/116 (5.2%)	3/111 (2.7%)	**RD 0.03** (-0.03 to 0.08)	**30 more per 1,000** (from 30 fewer to 80 more) [u]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the follow-up was less than the minimum of 3 months specified in the protocol for the majority of the evidence

c. MID used to assess imprecision was ±4.48

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±3.55

f. MID used to assess imprecision was ±3.70

g. MID used to assess imprecision was ±0.94

h. MID used to assess imprecision was ±7.30

i. MID used to assess imprecision was ±7.58

j. MID used to assess imprecision was ±3.03

k. MID used to assess imprecision was ±1.98

l. MID used to assess imprecision was ±5.25

m. MID used to assess imprecision was ±4.01

n. MID used to assess imprecision was ±4.93

o. MID used to assess imprecision was ±6.72

p. MID used to assess imprecision was ±0.84

q. MID used to assess imprecision was ±6.48

r. MID used to assess imprecision was ±3.88

s. MID used to assess imprecision was ±2.67

t. Imprecision assessed using sample size as zero events in both arms of all studies. Downgraded by 2 increments as sample size <70.

u. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study.

v. Imprecision assessed based on OIS as zero events in both arms of at least one study. Downgraded by 1 increment if power 80-90% and 2 increments if power <80%.

Table 39: Clinical evidence profile: Vestibular/balance training vs. standard neurorehabilitation – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	standard neurorehabilitation	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: 4 weeks; Scale from: 9 to 63)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,d]	none	13	10	-	MD **2.1 higher** (6.35 lower to 10.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional - Barthel Index (0-100) (follow up: 4 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,e]	none	13	10	-	MD **3.2 higher** (6.41 lower to 12.81 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence was at a follow-up less than the 3 months minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±5.23

e. MID used to assess imprecision was ±6.2

Table 40: Clinical evidence profile: Resistance training vs. aerobic exercise – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact Scale - physical (0-36) (follow up: 8 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	16	16	-	MD **1.1 higher** (1.96 lower to 4.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - cognitive (0-40) (follow up: 8 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	16	16	-	MD **1 lower** (5.82 lower to 3.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - psychosocial (0-8) (follow up: 8 weeks; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,f]	none	16	16	-	MD **0.8 lower** (6.53 lower to 4.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	16	16	-	MD **3.9 higher** (0.88 lower to 8.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	16	16	-	MD **4.2 lower** (11.24 lower to 2.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,i]	none	16	16	-	MD **2.9 lower** (6.16 lower to 0.36 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
Incidence of adverse events (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [i]	none	0/16 (0.0%)	0/16 (0.0%)	**RD 0.00** (-0.11 to 0.11)	**0 fewer per 1,000** (from 110 fewer to 110 more) [k]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as follow-up for the majority of the evidence was less than the 3 months minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±3.78

e. MID used to assess imprecision was ±5.05

f. MID used to assess imprecision was ±0.83

g. MID used to assess imprecision was ±3.95

h. MID used to assess imprecision was ±6.13

i. MID used to assess imprecision was ±5.15

j. Imprecision assessed using sample size as zero events in both arms of at least one study. Downgraded by 2 increments as sample size <70.

k. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study.

Table 41: Clinical evidence profile: Vestibular/balance training vs. aerobic exercise – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact Scale - total (0-84) (follow up: 10 weeks; Scale from: 0 to 84)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,d]	none	12	13	-	MD **14.4 lower** (29.13 lower to 0.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: 8 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	24	26	-	MD **5.23 lower** (14.21 lower to 3.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement in MFIS from baseline (follow up: 3 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	9/10 (90.0%)	66.7%	**OR 4.50** (0.37 to 54.16)	**233 more per 1,000** (from 241 fewer to 324 more)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement in MFIS (motor) from baseline (follow up: 3 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	9/10 (90.0%)	88.9%	**OR 1.13** (0.06 to 21.09)	**12 more per 1,000** (from 565 fewer to 105 more)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement in HAQUAMS (motor) from baseline (follow up: 3 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	7/10 (70.0%)	55.6%	**OR 1.87** (0.28 to 12.31)	**145 more per 1,000** (from 296 fewer to 383 more)	⨁◯◯◯ VERY LOW	CRITICAL
EDSS (0-10) (follow up: 8 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	24	26	-	MD **0.83 higher** (0.15 lower to 1.81 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 10 weeks; Scale from: 0 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c,g]	none	12	13	-	MD **1.3 lower** (9.51 lower to 6.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory - fast screen (0-21) (follow up: 8 weeks; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,h]	none	24	26	-	MD **0.17 higher** (2.74 lower to 3.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Improvement in Beck Depression Inventory from baseline (follow up: 3 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	9/10 (90.0%)	66.7%	**OR 4.50** (0.37 to 54.16)	**233 more per 1,000** (from 241 fewer to 324 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (follow up: 6 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	0/12 (0.0%)	7.7%	**OR 0.15** (0.00 to 7.39)	**77 fewer per 1,000** (from 270 fewer to 116 more) [i]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up of less than the 3 months minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±3.85

e. MID used to assess imprecision was ±8.10

f. MID used to assess imprecision was ±0.84

g. MID used to assess imprecision was ±4.43

h. MID used to assess imprecision was ±2.95

i. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 42: Clinical evidence profile: Vestibular/balance training vs. resistance training – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vestibular/balance training	resistance training	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact Scale - total (0-84) (follow up: 10 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	28	23	-	MD **1.7 higher** (4.43 lower to 7.83 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 10 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious	none	0/28 (0.0%)	21.7%	**OR 0.09** (0.01 to 0.56)	**217 fewer per 1,000** (from 43 fewer to 392 fewer) [e]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the follow-up for the majority of the evidence was less than the minimum of 3 months specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±6.73

e. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 43: Clinical evidence profile: Resistance training + aerobic exercise vs. control (waitlist control, no intervention, information only) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic	control (waitlist, no intervention, information only)	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: range 12 weeks to 6 months; Scale from: 0 to 84)												
3	randomised trials	very serious [a]	serious [b]	not serious	serious [c,d]	none	170	142	-	MD **5.43 lower** (9.93 lower to 0.92 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 12 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,e]	none	63	49	-	MD **4.3 lower** (6.42 lower to 2.18 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 12 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,f]	none	63	49	-	MD **1.59 lower** (3.15 lower to 0.03 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: 8 weeks; Scale from: 9 to 63)												
1	randomised trials	serious [a]	not serious	serious [g]	not serious [h]	none	18	18	-	MD **15.94 lower** (24.2 lower to 7.68 lower)	⨁⨁◯◯ LOW	CRITICAL
WEIMuS Fatigue score (0-68) (follow up: 6 months; Scale from: 0 to 68)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [i]	none	93	84	-	MD **2.05 lower** (5.26 lower to 1.16 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 physical (0-100) (follow up: 12 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic	control (waitlist, no intervention, information only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,j]	none	63	49	-	MD **7.2 lower** (12.87 lower to 1.53 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 mental composite (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,k]	none	14	9	-	MD **16.3 higher** (2.78 higher to 29.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 physical composite (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,l]	none	14	9	-	MD **6.7 higher** (13.13 lower to 26.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) - Maurer 18 - e-training individualised exercise protocol (follow up: 6 months; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [m]	none	93	84	-	MD **0.65 lower** (2.94 lower to 1.64 higher)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory (0-63) - Razazian 2016 - aquatic exercises at rehab centre (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	serious [a]	not serious	serious [g]	not serious [n]	none	18	18	-	MD **16.55 lower** (20.1 lower to 13 lower)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory (0-63) - Correale 2021 - training sessions at centre (follow up: 12 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,o]	none	14	9	-	MD **4.7 lower** (11.39 lower to 1.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: range 12 weeks to 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic	control (waitlist, no intervention, information only)	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	serious [b]	not serious	very serious [c]	none	5/152 (3.3%)	7.7%	**RR 0.57** (0.12 to 2.81)	**33 fewer per 1,000** (from 67 fewer to 138 more)	⨁◯◯◯ VERY LOW	CRITICAL

Any adverse event (follow up: 6 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	55/94 (58.5%)	60.7%	**OR 0.91** (0.50 to 1.66)	**23 fewer per 1,000** (from 171 fewer to 112 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Heterogeneity that cannot be explained by subgroup analysis exists, based on point estimates varying between studies and I2 >50%

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±7.48

e. MID used to assess imprecision was ±3.63

f. MID used to assess imprecision was ±2.63

g. Downgraded by 1 increment as the follow-up for the majority of the evidence is less than the minimum 3 months specified in the protocol

h. MID used to assess imprecision was ±7.08

i. MID used to assess imprecision was ±7.2

j. MID used to assess imprecision was ±10.33

k. MID used to assess imprecision was ±9.38

l. MID used to assess imprecision was ±11.55

m. MID used to assess imprecision was ±3.36

n. MID used to assess imprecision was ±3.51

o. MID used to assess imprecision was ±4.13

p. Heterogeneity that cannot be explained by subgroup analysis exists, based on point estimates differing widely between the two studies

Table 44: Clinical evidence profile: Resistance training + balance exercises vs. control (no intervention, waitlist control) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training + balance	control (no intervention, waitlist control)	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: range 8 weeks to 12 weeks; Scale from: 9 to 63)												
2	randomised trials	very serious [a]	very serious [b]	serious [c]	very serious [d,e]	none	75	57	-	MD **5.7 lower** (16.5 lower to 5.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - Physical functioning (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,f]	none	24	9	-	MD **9.71 higher** (2.75 higher to 16.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - Role-physical functioning (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,g]	none	24	9	-	MD **12.75 higher** (19.28 lower to 44.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - Bodily pain (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [h]	none	24	9	-	MD **1.97 higher** (1.51 lower to 5.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - General health (follow up: 8 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training + balance	control (no intervention, waitlist control)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,i]	none	24	9	-	MD **0.31 higher** (8.29 lower to 8.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - vitality (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,j]	none	24	9	-	MD **0.75 lower** (16.45 lower to 14.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - Social functioning (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,k]	none	24	9	-	MD **1.15 higher** (12.37 lower to 14.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - Role-emotional functioning (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,l]	none	24	9	-	MD **8.57 lower** (46.08 lower to 28.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100) - Mental health (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [m]	none	24	9	-	MD **1.55 lower** (7.84 lower to 4.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MusiQoL (0-100) (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	51	48	-	MD **2.38 higher** (0.41 higher to 4.35 higher)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance training + balance	control (no intervention, waitlist control)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [o]	none	24	9	-	MD **0.94 lower** (5.5 lower to 3.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Adverse events leading to withdrawal (follow up: range 8 weeks to 12 weeks)

2	randomised trials	very serious [a]	not serious	serious [c]	very serious [d]	none	4/79 (5.1%)	15.4%	**RR 0.39** (0.11 to 1.36)	**94 fewer per 1,000** (from 137 fewer to 56 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Heterogeneity that cannot be explained by subgrouping analyses is present and I2 >75%

c. Downgraded by 1 increment as the majority of the evidence has a follow-up of less than the 3 months specified in the protocol

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±3.9

f. MID used to assess imprecision was ±8.79

g. MID used to assess imprecision was ±8.92

h. MID used to assess imprecision was ±12.31

i. MID used to assess imprecision was ±8.45

j. MID used to assess imprecision was ±10.67

k. MID used to assess imprecision was ±8.34

l. MID used to assess imprecision was ±21.36

m. MID used to assess imprecision was ±8.96

n. MID used to assess imprecision was ±4.73

o. MID used to assess imprecision was ±8.63

Table 45: Clinical evidence profile: Vestibular/balance training + aerobic exercise vs. control (education only) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Balance + aerobic exercise	control (education only)	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 8 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	17	15	-	MD **28.2 lower** (33.21 lower to 23.19 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 8 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [d]	none	17	15	-	MD **15.3 lower** (18.45 lower to 12.15 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 8 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [e]	none	17	15	-	MD **10.4 lower** (13.19 lower to 7.61 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Psychosocial scale (0-8) (follow up: 8 weeks; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [f]	none	17	15	-	MD **2.5 lower** (3.54 lower to 1.46 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum specified in the protocol

c. MID used to assess imprecision was ±5.98

d. MID used to assess imprecision was ±3.68

e. MID used to assess imprecision was ±3.75

f. MID used to assess imprecision was ±0.78

Table 46: Clinical evidence profile: Resistance training + balance exercise + aerobic exercise vs. control (usual care, no intervention) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + balance + aerobic exercise	control (usual care, no intervention), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 8 weeks; Scale from: 0 to 84)												
2	randomised trials	very serious [a]	very serious [b]	serious [c]	serious [d,e]	none	28	30	-	MD **19.25 lower** (37.92 lower to 0.58 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 8 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [f]	none	10	11	-	MD **15.5 lower** (19.49 lower to 11.51 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 8 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [g]	none	10	11	-	MD **10.1 lower** (13.95 lower to 6.25 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Psychosocial scale (0-8) (follow up: 8 weeks; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [h]	none	10	11	-	MD **2.8 lower** (4.18 lower to 1.42 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: range 5 weeks to 12 weeks; Scale from: 9 to 63)												
3	randomised trials	very serious [a]	serious [i]	serious [c]	serious [d,j]	none	18	19	-	MD **8.59 lower** (14.44 lower to 2.74 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + balance + aerobic exercise	control (usual care, no intervention), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-7) (follow up: 3 months; Scale from: 1 to 7)												
2	randomised trials	very serious [a]	not serious	not serious	serious [d,k]	none	27	22	-	MD **0.64 lower** (1.2 lower to 0.07 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 - physical summary (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [l]	none	10	11	-	MD **21.2 higher** (16.35 higher to 26.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 - mental summary (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [m]	none	10	11	-	MD **26.6 higher** (20.26 higher to 32.94 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 - physical score (0-100) (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [d,n]	none	12	12	-	MD **3.84 lower** (17.9 lower to 10.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 - psychological score (0-100) (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,o]	none	12	12	-	MD **10.74 lower** (23.79 lower to 2.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multicultural quality of life index (MQLIM; scale 0-100) (follow up: 8 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + balance + aerobic exercise	control (usual care, no intervention), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [p]	none	18	19	-	MD **13.54 higher** (7.52 higher to 19.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MS-specific quality of life - mental domain (name and range of scale unclear) - MS-specific quality of life - mental domain (name and range of scale unclear) (follow up: 11 weeks)

1	randomised trials	very serious [a]	not serious	serious [c]	not serious [q]	none	39	22	-	MD **16.36 higher** (7.1 higher to 25.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL

MS-specific quality of life - physical domain (name and range of scale unclear) (follow up: 11 weeks)

1	randomised trials	very serious [a]	not serious	serious [c]	not serious [r]	none	39	22	-	MD **12.17 higher** (5.28 higher to 19.06 higher)	⨁◯◯◯ VERY LOW	CRITICAL

EDSS (0-10) (follow up: 11 weeks; Scale from: 0 to 10)

1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d,s]	none	39	22	-	MD **0.13 lower** (0.61 lower to 0.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Hospital Anxiety and Depression Scale (0-63) (follow up: 12 weeks; Scale from: 0 to 63)

1	randomised trials	very serious [a]	not serious	not serious	serious [d,t]	none	15	10	-	MD **2.1 lower** (7.16 lower to 2.96 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Leeds MS quality of life (0-24) (follow up: 12 weeks; Scale from: 0 to 24)

1	randomised trials	very serious [a]	not serious	not serious	serious [d,u]	none	15	10	-	MD **1.5 lower** (4.25 lower to 1.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Adverse events leading to withdrawal (follow up: 11 weeks)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + balance + aerobic exercise	control (usual care, no intervention), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d]	none	2/41 (4.9%)	4.3%	**RR 1.12** (0.11 to 11.71)	**5 more per 1,000** (from 39 fewer to 466 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Heterogeneity that could not be explained by subgrouping strategies and I2 >75%

c. Downgraded by 1 increment as the majority of the evidence has a follow-up less than the minimum 3 months specified in the protocol

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±6.66

f. MID used to assess imprecision was ±3.7

g. MID used to assess imprecision was ±3.83

h. MID used to assess imprecision was ±0.83

i. Heterogeneity present that could not be explained by subgrouping analyses

j. MID used to assess imprecision was ±5.10

k. MID used to assess imprecision was ±0.61

l. MID used to assess imprecision was ±3.15

m. MID used to assess imprecision was ±4.95

n. MID used to assess imprecision was ±8.57

o. MID used to assess imprecision was ±10.18

p. MID used to assess imprecision was ±5.69

q. MID used to assess imprecision was ±1.41

r. MID used to assess imprecision was ±1.81

s. MID used to assess imprecision was ±0.12

t. MID used to assess imprecision was ±3.95

u. MID used to assess imprecision was ±2.2

Table 47: Clinical evidence profile: Resistance training + balance exercise + aerobic exercise vs. control (usual care, no intervention) – outcomes >6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + balance + aerobic exercise	control (usual care, no intervention), >6 months	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) - Fatigue Severity Scale (9-63) (follow up: 1 years; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	35	20	-	MD **10.2 lower** (16.84 lower to 3.56 lower)	⨁⨁◯◯ LOW	CRITICAL
MS-specific quality of life - mental domain (name and range of scale unclear) - MS-specific quality of life - mental domain (name and range of scale unclear) (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,d]	none	35	20	-	MD **13.54 higher** (2.48 higher to 24.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MS-specific quality of life - physical domain (name and range of scale unclear) - MS-specific quality of life - physical domain (name and range of scale unclear) (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,e]	none	35	20	-	MD **10.9 higher** (1.99 higher to 19.81 higher)	⨁◯◯◯ VERY LOW	CRITICAL
EDSS (0-10) (follow up: 1 years; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [f]	none	35	20	-	MD **0.28 lower** (0.86 lower to 0.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MID used to assess imprecision was ±1.71

c. MID used to assess imprecision was ±2.69

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±2.28

f. MID used to assess imprecision was ±0.15

Table 48: Clinical evidence profile: Standard exercises (resistance + balance + aerobic) + high-intensity lower limb resistance training vs. standard exercises alone – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Standard exercises (resistance + balance + aerobic) + high-intensity lower limb resistance training	standard exercises alone	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (10 max score) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	10	9	-	MD **0.44 higher** (0.5 lower to 1.38 higher)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	0/10 (0.0%)	11.1%	**OR 0.12** (0.00 to 6.14)	**96 fewer per 1,000** (111 fewer to 323 more) [d]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MID used to assess imprecision was ±2.89

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 49: Clinical evidence profile: Resistance + balance + aerobic exercise vs. massage – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + balance + aerobic exercise	massage	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: 5 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	not serious [b]	serious [c,d]	none	12	12	-	MD **2.67 lower** (8.61 lower to 3.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±6.12

Table 50: Clinical evidence profile: Massage + exercise (resistance, balance + aerobic) vs. control (no intervention) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage + exercise (resistance, balance, aerobic)	control (no intervention)	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: 5 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	12	12	-	MD **12.42 lower** (18.87 lower to 5.97 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. MID used to assess imprecision was ±6.20

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 51: Clinical evidence profile: Massage + exercise (resistance, balance + aerobic) vs. exercise only – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage + exercise (resistance, balance, aerobic)	exercise alone	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: 5 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	12	12	-	MD **1.33 higher** (5.96 lower to 8.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±4.32

Table 52: Clinical evidence profile: Massage + exercise (resistance, balance + aerobic) vs. massage only – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage + exercise (resistance, balance, aerobic)	massage alone	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: 5 weeks; Scale from: 9 to 63)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage + exercise (resistance, balance, aerobic)	massage alone	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [a,c,d]	none	12	12	-	MD **1.34 lower** (8.73 lower to 6.05 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence has a follow-up less than the 3 months minimum in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±6.35

Table 53: Clinical evidence profile: Resistance + aerobic exercise vs. yoga – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic	yoga	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 24 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	41	37	-	MD **1 lower** (8.63 lower to 6.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 12 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	63	63	-	MD **1.8 lower** (4.09 lower to 0.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 12 weeks; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic	yoga	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	63	63	-	MD **1.14 lower** (2.5 lower to 0.22 higher)	⨁⨁◯◯ LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: 8 weeks; Scale from: 9 to 63)												
1	randomised trials	serious [a]	not serious	serious [f]	serious [b,g]	none	18	18	-	MD **13.66 lower** (21.96 lower to 5.36 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 (0-100) - Physical domain (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	41	37	-	MD **6.3 lower** (14.9 lower to 2.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 (0-100) - Psychological domain (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	41	37	-	MD **6.7 lower** (14.82 lower to 1.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	serious [a]	not serious	serious [f]	not serious [j]	none	18	18	-	MD **0.28 lower** (2.36 lower to 1.8 higher)	⨁⨁◯◯ LOW	CRITICAL
Adherence - classes attended out of possible 10 (follow up: 12 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [k]	none	63	63	-	MD **0.3 higher** (0.53 lower to 1.13 higher)	⨁⨁◯◯ LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic	yoga	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	8/49 (16.3%)	7.3%	**RR 2.23** (0.63 to 7.87)	**90 more per 1,000** (from 27 fewer to 503 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±7.3

d. MID used to assess imprecision was ±3.45

e. MID used to assess imprecision was ±2.55

f. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

g. MID used to assess imprecision was ±6.27

h. MID used to assess imprecision was ±9.35

i. MID used to assess imprecision was ±9.15

j. MID used to assess imprecision was ±3.72

k. MID used to assess imprecision was ±1.19

Table 54: Clinical evidence profile: Fatigue/energy management programme vs. control (waitlist, no intervention, information only) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-7) (follow up: range 4 weeks to 4.25 months; Scale from: 1 to 7)												
4	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	147	149	-	MD **0.07 lower** (0.29 lower to 0.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: 6 weeks; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,e]	none	15	15	-	MD **2.78 higher** (1.43 lower to 6.99 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - total (0-84) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 84)												
2	randomised trials	very serious [a]	serious [f]	serious [b]	serious [d,g]	none	49	52	-	MD **2.6 lower** (8.84 lower to 3.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - physical (0-36) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 36)												
2	randomised trials	very serious [a]	serious [f]	serious [b]	serious [d,h]	none	49	52	-	MD **0.78 lower** (3.29 lower to 1.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - cognitive (0-40) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 40)												
2	randomised trials	very serious [a]	serious [f]	serious [b]	serious [d,i]	none	49	52	-	MD **1.63 lower** (4.43 lower to 1.16 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - psychosocial (0-8) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 8)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	very serious [j]	serious [b]	serious [d,k]	none	49	52	-	MD **0.23 lower** (1.06 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact Scale - total (0-160) (follow up: 4.25 months; Scale from: 0 to 160)												
1	randomised trials	serious [a]	not serious	not serious	serious [d,l]	none	13	10	-	MD **20.7 lower** (43.1 lower to 1.7 higher)	⨁⨁◯◯ LOW	CRITICAL
Fatigue Impact Scale - cognitive (0-40) (follow up: range 6 weeks to 4.25 months; Scale from: 0 to 40)												
3	randomised trials	very serious [a]	not serious	serious [b]	serious [d,m]	none	180	197	-	MD **3.14 lower** (4.55 lower to 1.73 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact Scale - physical (0-40) (follow up: range 6 weeks to 4.25 months; Scale from: 0 to 40)												
3	randomised trials	very serious [a]	not serious	serious [b]	not serious [n]	none	180	197	-	MD **3.05 lower** (4.53 lower to 1.56 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact Scale - psychosocial (0-80) (follow up: range 6 weeks to 4.25 months; Scale from: 0 to 80)												
3	randomised trials	very serious [a]	not serious	serious [b]	serious [d,o]	none	180	197	-	MD **6.1 lower** (8.79 lower to 3.41 lower)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - fatigue (8-56) (follow up: 26 weeks; Scale from: 8 to 56)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,p]	none	34	37	-	MD **3.55 lower** (7.52 lower to 0.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Clinically significant improvement in fatigue - 0.5-point reduction on FSS (follow up: 4 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [d]	none	2/11 (18.2%)	11.1%	**RR 1.64** (0.18 to 15.26)	**71 more per 1,000** (from 91 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinically significant improvement in fatigue - 10-point improvement on MFIS (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d]	none	4/24 (16.7%)	43.8%	**RR 0.38** (0.13 to 1.09)	**271 fewer per 1,000** (from 381 fewer to 39 more)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical function (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	not serious	serious [b]	not serious [q]	none	201	224	-	MD **1.68 higher** (1.21 lower to 4.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 role physical (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	serious [f]	serious [b]	serious [d,r]	none	201	224	-	MD **9.45 higher** (5.45 lower to 24.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 body pain (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	not serious	serious [b]	not serious [s]	none	201	224	-	MD **3.34 higher** (0.93 lower to 7.62 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 general health (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [a]	not serious	serious [b]	not serious [t]	none	201	224	-	MD **2.71 higher** (0.33 lower to 5.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 vitality (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	serious [f]	serious [b]	serious [d,u]	none	201	224	-	MD **6.04 higher** (1.48 lower to 13.57 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 social function (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	not serious	serious [b]	not serious [v]	none	201	224	-	MD **4.43 higher** (0.29 lower to 9.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 role emotional (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	serious [f]	serious [b]	not serious [w]	none	201	224	-	MD **4.67 higher** (7.15 lower to 16.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental health (0-100) (follow up: range 6 weeks to 26 weeks; Scale from: 0 to 100)												
3	randomised trials	very serious [a]	not serious	serious [b]	serious [d,x]	none	201	224	-	MD **4.74 higher** (1.73 higher to 7.76 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 - total (0-100) (follow up: 4.25 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d,y]	none	13	10	-	MD **4.65 lower** (17.97 lower to 8.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
MSIS-29 - physical (0-100) (follow up: 4.25 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d,z]	none	13	10	-	MD **6.66 lower** (21.22 lower to 7.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 - psychological (0-100) (follow up: 4.25 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [aa,d]	none	13	10	-	MD **1.17 lower** (16.95 lower to 14.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - concentration (5-35) (follow up: 26 weeks; Scale from: 5 to 35)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [ab]	none	34	37	-	MD **0.4 higher** (2.54 lower to 3.34 higher)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [ac]	none	0/89 (0.0%)	0/92 (0.0%)	**RD 0.00** (-0.02 to 0.02)	**0 fewer per 1,000** (from 20 fewer to 20 more) [ad]	⨁◯◯◯ VERY LOW	CRITICAL
BDI fast screen (0-21) (follow up: 4.25 months; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	very serious [ae,d]	none	13	10	-	MD **0.11 higher** (2.02 lower to 2.24 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. MID used to assess imprecision was ±0.53

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±3.80

f. Heterogeneity that cannot be explained by subgrouping strategies

g. MID used to assess imprecision was ±5.92

h. MID used to assess imprecision was ±2.51

i. MID used to assess imprecision was ±3.60

j. Heterogeneity that cannot be explained by subgrouping strategies and I2 >75%

k. MID used to assess imprecision was ±0.86

l. MID used to assess imprecision was ±9.50

m. MID used to assess imprecision was ±2.92

n. MID used to assess imprecision was ±7.30

o. MID used to assess imprecision was ±6.2

p. MID used to assess imprecision was ±3.5

q. MID used to assess imprecision was ±12.58

r. MID used to assess imprecision was ±17.75

s. MID used to assess imprecision was ±10.88

t. MID used to assess imprecision was ±6.98

u. MID used to assess imprecision was ±6.9

v. MID used to assess imprecision was ±9.6

w. MID used to assess imprecision was ±20.45

x. MID used to assess imprecision was ±7.38

y. MID used to assess imprecision was ±7.79

z. MID used to assess imprecision was ±7.30

aa. MID used to assess imprecision was ±7.07

ab. MID used to assess imprecision was ±3.65

ac. Imprecision assessed using sample size as zero events in both arms of a single study. Downgraded by 1 increment as sample size <350 and >70

ad. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study.

ae. MID used to assess imprecision was ±1.33

Table 55: Clinical evidence profile: Fatigue/energy management programme vs. control (waitlist, no intervention, information only) – outcomes >6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), >6 months	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-7) (follow up: 52 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b,c]	none	34	35	-	MD **0.02 lower** (0.37 lower to 0.33 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS - total (0-84) (follow up: 52 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b,d]	none	34	35	-	MD **0.1 higher** (5.46 lower to 5.66 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS - physical (0-36) (follow up: 52 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	34	35	-	MD **0.07 higher** (2.56 lower to 2.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - cognitive (0-40) (follow up: 52 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [f]	none	34	35	-	MD **0.2 higher** (2.66 lower to 3.06 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS - psychosocial (0-8) (follow up: 52 weeks; Scale from: 0 to 8)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), >6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	34	35	-	MD **0.22 higher** (0.48 lower to 0.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - fatigue (8-56) (follow up: 52 weeks; Scale from: 8 to 56)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	34	39	-	MD **1.45 lower** (5.46 lower to 2.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical function (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [i]	none	34	35	-	MD **2.91 higher** (3.45 lower to 9.27 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 role physical (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	34	35	-	MD **3.88 higher** (13.53 lower to 21.29 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 body pain (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	34	35	-	MD **5.37 lower** (13.62 lower to 2.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 general health (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	34	35	-	MD **1.88 higher** (3.52 lower to 7.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), >6 months	Relative (95% CI)	Absolute (95% CI)		
SF-36 vitality (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,m]	none	34	35	-	MD **2.87 higher** (3.98 lower to 9.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 social function (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	34	35	-	MD **1.14 lower** (9.48 lower to 7.2 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 role emotional (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,o]	none	34	35	-	MD **7.3 higher** (9.98 lower to 24.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental health (0-100) (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [p]	none	34	35	-	MD **0.56 higher** (5.92 lower to 7.04 higher)	⨁⨁◯◯ LOW	CRITICAL
CIS20r - concentration (5-35) (follow up: 52 weeks; Scale from: 5 to 35)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [q]	none	34	35	-	MD **0.26 lower** (3.23 lower to 2.71 higher)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (serious) (follow up: 52 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	control (waitlist, no intervention, information only), >6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4/36 (11.1%)	10.0%	**RR 1.11** (0.30 to 4.12)	**11 more per 1,000** (from 70 fewer to 312 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 52 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [r]	none	0/36 (0.0%)	0/40 (0.0%)	**RD 0.00** (-0.05 to 0.05)	**0 fewer per 1,000** (from 50 fewer to 50 more) [s]	⨁◯◯◯ VERY LOW	CRITICAL
Adherence to programme												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	35/42 (83.3%)	86.4%	**OR 0.79** (0.24 to 2.58)	**30 fewer per 1,000** (from 260 fewer to 79 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±0.38

d. MID used to assess imprecision was ±5.98

e. MID used to assess imprecision was ±2.43

f. MID used to assess imprecision was ±3.8

g. MID used to assess imprecision was ±0.85

h. MID used to assess imprecision was ±3.5

i. MID used to assess imprecision was ±12.58

j. MID used to assess imprecision was ±17.75

k. MID used to assess imprecision was ±10.88

l. MID used to assess imprecision was ±6.98

m. MID used to assess imprecision was ±6.9

n. MID used to assess imprecision was ±9.6

o. MID used to assess imprecision was ±20.45

p. MID used to assess imprecision was ±7.38

q. MID used to assess imprecision was ±3.65

r. Imprecision assessed using sample size as zero events in both arms of a single study. Downgraded by 1 increment as sample size <350 and >70.

s. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 56: Clinical evidence profile: Fatigue/energy management programme vs. general self-management programme – outcomes up to 6 months and >6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	general self-management programme	Relative (95% CI)	Absolute (95% CI)		
MFIS - total (0-84) - 6 months (follow up: 6 months; Scale from: 0 to 84)												
1	randomised trials	serious [a]	not serious	not serious	not serious [b]	none	99	104	-	MD **1 lower** (5.33 lower to 3.33 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
MFIS - total (0-84) - 12 months (follow up: 12 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	38	40	-	MD **5.1 lower** (12.17 lower to 1.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
BDI (0-63) - 6 weeks (follow up: 6 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [d]	serious [c,e]	none	100	104	-	MD **1.2 lower** (3.31 lower to 0.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	general self-management programme	Relative (95% CI)	Absolute (95% CI)		
Adverse events (all relapses) - 6 weeks (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	serious [d]	very serious [c]	none	4/100 (4.0%)	3.9%	**RR 1.04** (0.27 to 4.05)	**2 more per 1,000** (from 28 fewer to 117 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - completed at least 4 sessions												
1	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	94/109 (86.2%)	86.2%	**OR 1.00** (0.46 to 2.16)	**0 fewer per 1,000** (from 120 fewer to 69 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MID used to assess imprecision was ±6.03

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months specified in the protocol

e. MID used to assess imprecision was ±3.28

Table 57: Clinical evidence profile: Fatigue/energy management programme vs. relaxation – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	relaxation	Relative (95% CI)	Absolute (95% CI)		
MFIS – Total (0-84) (follow up: 3 months; Scale from: 0 to 84)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	relaxation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	14	11	-	MD **9.6 lower** (20.4 lower to 1.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS – Physical (0-36) (follow up: 3 months; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	14	11	-	MD **3.8 lower** (9.06 lower to 1.46 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS – Cognitive (0-40) (follow up: 3 months; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	14	11	-	MD **4.9 lower** (10.93 lower to 1.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS – Psychosocial (0-8) (follow up: 3 months; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	14	11	-	MD **0.9 lower** (2.41 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Checklist individual strength – Total (20-140) (follow up: 3 months; Scale from: 20 to 140)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,g]	none	14	11	-	MD **2.2 higher** (18.58 lower to 22.98 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Checklist individual strength – Concentration (5-35) (follow up: 3 months; Scale from: 5 to 35)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,h]	none	14	11	-	MD **1.5 higher** (5.35 lower to 8.35 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Checklist individual strength – Physical activity (3-21) (follow up: 3 months; Scale from: 3 to 21)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	relaxation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,i]	none	14	11	-	MD **1.2 higher** (3.14 lower to 5.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Checklist individual strength – Motivation (4-28) (follow up: 3 months; Scale from: 4 to 28)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	14	11	-	MD **1.2 higher** (3.14 lower to 5.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Checklist individual strength – Subjective fatigue (8-56) (follow up: 3 months; Scale from: 8 to 56)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,k]	none	14	11	-	MD **1.3 higher** (9.04 lower to 11.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Physical functioning (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	126	99	-	MD **8.6 higher** (8.17 lower to 25.37 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Role physical function (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,m]	none	14	11	-	MD **7.3 lower** (36.91 lower to 22.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Physical pain (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	14	11	-	MD **24.1 higher** (12.31 higher to 35.89 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 (0-100 for all) – General health (follow up: 3 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue/energy management programme	relaxation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,o]	none	14	11	-	MD **1.2 higher** (11 lower to 13.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Vitality (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,p]	none	14	11	-	MD **5.5 higher** (7.59 lower to 18.59 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Social functioning (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,q]	none	14	11	-	MD **3.8 higher** (9.63 lower to 17.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Role emotional function (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,r]	none	14	11	-	MD **6 lower** (33.25 lower to 21.25 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Mental health (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,s]	none	14	11	-	MD **6.7 lower** (18.87 lower to 5.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 (0-100 for all) – Health change (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,t]	none	14	11	-	MD **14.5 lower** (31.63 lower to 2.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±5.68

d. MID used to assess imprecision was ±2.63

e. MID used to assess imprecision was ±3.38

f. MID used to assess imprecision was ±1.48

g. MID used to assess imprecision was ±9.53

h. MID used to assess imprecision was ±3.88

i. MID used to assess imprecision was ±2.48

j. MID used to assess imprecision was ±3.2

k. MID used to assess imprecision was ±4.33

l. MID used to assess imprecision was ±10.85

m. MID used to assess imprecision was ±17.15

n. MID used to assess imprecision was ±12.13

o. MID used to assess imprecision was ±8.88

p. MID used to assess imprecision was ±7.98

q. MID used to assess imprecision was ±9.58

r. MID used to assess imprecision was ±17.25

s. MID used to assess imprecision was ±7.58

t. MID used to assess imprecision was ±13.93

Table 58: Clinical evidence profile: Aerobic exercise + fatigue self-management vs. control (information only) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise + fatigue self-management	control (information only)	Relative (95% CI)	Absolute (95% CI)		

Fatigue Impact scale - total (0-160) (follow up: 24 weeks; Scale from: 0 to 160)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise + fatigue self-management	control (information only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	70	69	-	MD **8.68 lower** (19.33 lower to 1.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 (0-100) - Physical function (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	70	69	-	MD **6.7 lower** (13.43 lower to 0.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 (0-100) - Mental function (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	70	69	-	MD **6.21 lower** (12.93 lower to 0.51 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (exacerbations) (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	14/70 (20.0%)	24.6%	**RR 0.81** (0.43 to 1.52)	**47 fewer per 1,000** (from 140 fewer to 128 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (orthopaedic problems) (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	28/70 (40.0%)	34.8%	**RR 1.15** (0.75 to 1.77)	**52 more per 1,000** (from 87 fewer to 268 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (at least 1 fall) (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	22/70 (31.4%)	30.4%	**RR 1.03** (0.63 to 1.70)	**9 more per 1,000** (from 113 fewer to 213 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - completed all 1-1 calls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise + fatigue self-management	control (information only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	56/70 (80.0%)	76.8%	**OR 1.21** (0.54 to 2.71)	**32 more per 1,000** (from 127 fewer to 132 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - completed all group calls with or without at least 1 makeup session												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	63/70 (90.0%)	84.1%	**OR 1.71** (0.62 to 4.70)	**60 more per 1,000** (from 75 fewer to 121 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±14.41

d. MID used to assess imprecision was ±9.2

e. MID used to assess imprecision was ±9.99

Table 59: Clinical evidence profile: Aerobic exercise + fatigue self-management vs. aerobic exercise only – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise + fatigue self-management	aerobic exercise only	Relative (95% CI)	Absolute (95% CI)		
Fatigue Impact scale - total (0-160) (follow up: 24 weeks; Scale from: 0 to 160)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	70	69	-	MD **14.08 lower** (24.07 lower to 4.09 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise + fatigue self-management	aerobic exercise only	Relative (95% CI)	Absolute (95% CI)		
MSIS-29 (0-100) - Physical function (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	70	69	-	MD **1.08 lower** (7.5 lower to 5.34 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 (0-100) - Mental function (follow up: 24 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	70	69	-	MD **1.52 lower** (8.09 lower to 5.05 higher)	⨁⨁◯◯ LOW	CRITICAL
Adverse events (exacerbations) (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	14/70 (20.0%)	17.4%	**RR 1.15** (0.57 to 2.31)	**26 more per 1,000** (from 75 fewer to 228 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (orthopaedic problems) (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	28/70 (40.0%)	23.2%	**RR 1.73** (1.03 to 2.89)	**169 more per 1,000** (from 7 more to 438 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (at least 1 fall) (follow up: 24 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	22/70 (31.4%)	17.4%	**RR 1.81** (0.97 to 3.36)	**141 more per 1,000** (from 5 fewer to 410 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - completed all 1-1 calls (follow up: 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aerobic exercise + fatigue self-management	aerobic exercise only	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	56/70 (80.0%)	68.1%	**OR 1.87** (0.86 to 4.06)	**119 more per 1,000** (from 34 fewer to 215 more)	⨁⨁◯◯ LOW	CRITICAL
Adherence - completed all group calls with or without at least 1 makeup session (follow up: 24 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	63/70 (90.0%)	85.5%	**OR 1.53** (0.55 to 4.27)	**45 more per 1,000** (from 91 fewer to 107 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±14.91

d. MID used to assess imprecision was ±9.49

e. MID used to asssess imprecision was ±9.70

Table 60: Clinical evidence profile: Fatigue management + CBT vs. control (local/standard care) – outcomes up to 6 months and >6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue management + CBT	control (local/standard care)	Relative (95% CI)	Absolute (95% CI)		
Global fatigue severity (1-7) - 5.5 months (follow-up: 5.5 months; Scale from: 1 to 7)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue management + CBT	control (local/standard care)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	NR	NR	-	MD **0.36 lower** (0.63 lower to 0.09 lower)	⨁⨁◯◯ Low	CRITICAL
Global fatigue severity (1-7) - 12 months (follow-up: 12 months; Scale from: 1 to 7)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	62	69	-	MD **0.3 lower** (0.61 lower to 0.01 lower)	⨁◯◯◯ Very low	CRITICAL
MFIS total (0-84) (follow-up: 10 weeks; Scale from: 0 to 84)												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b,e]	none	23	17	-	MD **3.88 lower** (6.28 lower to 1.48 lower)	⨁◯◯◯ Very low	CRITICAL
Chalder fatigue scale (0-33) (follow-up: range 10 weeks to 12 weeks; Scale from: 0 to 33)												
2	randomised trials	not serious	very serious[f]	not serious	serious[b,g]	none	159	156	-	MD **4.39 lower** (9.25 lower to 0.46 higher)	⨁◯◯◯ Very low	CRITICAL
MS fatigue self-efficacy scale (10-100) - 5.5 months (follow-up: 5.5 months; Scale from: 10 to 100)												
1	randomised trials	serious[a]	not serious	not serious	serious[b,h]	none	NR	NR	-	MD **6 higher** (0 to 12 higher)	⨁⨁◯◯ Low	CRITICAL
MS fatigue self-efficacy scale (10-100) - 12 months (follow-up: 12 months; Scale from: 10 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,h]	none	62	69	-	MD **6 higher** (1 lower to 13 higher)	⨁◯◯◯ Very low	CRITICAL
Fatigue Scale of Motor and Cognition - Total (20-100) (follow-up: 12 weeks; Scale from: 20 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue management + CBT	control (local/standard care)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious[l]	none	136	139	-	MD **3.47 lower** (5.89 lower to 1.05 lower)	⨁⨁⨁⨁ High	CRITICAL
Fatigue Scale of Motor and Cognition - Motor (0-50) (follow-up: 12 weeks; Scale from: 0 to 50)												
1	randomised trials	not serious	not serious	not serious	not serious[l]	none	136	139	-	MD **1.49 lower** (2.74 lower to 0.24 lower)	⨁⨁⨁⨁ High	CRITICAL
Fatigue Scale of Motor and Cognition - Cognition (0-50) (follow-up: 12 weeks; Scale from: 0 to 50)												
1	randomised trials	not serious	not serious	not serious	not serious[k]	none	136	139	-	MD **2.01 lower** (3.38 lower to 0.64 lower)	⨁⨁⨁⨁ High	CRITICAL
SF-36 vitality (0-100) - 5.5 months (follow-up: 5.5 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,l]	none	NR	NR	-	MD **6.38 higher** (0.45 higher to 12.31 higher)	⨁◯◯◯ Very low	CRITICAL
SF-36 vitality - 12 months (follow-up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,l]	none	62	69	-	MD **6.64 higher** (0.84 lower to 12.44 higher)	⨁◯◯◯ Very low	CRITICAL
MSIS-29 total (0-100) - 5.5 months (follow-up: 5.5 months; Scale from: 0 to 100)												
1	randomised trials	serious[a]	not serious	not serious	not serious[m]	none	NR	NR	-	MD **1.56 lower** (6.45 lower to 3.33 higher)	⨁⨁⨁◯ Moderate	CRITICAL
MSIS-29 total (0-100) - 12 months (follow-up: 12 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue management + CBT	control (local/standard care)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	not serious[m]	none	62	69	-	MD **4.34 lower** (8.61 lower to 0.07 lower)	⨁⨁◯◯ Low	CRITICAL
MSIS-29 physical subscale (0-100) - 5.5 months (follow-up: 5.5 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[n]	none	NR	NR	-	MD **0.81 lower** (5.91 lower to 4.29 higher)	⨁⨁◯◯ Low	CRITICAL
MSIS-29 physical (0-100) - 12 months (follow-up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	not serious	not serious[n]	none	62	69	-	MD **4.74 lower** (9.4 lower to 0.08 lower)	⨁⨁◯◯ Low	CRITICAL
MS neuropsychological screening questionnaire (0-60?) (follow-up: 12 weeks; Scale from: 0 to 60)												
1	randomised trials	not serious	not serious	not serious	not serious[o]	none	136	139	-	MD **0.27 lower** (2.21 lower to 1.67 higher)	⨁⨁⨁⨁ High	CRITICAL
HADS anxiety (0-21) (follow-up: range 10 weeks to 12 weeks; Scale from: 0 to 21)												
2	randomised trials	not serious	very serious[f]	not serious	serious[b,p]	none	159	156	-	MD **2.72 lower** (7.11 lower to 1.66 higher)	⨁◯◯◯ Very low	CRITICAL
HADS depression (0-21) (follow-up: range 10 weeks to 12 weeks; Scale from: 0 to 21)												
2	randomised trials	not serious	very serious[f]	not serious	serious[b,q]	none	159	156	-	MD **0.76 lower** (1.41 lower to 0.11 lower)	⨁◯◯◯ Very low	CRITICAL
Withdrawal due to adverse events (relapse) - 5.5 months (follow-up: 5.5 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fatigue management + CBT	control (local/standard care)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/61 (3.3%)	0/72 (0.0%)	**OR 9.00** (0.55 to 146.78)	**33 more per 1,000** (from 20 fewer to 85 more)[r]	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±0.52

d. Downgraded by 1 increment as the majority of the evidence had a follow-up of less than the 3 months minimum specified in the protocol

e. MID used to assess imprecision was ±1.92

f. Heterogeneity present that could not be explained by subgrouping strategies and I2 >75%

g. MID used to assess imprecision was ±2.33

h. MID used to assess imprecision was ±8.25

i. MID used to assess imprecision was ±5.92

j. MID used to assess imprecision was ±3.04

k. MID used to assess imprecision was ±3.72

l. MID used to assess imprecision was ±9.13

m. MID used to assess imprecision was ±9.18

n. MID used to assess imprecision was ±10.43

o. MID used to assess imprecision was ±5.11

p. MID used to assess imprecision was ±2.12

q. MID used to assess imprecision was ±1.81

r. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 61: Clinical evidence profile: Multidisciplinary rehabilitation + fatigue self-management vs. control (consultation only)– outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multidisciplinary rehabilitation + fatigue self-management	control (consultation only)	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 3 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	22	24	-	MD **1.8 higher** (5 lower to 8.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 3 months; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	22	24	-	MD **1.7 higher** (1.42 lower to 4.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 3 months; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	22	24	-	MD **0.2 lower** (4.16 lower to 3.76 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Psychosocial scale (0-8) (follow up: 3 months; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	22	24	-	MD **0.2 higher** (0.79 lower to 1.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (1-7) (follow up: 3 months; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	22	24	-	MD **1.9 lower** (6.41 lower to 2.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 (0-100) - Physical function (follow up: 3 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multidisciplinary rehabilitation + fatigue self-management	control (consultation only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	22	24	-	MD **1 lower** (4.67 lower to 2.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 (0-100) - Mental function (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	22	24	-	MD **1 lower** (4.21 lower to 2.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional independence measure (1-7) (follow up: 3 months; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	22	24	-	MD **3 higher** (0.39 higher to 5.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - Total (0-140) (follow up: 3 months; Scale from: 0 to 140)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	22	24	-	MD **3 lower** (8.08 lower to 2.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - Subjective fatigue (8-56) (follow up: 3 months; Scale from: 8 to 56)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	22	24	-	MD **1.1 lower** (3.51 lower to 1.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - Concentration (5-35) (follow up: 3 months; Scale from: 5 to 35)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	22	24	-	MD **0.8 lower** (2.87 lower to 1.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r - Motivation (4-28) (follow up: 3 months; Scale from: 4 to 28)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multidisciplinary rehabilitation + fatigue self-management	control (consultation only)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	22	24	-	MD **0.9 lower** (2.75 lower to 0.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CIS20r - Physical activity (3-21) (follow up: 3 months; Scale from: 3 to 21)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,l]	none	22	24	-	MD **0.3 lower** (1.75 lower to 1.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±6.9

d. MID used to assess imprecision was ±3.15

e. MID used to assess imprecision was ±3.7

f. MID used to assess imprecision was ±0.95

g. MID used to assess imprecision was ±4.25

h. MID used to assess imprecision was ±4.5

i. MID used to assess imprecision was ±2.5

j. MID used to assess imprecision was ±5.15

k. MID used to assess imprecision was ±1.65

l. MID used to assess imprecision was ±1.45

Table 62: Clinical evidence profile: Multidisciplinary rehabilitation + fatigue self-management vs. relaxation – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multidisciplinary rehabilitation + fatigue self-management	relaxation	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - total (0-84) (follow up: 4 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	14	15	-	MD **0** (10.3 lower to 10.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical functioning (0-100) (follow up: 4 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	14	15	-	MD **14.8 higher** (0.6 lower to 30.2 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 fatigue/vitality (0-100) (follow up: 4 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,e]	none	14	15	-	MD **3 higher** (9.7 lower to 15.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±6.78

d. MID used to assess imprecision was ±9.5

e. MID used to assess imprecision was ±6.88

Table 63: Clinical evidence profile: Multidisciplinary rehabilitation (medical, exercise, counselling and fatigue self-management) vs. no rehabilitation in those treated with methylprednisolone for a relapse – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multidisciplinary rehab (medical, exercise, counselling + fatigue SM)	no rehab in those treated with methylprednisolone for relapse	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) (follow up: 3 months; Scale from: 9 to 63)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b,c]	none	19	20	-	MD **4 lower** (15.77 lower to 7.77 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±7.05

Table 64: Clinical evidence profile: Self-management programme vs. control – outcomes up to 6 months and >6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management programme	control	Relative (95% CI)	Absolute (95% CI)		
Fatigue severity scale (1-7) (follow up: 11 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	32	31	-	MD **5.86 lower** (6.08 lower to 5.64 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue VAS (0-10) (follow up: 4 months; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,e]	none	78	64	-	MD **0.5 higher** (0.54 lower to 1.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management programme	control	Relative (95% CI)	Absolute (95% CI)		
MFIS - total (0-84) - 6 months (follow up: 6 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,f]	none	64	81	-	MD **4.4 lower** (9.67 lower to 0.87 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - total (0-84) - 12 month (follow up: 12 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,f]	none	64	81	-	MD **3.1 lower** (8.41 lower to 2.21 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - at least 10 point reduction vs. baseline - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	-/64	32/81 (39.5%)	**OR 1.74** (0.78 to 3.88)	**137 more per 1,000** (from 58 fewer to 322 more)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - at least 10 point reduction vs. baseline - 12 months (follow up: 12 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	-/64	29/81 (35.8%)	**OR 1.74** (0.79 to 3.83)	**134 more per 1,000** (from 52 fewer to 323 more)	⨁◯◯◯ VERY LOW	CRITICAL
SF-8 physical domain (0-100) - 6 months (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [g]	none	64	81	-	MD **0.1 lower** (3.17 lower to 2.97 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-8 physical domain (0-100) - 12 month (follow up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [g]	none	64	81	-	MD **1.7 lower** (4.59 lower to 1.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management programme	control	Relative (95% CI)	Absolute (95% CI)		
SF-8 mental health domain (0-100) - 6 months (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	64	81	-	MD **1.2 higher** (1.97 lower to 4.37 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-8 mental health domain (0-100) - 12 month (follow up: 12 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	64	81	-	MD **0.5 higher** (2.63 lower to 3.63 higher)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 (0-100) - Physical (follow up: 4 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [i]	none	78	64	-	MD **6.6 lower** (12.44 lower to 0.76 lower)	⨁⨁◯◯ LOW	CRITICAL
MSIS-29 (0-100) - Psychological (follow up: 4 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,j]	none	78	64	-	MD **3.6 lower** (12.64 lower to 5.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HADS - anxiety (0-21) (follow up: 4 months; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [k]	none	78	64	-	MD **0.5 lower** (1.82 lower to 0.82 higher)	⨁⨁◯◯ LOW	CRITICAL
HADS - depression (0-21) (follow up: 4 months; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [l]	none	78	64	-	MD **0.9 lower** (1.85 lower to 0.05 higher)	⨁⨁◯◯ LOW	CRITICAL
PHQ-9 (depression; 0-27) - 6 months (follow up: 6 months; Scale from: 0 to 27)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management programme	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [d,m]	none	64	81	-	MD **1 lower** (2.47 lower to 0.47 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PHQ-9 (depression; 0-27) - 12 months (follow up: 12 months; Scale from: 0 to 27)												
1	randomised trials	very serious [a]	not serious	not serious	serious [d,m]	none	64	81	-	MD **1 lower** (2.5 lower to 0.5 higher)	⨁◯◯◯ VERY LOW	CRITICAL
PHQ-9 (depression) - at least 50% reduction vs. baseline - 6 months (follow up: 6 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	-/64	10/81 (12.3%)	**OR 1.41** (0.45 to 4.42)	**42 more per 1,000** (from 64 fewer to 260 more)	⨁◯◯◯ VERY LOW	CRITICAL
PHQ-9 (depression) - at least 50% reduction vs. baseline - 12 months (follow up: 12 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	-/64	14/81 (17.3%)	**OR 1.00** (0.31 to 3.23)	**0 fewer per 1,000** (from 112 fewer to 230 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 11 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [n]	none	0/32 (0.0%)	0/31 (0.0%)	**RD 0.00** (-0.06 to 0.06)	**0 fewer per 1,000** (from 60 fewer to 60 more) [o]	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events - 6 months (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [n]	none	0/62 (0.0%)	0/79 (0.0%)	**RD 0.00** (-0.03 to 0.03)	**0 fewer per 1,000** (from 30 fewer to 30 more) [o]	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events - 12 months (follow up: 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management programme	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [n]	none	0/60 (0.0%)	0/80 (0.0%)	**RD 0.00** (-0.03 to 0.03)	**0 fewer per 1,000** (from 30 fewer to 30 more) [o]	⨁◯◯◯ VERY LOW	CRITICAL

Treatment adherence - attending all 8 sessions

1	randomised trials	not serious	not serious	not serious	serious [d]	none	58/75 (77.3%)	87.5%	**OR 0.49** (0.21 to 1.12)	**101 fewer per 1,000** (from 280 fewer to 12 more)	⨁⨁⨁◯ MODERATE	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up of less than the 3 months minimum in the protocol

c. MID used to assess imprecision was ±0.19

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±1.4

f. MID used to assess imprecision was ±6.85

g. MID used to assess imprecision was ±4.03

h. MID used to assess imprecision was ±4.63

i. MID used to assess imprecision was ±13.18

j. MID used to assess imprecision was ±11.68

k. MID used to assess imprecision was ±2.15

l. MID used to assess imprecision was ±2.0

m. MID used to assess imprecision was ±2.08

n. Imprecision assessed based on sample size as zero events in both arms of a single study. Downgraded by 2 increments if sample size was <70 and 1 increment if sample size was >70 and <350

o. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 65: Clinical evidence profile: Self-management programme + exercise vs. control (waitlist) – outcomes up to 6 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Self-management + exercise	control (waitlist)	Relative (95% CI)	Absolute (95% CI)		
WEIMuS fatigue scale - Total (0-68) (follow up: 6 weeks; Scale from: 0 to 68)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	8	6	-	MD **3.3 higher** (9.72 lower to 16.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
WEIMuS fatigue scale - Mental (0-36) (follow up: 6 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,e]	none	8	6	-	MD **2 higher** (4.1 lower to 8.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL
WEIMuS fatigue scale - Physical (0-32) (follow up: 6 weeks; Scale from: 0 to 32)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,f]	none	8	6	-	MD **1.3 higher** (7.55 lower to 10.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MusiQoL score (0-100) (follow up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,g]	none	8	6	-	MD **2.6 higher** (9.53 lower to 14.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (follow up: 6 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [h]	none	0/8 (0.0%)	0/6 (0.0%)	**RD 0.00** (-0.24 to 0.24)	**0 fewer per 1,000** (from 240 fewer to 240 more) [i]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence has a follow-up less than the 3 months specified in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±5.95

e. MID used to assess imprecision was ±3.53

f. MID used to assess imprecision was ±3.95

g. MID used to assess imprecision was ±4.6

h. Imprecision assessed using sample size as zero events in both arms of a single study. Downgraded by 2 increments as sample size <70.

i. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 66: Clinical evidence profile: CBT vs. control – up to 6 months and >6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
CIS20r fatigue (8-56) - 16 weeks (follow up: 16 weeks; Scale from: 8 to 56)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	39	35	-	MD **6.3 lower** (10.74 lower to 1.86 lower)	⨁⨁◯◯ LOW	CRITICAL
CIS20r fatigue (8-56) - 52 weeks (follow up: 52 weeks; Scale from: 8 to 56)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,c]	none	39	35	-	MD **0.6 lower** (4.86 lower to 3.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r fatigue - at least 8-point improvement - 16 weeks (follow up: 16 weeks)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	22/39 (56.4%)	25.7%	**RR 2.19** (1.17 to 4.11)	**306 more per 1,000** (from 44 more to 800 more)	⨁⨁◯◯ LOW	CRITICAL
FSS score (1-7) - 16 weeks (follow up: 16 weeks; Scale from: 1 to 7)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	39	35	-	MD **0.7 lower** (1.12 lower to 0.28 lower)	⨁⨁◯◯ LOW	CRITICAL
FSS score (1-7) - 52 weeks (follow up: 52 weeks; Scale from: 1 to 7)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	39	35	-	MD **0.1 lower** (0.51 lower to 0.31 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS total (0-84) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 84)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,e]	none	39	35	-	MD **2.5 lower** (8.98 lower to 3.98 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS total (0-84) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 84)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,e]	none	39	35	-	MD **3.4 higher** (2.56 lower to 9.36 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS physical subscale (0-36) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 36)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	39	35	-	MD **1.8 lower** (4.9 lower to 1.3 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS physical subscale (0-36) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 36)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	39	35	-	MD **2.2 higher** (0.76 lower to 5.16 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS cognitive subscale (0-40) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	39	35	-	MD **0.7 lower** (4.37 lower to 2.97 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS cognitive subscale (0-40) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	39	35	-	MD **1 higher** (2.28 lower to 4.28 higher)	⨁⨁◯◯ LOW	CRITICAL
MFIS psychosocial (0-8) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 8)												
1	randomised trials	serious [a]	not serious	not serious	not serious [h]	none	39	35	-	MD **0** (0.71 lower to 0.71 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
MFIS psychosocial (0-8) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 8)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,h]	none	39	35	-	MD **0.2 higher** (0.53 lower to 0.93 higher)	⨁⨁◯◯ LOW	CRITICAL
Piper Fatigue Scale (0-10?) (follow up: 4 months; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	70	70	-	MD **2.27 lower** (3.9 lower to 0.64 lower)	⨁◯◯◯ VERY LOW	CRITICAL
DASS-21 - anxiety subscale (0-21) (follow up: 4 months; Scale from: 0 to 21)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	70	70	-	MD **1.15 lower** (2.04 lower to 0.26 lower)	⨁◯◯◯ VERY LOW	CRITICAL
DASS-21 - depression subscale (0-21) (follow up: 4 months; Scale from: 0 to 21)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,k]	none	70	70	-	MD **1.4 lower** (2.16 lower to 0.64 lower)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 vitality (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,l]	none	39	35	-	MD **7.8 higher** (1.04 higher to 14.56 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 vitality (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [l]	none	39	35	-	MD **0.7 higher** (7 lower to 8.4 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 physical functioning (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,m]	none	39	35	-	MD **3.1 lower** (13.39 lower to 7.19 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 physical functioning (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,m]	none	39	35	-	MD **4.4 lower** (14.5 lower to 5.7 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 physical role functioning (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,n]	none	39	35	-	MD **15.6 higher** (1.63 lower to 32.83 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 physical role functioning (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,n]	none	39	35	-	MD **9.7 lower** (27.25 lower to 7.85 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 emotional role functioning (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious [o]	none	39	35	-	MD **2.6 higher** (14.73 lower to 19.93 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
SF-36 emotional role functioning (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious [o]	none	39	35	-	MD **0.6 higher** (17.49 lower to 18.69 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
SF-36 social functioning (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,p]	none	39	35	-	MD **7.2 higher** (1.89 lower to 16.29 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 social functioning (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,p]	none	39	35	-	MD **5.9 lower** (14.96 lower to 3.16 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 mental health (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	not serious [q]	none	39	35	-	MD **0** (6.03 lower to 6.03 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
SF-36 mental health (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,q]	none	39	35	-	MD **2.8 lower** (10 lower to 4.4 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 general health (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,r]	none	39	35	-	MD **1.7 lower** (8.45 lower to 5.05 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 general health (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,r]	none	39	35	-	MD **1.7 lower** (8.68 lower to 5.28 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 bodily pain (0-100) - 16 weeks (follow up: 16 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,s]	none	39	35	-	MD **4.7 higher** (4.68 lower to 14.08 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 bodily pain (0-100) - 52 weeks (follow up: 52 weeks; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,s]	none	39	35	-	MD **0.1 lower** (10.78 lower to 10.58 higher)	⨁◯◯◯ VERY LOW	CRITICAL
CIS20r concentration (5-35) - 16 weeks (follow up: 16 weeks; Scale from: 5 to 35)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,t]	none	39	35	-	MD **1.2 lower** (4.6 lower to 2.2 higher)	⨁⨁◯◯ LOW	CRITICAL
CIS20r concentration (5-35) - 52 weeks (follow up: 52 weeks; Scale from: 5 to 35)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,t]	none	39	35	-	MD **0.4 higher** (3.04 lower to 3.84 higher)	⨁⨁◯◯ LOW	CRITICAL

Serious adverse events - 16 weeks (follow up: 16 weeks)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/39 (2.6%)	5.7%	**RR 0.45** (0.04 to 4.74)	**31 fewer per 1,000** (from 55 fewer to 214 more)	⨁◯◯◯ VERY LOW	CRITICAL

Serious adverse events - 52 weeks (follow up: 52 weeks)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	4/39 (10.3%)	8.6%	**RR 1.20** (0.29 to 4.98)	**17 more per 1,000** (from 61 fewer to 341 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±3.63

d. MID used to assess imprecision was ±0.38

e. MID used to assess imprecision was ±5.53

f. MID used to assess imprecision was ±2.68

g. MID used to assess imprecision was ±3.5

h. MID used to assess imprecision was ±0.75

i. MID used to assess imprecision was ±2.45

j. MID used to assess imprecision was ±1.09

k. MID used to assess imprecision was ±1.25

l. MID used to assess imprecision was ±7.03

m. MID used to assess imprecision was ±10.63

n. MID used to assess imprecision was ±15.03

o. MID used to assess imprecision was ±20.85

p. MID used to assess imprecision was ±9.35

q. MID used to assess imprecision was ±6.53

r. MID used to assess imprecision was ±6.78

s. MID used to assess imprecision was ±9.43

t. MID used to assess imprecision was ±3.78

Table 67: Clinical evidence profile: CBT vs. relaxation – up to 6 months and >6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	relaxation	Relative (95% CI)	Absolute (95% CI)		
Chalder fatigue scale (0-33) - 5 months (follow up: 5 months; Scale from: 0 to 33)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	35	37	-	MD **2.12 lower** (4.41 lower to 0.17 higher)	⨁⨁◯◯ LOW	CRITICAL
Chalder fatigue scale (0-33) - 8 months (follow up: 8 months; Scale from: 0 to 33)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	35	37	-	MD **2.12 lower** (4.82 lower to 0.58 higher)	⨁⨁◯◯ LOW	CRITICAL
Fatigue-related impairment (work and social adjustment scale; 0-40) - 5 months (follow up: 5 months; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	35	37	-	MD **5.86 lower** (9.99 lower to 1.73 lower)	⨁⨁◯◯ LOW	CRITICAL
Fatigue-related impairment (work and social adjustment scale; 0-40) - 8 months (follow up: 8 months; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBT	relaxation	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	35	37	-	MD **5.19 lower** (9.9 lower to 0.48 lower)	⨁⨁◯◯ LOW	CRITICAL
HADS - depression (0-21) - 5 months (follow up: 5 months; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,e]	none	35	37	-	MD **1.51 lower** (2.87 lower to 0.15 lower)	⨁⨁◯◯ LOW	CRITICAL
HADS - depression (0-21) - 8 months (follow up: 8 months; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,e]	none	35	37	-	MD **1.08 lower** (2.56 lower to 0.4 higher)	⨁⨁◯◯ LOW	CRITICAL
HADS - anxiety (0-21) - 5 months (follow up: 5 months; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	not serious [f]	none	35	37	-	MD **0.21 lower** (1.71 lower to 1.29 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
HADS - anxiety (0-21) - 8 months (follow up: 8 months; Scale from: 0 to 21)												
1	randomised trials	serious [a]	not serious	not serious	not serious [f]	none	35	37	-	MD **0.19 higher** (1.48 lower to 1.86 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Acceptability - usefulness end of treatment (0-4)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	35	37	-	MD **0.21 lower** (0.63 lower to 0.21 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±2.13

d. MID used to assess imprecision was ±4.03

e. MID used to assess imprecision was ±1.54

f. MID used to assess imprecision was ±1.97

g. MID used to assess imprecision was ±0.43

Table 68: Clinical evidence profile: Motivational interviewing vs. control – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Motivational interviewing	control	Relative (95% CI)	Absolute (95% CI)		
MFIS - total (0-84) (follow up: 9 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	32	28	-	MD **20.38 lower** (26.11 lower to 14.65 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum specified in the protocol

c. MID used to assess imprecision was ±3.85

Table 69: Clinical evidence profile: Resistance + aerobic + CBT vs. control (waitlist) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic exercise + CBT	control (waitlist), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 3 months; Scale from: 0 to 84)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic exercise + CBT	control (waitlist), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	53	54	-	MD **7.4 lower** (14.13 lower to 0.67 lower)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 3 months; Scale from: 0 to 36)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,d]	none	53	54	-	MD **3.3 lower** (6.56 lower to 0.04 lower)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 3 months; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,e]	none	53	54	-	MD **2.8 lower** (6.19 lower to 0.59 higher)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact scale - Psychosocial scale (0-8) (follow up: 3 months; Scale from: 0 to 8)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	53	54	-	MD **1.3 lower** (2.12 lower to 0.48 lower)	⨁⨁◯◯ LOW	CRITICAL
MSQOL-54 score (0-100) (follow up: 3 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	53	54	-	MD **7.5 higher** (0.01 higher to 14.99 higher)	⨁⨁◯◯ LOW	CRITICAL
EQ-5D (follow up: 3 months)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,h]	none	53	54	-	MD **0.06 higher** (0.03 lower to 0.15 higher)	⨁⨁◯◯ LOW	CRITICAL
EDSS (0-10) (follow up: 3 months; Scale from: 0 to 10)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic exercise + CBT	control (waitlist), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	not serious [i]	none	53	54	-	MD **0.2 lower** (0.73 lower to 0.33 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Cognitive - PASAT (follow up: 3 months)

1	randomised trials	serious [a]	not serious	not serious	serious [b,j]	none	53	54	-	MD **4.1 lower** (9.55 lower to 1.35 higher)	⨁⨁◯◯ LOW	CRITICAL

Adverse events (MS relapse) leading to withdrawal (follow up: 3 months)

1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/55 (1.8%)	1.9%	**RR 0.98** (0.06 to 15.30)	**0 fewer per 1,000** (from 17 fewer to 265 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±8.18

d. MID used to assess imprecision was ±3.85

e. MID used to assess imprecision was ±4.33

f. MID used to assess imprecision was ±1.03

g. MID used to assess imprecision was ±10.53

h. MID used to assess imprecision was ±0.13

i. MID used to assess imprecision was ±0.75

j. MID used to assess imprecision was ±7.0

Table 70: Clinical evidence profile: Resistance + aerobic + CBT vs. control (waitlist) – >6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic exercise + CBT	control (waitlist), >6 months	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 9 months; Scale from: 0 to 84)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,c]	none	50	49	-	MD **1.7 lower** (8.69 lower to 5.29 higher)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 9 months; Scale from: 0 to 84)												
1	randomised trials	serious [a]	not serious	not serious	not serious [d]	none	50	49	-	MD **0.6 lower** (3.82 lower to 2.62 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 9 months; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	not serious	not serious [e]	none	50	49	-	MD **0.7 lower** (4.33 lower to 2.93 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Modified Fatigue Impact scale - Psychosocial scale (0-8) (follow up: 9 months; Scale from: 0 to 8)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,f]	none	50	49	-	MD **0.5 lower** (1.35 lower to 0.35 higher)	⨁⨁◯◯ LOW	CRITICAL
MSQOL-54 score (0-100) (follow up: 9 months; Scale from: 0 to 100)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,g]	none	50	49	-	MD **5.5 higher** (2.62 lower to 13.62 higher)	⨁⨁◯◯ LOW	CRITICAL
EQ-5D (follow up: 9 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [h]	none	50	49	-	MD **0.01 higher** (0.09 lower to 0.1 higher)	⨁⨁⨁◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Resistance + aerobic exercise + CBT	control (waitlist), >6 months	Relative (95% CI)	Absolute (95% CI)		
EDSS (0-10) (follow up: 9 months; Scale from: 0 to 10)												
1	randomised trials	serious [a]	not serious	not serious	serious [b,j]	none	50	49	-	MD **0.2 lower** (0.83 lower to 0.43 higher)	⨁⨁◯◯ LOW	CRITICAL
Cognitive - PASAT (follow up: 9 months)												
1	randomised trials	serious [a]	not serious	not serious	not serious [i]	none	50	49	-	MD **0.5 higher** (4.26 lower to 5.26 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse events (relapse) (follow up: 9 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	9/60 (15.0%)	23.3%	**RR 0.64** (0.30 to 1.37)	**84 fewer per 1,000** (from 163 fewer to 86 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (MS relapse) leading to withdrawal (follow up: 9 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/51 (3.9%)	2.0%	**RR 2.00** (0.19 to 21.37)	**20 more per 1,000** (from 16 fewer to 399 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±8.18

d. MID used to assess imprecision was ±3.85

e. MID used to assess imprecision was ±4.33

f. MID used to assess imprecision was ±1.03

g. MID used to assess imprecision was ±10.53

h. MID used to assess imprecision was ±0.13

i. MID used to assess imprecision was ±0.75

j. MID used to assess imprecision was ±7.0

Table 71: Clinical evidence profile: Diet vs. control – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet	control (usual care/no dietary intervention)	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-9) (follow up: 3 months; Scale from: 1 to 9)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	8	9	-	MD **1.6 lower** (3.07 lower to 0.13 lower)	⨁◯◯◯ VERY LOW	CRITICAL
>1-point reduction on FSS (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	4/8 (50.0%)	0/9 (0.0%)	**OR 13.67** (1.55 to 120.73)	**500 more per 1,000** (from 147 more to 854 more) [d]	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact Scale - total score (follow up: 6 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	68	79	-	MD **12 lower** (16.77 lower to 7.23 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - physical subscale (follow up: 6 months; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	68	79	-	MD **5.2 lower** (8.27 lower to 2.13 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - cognitive subscore (follow up: 6 months; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet	control (usual care/no dietary intervention)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	68	79	-	MD **5.9 lower** (8.46 lower to 3.34 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Modified Fatigue Impact Scale - psychosocial subscore (follow up: 6 months; Scale from: 0 to 8)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	68	79	-	MD **0.9 lower** (1.87 lower to 0.07 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Neurological fatigue index - MS (scale unclear but likely 0-30) (follow up: 6 months; Scale from: 0 to 30)

1	randomised trials	very serious [a]	not serious	not serious	serious [a,b,i]	none	18	18	-	MD **4.55 lower** (7.65 lower to 1.45 lower)	⨁◯◯◯ VERY LOW	CRITICAL

At least 5-point reduction on MSQOL-54 mental health composite (follow up: 3 months)

1	randomised trials	very serious [a]	not serious	not serious	not serious	none	8/8 (100.0%)	33.3%	**OR 31.57** (1.37 to 725.23)	**607 more per 1,000** (from 73 more to 664 more)	⨁⨁◯◯ LOW	CRITICAL

Improvement (no threshold) on MSQOL-54 physical health composite (follow up: 3 months)

1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	7/8 (87.5%)	33.3%	**OR 14.00** (1.14 to 172.64)	**542 more per 1,000** (from 30 more to 655 more)	⨁◯◯◯ VERY LOW	CRITICAL

MSIS-29 (0-100) (follow up: 6 months; Scale from: 0 to 100)

1	randomised trials	very serious [a]	not serious	not serious	serious [b,j]	none	18	18	-	MD **7.36 lower** (16.32 lower to 1.6 higher)	⨁◯◯◯ VERY LOW	CRITICAL

EDSS score (0-10) (follow up: 6 months; Scale from: 0 to 10)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet	control (usual care/no dietary intervention)	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	serious [k]	not serious	serious [b,l]	none	86	97	-	MD **0.59 lower** (1.12 lower to 0.06 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (follow up: 3-6 months)												
2	randomised trials	very serious [a]	not serious	not serious	very serious [m]	none	1/77 (1.3%)	9.1%	**RD -0.01** (-0.05 to 0.04)	**10 fewer per 1,000** (from 50 fewer to 40 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 3 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	1/9 (11.1%)	18.2%	**RR 0.61** (0.07 to 5.70)	**71 fewer per 1,000** (from 169 fewer to 854 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence to intervention or control												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	8/10 (80.0%)	100.0%	**RR 0.81** (0.57 to 1.15) [n]	**190 fewer per 1,000** (from 430 fewer to 150 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±0.7

d. Absolute effect calculated manually using risk difference as there are zero events in at least one arm of at least one study

e. MID used to assess imprecision was ±7.60

f. MID used to assess imprecision was ±4.90

g. MID used to assess imprecision was ±5.25

h. MID used to assess imprecision was ±1.50

i. MID used to assess imprecision was ±3.86

j. MID used to assess imprecision was ±11.11

k. Downgraded by 1 increment as heterogeneity is present that cannot be explained by subgroup analyses, based on I2 value >50%

l. MID used to assess imprecision was ±0.88

m. Imprecision assessed by calculating OIS and assessing power, as zero events in both arms of some but not all studies. Downgraded by 2 increments as power <80%.

n. Presented as RR despite event rate >50%, as using OR would not allow absolute effect to be calculated given the risk in the control group is 100%

Table 72: Clinical evidence profile: Diet (individualised) vs. standard healthy diet recommendations – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet (individualised)	standard healthy diet recommendations	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - Total score (0-84) (follow up: 12 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	50	50	-	MD **0.7 lower** (5.34 lower to 3.94 higher)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact scale - Physical subscale (0-36) (follow up: 12 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,d]	none	50	50	-	MD **0.8 lower** (2.92 lower to 1.32 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 12 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [e]	none	50	50	-	MD **0.48 lower** (3.62 lower to 2.66 higher)	⨁⨁◯◯ LOW	CRITICAL
Modified Fatigue Impact scale - Psychosocial scale (0-8) (follow up: 12 weeks; Scale from: 0 to 8)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet (individualised)	standard healthy diet recommendations	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,f]	none	50	50	-	MD **0.38 higher** (0.25 lower to 1.01 higher) [g]	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 (0-100) - Physical composite (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,h]	none	50	50	-	MD **2.93 higher** (6.32 lower to 12.18 higher) [i]	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 (0-100) - Mental health composite (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,j]	none	50	50	-	MD **5.91 lower** (16.21 lower to 4.39 higher) [k]	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (relapse) (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c]	none	2/52 (3.8%)	2.0%	**RR 1.96** (0.18 to 20.97)	**19 more per 1,000** (from 16 fewer to 391 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MID used to assess imprecision was ±5.95

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±2.65

e. MID used to assess imprecision was ±4.02

f. MID used to assess imprecision was ±0.82

g. Note there is a larger baseline difference between groups for this outcome - scores improved from baseline in the intervention group and worsened slightly in the control group.

h, MID used to assess imprecision was ±11.39

i. Note differences at baseline may mislead interpretation - results changed very little in both groups from baseline but were higher at baseline in the intervention group

j. MID used to assess imprecision was ±13.08

k. Note differences at baseline may mislead interpretation - results changed very little in both groups from baseline but were lower at baseline in the intervention group

Table 73: Clinical evidence profile: Diet (individualised) vs. standard healthy diet recommendations – >6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet (individualised)	standard healthy diet recommendations > 6 months	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale (follow up: 1 years; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	34	38	-	MD **4.05 lower** (5.38 lower to 2.72 lower)	⨁⨁◯◯ LOW	CRITICAL
PASAT - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [c]	none	27	29	-	MD **0.31 higher** (3.36 lower to 3.98 higher)	⨁⨁◯◯ LOW	CRITICAL
SDMT - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [d]	none	27	29	-	MD **2.52 lower** (6.03 lower to 0.99 higher)	⨁⨁◯◯ LOW	CRITICAL
California Verbal Learning Test II - delayed recall - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,f]	none	27	29	-	MD **1.38 higher** (0.21 lower to 2.97 higher)	⨁◯◯◯ VERY LOW	CRITICAL
California Verbal Learning Test II - total learning - cognitive (follow up: 1 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet (individualised)	standard healthy diet recommendations > 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [f,g]	none	27	29	-	MD **0.15 lower** (5.15 lower to 4.85 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Judgement of line orientation test - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	serious [f,h]	none	27	29	-	MD **0.95 lower** (2.72 lower to 0.82 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Brief Visuospatial Memory Test-Revised - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	serious [f,i]	none	27	29	-	MD **3.17 lower** (5.74 lower to 0.6 lower)	⨁◯◯◯ VERY LOW	CRITICAL
North American Adult Reading Test - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [j]	none	27	29	-	MD **0.57 higher** (1.15 lower to 2.29 higher)	⨁⨁◯◯ LOW	CRITICAL
Controlled Oral Word Association Test - cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [k]	none	27	29	-	MD **0.19 higher** (0.85 lower to 1.23 higher)	⨁⨁◯◯ LOW	CRITICAL
Delis-Kaplan Executive Function System description- cognitive (follow up: 1 years)												
1	randomised trials	very serious [a]	not serious	not serious	serious [f,l]	none	27	29	-	MD **0.72 lower** (2.72 lower to 1.28 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Delis-Kaplan Executive Function System total scoring - cognitive (follow up: 1 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diet (individualised)	standard healthy diet recommendations > 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [f,m]	none	27	29	-	MD **0.47 lower** (1.04 lower to 0.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL

Adherence to intervention (scale 0-14) (follow up: 1 years; Scale from: 0 to 14)

1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	34	38	-	MD **2.45 higher** (1.29 higher to 3.61 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. MID used to assess imprecision was ±2.06

c. MID used to assess imprecision was ±8.38

d. MID used to assess imprecision was ±6.13

e. MID used to assess imprecision was ±1.52

f. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

g. MID used to assess imprecision was ±4.56

h. MID used to assess imprecision was ±2.56

i. MID used to assess imprecision was ±3.99

j. MID used to assess imprecision was ±2.81

k. MID used to assess imprecision was ±1.65

l. MID used to assess imprecision was ±2.58

m. MID used to assess imprecision was ±0.67

n. MID used to assess imprecision was ±1.27 (0.5 x control group SD as no baseline values)

Table 74: Clinical evidence profile: Wahls diet (modified Palaeolithic elimination diet) vs. Swank diet (low-saturated fat diet) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Wahls diet (modified Palaeolithic elimination diet)	Swank diet (low-saturated fat diet), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Score (scale 1-9) (follow up: 6 months; Scale from: 1 to 9)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	35	37	-	MD **0.45 lower** (1.17 lower to 0.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - Total score (0-84) (follow up: 6 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	35	37	-	MD **3.7 lower** (11.52 lower to 4.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - Physical subscore (0-36) (follow up: 6 months; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	35	37	-	MD **3.4 lower** (6.98 lower to 0.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - Cognitive subscore (0-40) (follow up: 6 months; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	35	37	-	MD **0.7 lower** (5.03 lower to 3.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Modified Fatigue Impact Scale - Psychosocial subscore (0-8) (follow up: 6 months; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,g]	none	35	37	-	MD **0.66 lower** (1.62 lower to 0.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (0-100) - Physical composite (follow up: 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Wahls diet (modified Palaeolithic elimination diet)	Swank diet (low-saturated fat diet), up to 6 months	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b,h]	none	35	37	-	MD **6.1 higher** (2.7 lower to 14.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQoL-54 (0-100) - Mental composite (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,i]	none	35	37	-	MD **2.7 higher** (6.24 lower to 11.64 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [j]	none	0/35 (0.0%)	0.0%	**RD 0.00** (-0.05 to 0.05)	**0 fewer per 1,000** (from 50 more to 50 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adherence to diet (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	26/35 (74.3%)	81.1%	**OR 0.67** (0.22 to 2.06)	**69 fewer per 1,000** (from 326 fewer to 87 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±0.63

d. MID used to assess imprecision was ±7.24

e. MID used to assess imprecision was ±3.86

f. MID used to assess imprecision was ±4.31

g. MID used to assess imprecision was ±1.17

h. MID used to assess imprecision was ±9.99

i. MID used to assess imprecision was ±10.53

j. Imprecision assessed based on sample size as zero events in both arms of a single study. Downgraded by 1 increment as sample size >70 and <350

Table 75: Clinical evidence profile: Mindfulness vs. control (usual care) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mindfulness	control (usual care)	Relative (95% CI)	Absolute (95% CI)		
Modified Fatigue Impact scale - total (0-84) (follow up: 6 months; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,c]	none	76	74	-	MD **6.03 lower** (10.08 lower to 1.98 lower)	⨁◯◯◯ VERY LOW	CRITICAL
HAQUAMS (1-5) (follow up: 6 months; Scale from: 1 to 5)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,d]	none	76	74	-	MD **0.18 lower** (0.35 lower to 0.01 lower)	⨁◯◯◯ VERY LOW	CRITICAL
CES-D depression (0-60) (follow up: 6 months; Scale from: 0 to 60)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,e]	none	76	74	-	MD **3.77 lower** (6.63 lower to 0.91 lower)	⨁◯◯◯ VERY LOW	CRITICAL
STAI anxiety (20-80) (follow up: 6 months; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b,f]	none	76	74	-	MD **3.55 lower** (6.09 lower to 1.01 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID used to assess imprecision was ±7.9

d. MID used to assess imprecision was ±0.33

e. MID used to assess imprecision was ±5.21

f. MID used to assess imprecision was ±5.38

Table 76: Clinical evidence profile: yoga vs. control – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control	Relative (95% CI)	Absolute (95% CI)		
Fatigue severity scale (1-7) (follow up: 8 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	11	10	-	MD **1.79 lower** (2.89 lower to 0.69 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (9-63) (follow up: 8 weeks)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious [d]	none	18	18	-	MD **25 lower** (32.66 lower to 17.34 lower)	⨁⨁◯◯ LOW	CRITICAL
MFIS - total (0-84) (follow up: 12 weeks; Scale from: 0 to 84)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,f]	none	63	49	-	MD **4.7 lower** (9.4 lower to 0)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - physical (0-36) (follow up: 12 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,g]	none	63	49	-	MD **2.5 lower** (4.55 lower to 0.45 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS - cognitive (0-40) (follow up: 12 weeks; Scale from: 0 to 40)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	63	49	-	MD **0.45 lower** (1.92 lower to 1.02 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control	Relative (95% CI)	Absolute (95% CI)		
Multidimensional Fatigue Inventory - general fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,i]	none	22	20	-	MD **1.9 lower** (3.69 lower to 0.11 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - physical fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,j]	none	22	20	-	MD **1.8 lower** (4.5 lower to 0.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - reduced activity (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [e,k]	none	22	20	-	MD **0.3 lower** (2.91 lower to 2.31 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - reduced motivation (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,l]	none	22	20	-	MD **0.6 lower** (2.42 lower to 1.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - mental fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,m]	none	22	20	-	MD **0.5 lower** (2.89 lower to 1.89 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Rhoten Fatigue Scale (0-10) (follow up: 12 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [n]	none	20	21	-	MD **0.2 lower** (0.83 lower to 0.43 higher)	⨁⨁◯◯ LOW	CRITICAL
MSQOL-54 physical health composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [e,o]	none	11	10	-	MD **0.94 lower** (11.15 lower to 9.27 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 mental health composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [e,p]	none	11	10	-	MD **8.76 higher** (4.18 lower to 21.7 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 change in health domain (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [e,q]	none	11	10	-	MD **0.23 lower** (22.25 lower to 21.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSIS-29 physical component (0-100) (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [r]	none	63	49	-	MD **4.3 lower** (9.72 lower to 1.12 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 physical functioning (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [s]	none	42	41	-	MD **11 higher** (5.4 higher to 16.59 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 emotional limitations (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	very serious [t]	not serious	very serious [e,u]	none	42	41	-	MD **0.88 higher** (25.13 lower to 26.88 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical role limitations (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	serious [e,v]	none	42	41	-	MD **6.5 lower** (13.21 lower to 0.22 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 energy/vitality (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [e,w]	none	42	41	-	MD **10.7 higher** (5.26 higher to 16.13 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental health (0-100) (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e,x]	none	20	21	-	MD **10.1 higher** (1.25 higher to 18.95 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 social functioning (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	very serious [t]	not serious	very serious [e,y]	none	42	41	-	MD **3.5 higher** (12.79 lower to 19.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 body pain (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	very serious [t]	not serious	very serious [e,z]	none	42	41	-	MD **9.27 lower** (26.67 lower to 8.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 general health (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [aa,e]	none	42	41	-	MD **7.79 higher** (2.93 higher to 12.65 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 health transition (0-100) (follow up: 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	control	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [ab,e]	none	22	20	-	MD **12.9 lower** (25.28 lower to 0.52 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Stroop colour word interference (attention/concentration) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [ac]	none	22	20	-	MD **0.4 higher** (2.29 lower to 3.09 higher)	⨁⨁◯◯ LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
2	randomised trials	serious [a]	very serious [t]	serious [b]	very serious [ad,e]	none	29	28	-	MD **9.43 lower** (23.95 lower to 5.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Anxiety Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [ae,e]	none	11	10	-	MD **1.75 lower** (6.8 lower to 3.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events leading to withdrawal (follow up: 12 weeks)												
1	randomised trials	very serious [a]	not serious	not serious	serious [e]	none	2/65 (3.1%)	14.0%	**RR 0.22** (0.05 to 0.99)	**110 fewer per 1,000** (from 133 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (MS exacerbation) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [e]	none	1/23 (4.3%)	0/20 (0.0%)	**OR 6.49** (0.13 to 329.99)	**44 more per 1,000** (from 73 fewer to 160 more) [af]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. MID used to assess imprecision was ±0.57

d. MID used to assess imprecision was ±7.08

e. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

f. MID used to assess imprecision was ±8.63

g. MID used to assess imprecision was ±3.63

h. MID used to assess imprecision was ±2.73

i. MID used to assess imprecision was ±1.68

j. MID used to assess imprecision was ±1.88

k. MID used to assess imprecision was ±2.23

l. MID used to assess imprecision was ±1.65

m. MID used to assess imprecision was ±2.05

n. MID used to assess imprecision was ±0.84

o. MID used to assess imprecision was ±6.47

p. MID used to assess imprecision was ±6.31

q. MID used to assess imprecision was ±14.51

r. MID used to assess imprecision was ±10.75

s. MID used to assess imprecision was ±5.05

t. Heterogeneity that cannot be explained by subgrouping analyses and I2 >75%

u. MID used to assess imprecision was ±10.39

v. MID used to assess imprecision was ±12.34

w. MID used to assess imprecision was ±7.47

x. MID used to assess imprecision was ±7.56

y. MID used to assess imprecision was ±8.87

z. MID used to assess imprecision was ±7.59

aa. MID used to assess imprecision was ±7.70

ab. MID used to assess imprecision was ±11.98

ac. MID used to assess imprecision was ±3.28

ad. MID used to assess imprecision was ±4.11

ae. MID used to assess imprecision was ±2.83

af. Absolute effect calculated manually using risk difference as zero events in at least one arm of at least one study

Table 77: Clinical evidence profile: yoga vs. aerobic exercise – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
Fatigue severity scale (1-7) (follow up: 8 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	11	10	-	MD **0.54 higher** (0.46 lower to 1.54 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - general fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,e]	none	22	15	-	MD **0.9 higher** (0.96 lower to 2.76 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - physical fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,f]	none	22	15	-	MD **1.3 higher** (1.43 lower to 4.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - reduced activity (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,g]	none	22	15	-	MD **1.3 higher** (1.31 lower to 3.91 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - reduced motivation (4-20) (follow up: 6 months; Scale from: 4 to 20)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [c,h]	none	22	15	-	MD **1.5 higher** (0.63 lower to 3.63 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Multidimensional Fatigue Inventory - mental fatigue (4-20) (follow up: 6 months; Scale from: 4 to 20)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,i]	none	22	15	-	MD **2.9 higher** (0.12 higher to 5.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Rhoten Fatigue Scale (0-10) (follow up: 12 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	not serious	serious [c,j]	none	20	20	-	MD **0.8 higher** (0.26 higher to 1.34 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 physical health composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,k]	none	11	10	-	MD **5.49 lower** (14.73 lower to 3.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 mental health composite (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,l]	none	11	10	-	MD **9.68 higher** (3.36 lower to 22.72 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MSQOL-54 change in health domain (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,m]	none	11	10	-	MD **0.23 lower** (22.25 lower to 21.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 physical functioning (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	not serious [c,n]	none	42	35	-	MD **1.68 lower** (7.86 lower to 4.51 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 emotional limitations (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	not serious [o]	none	42	35	-	MD **0.73 lower** (7.86 lower to 6.39 higher)	⨁⨁◯◯ LOW	CRITICAL
SF-36 physical role limitations (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	serious [p]	not serious	not serious [q]	none	42	35	-	MD **1.59 lower** (8.74 lower to 5.57 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 energy/vitality (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [c,r]	none	42	35	-	MD **2.32 lower** (8.5 lower to 3.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 mental health (0-100) (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,s]	none	20	20	-	MD **1.24 lower** (9.16 lower to 6.68 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 social functioning (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	very serious [t]	not serious	very serious [c,u]	none	42	35	-	MD **5.18 lower** (25.78 lower to 15.41 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 body pain (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	not serious	not serious	serious [c,v]	none	42	35	-	MD **1.13 lower** (6.69 lower to 4.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 general health (0-100) (follow up: range 12 weeks to 6 months; Scale from: 0 to 100)												
2	randomised trials	very serious [a]	not serious	not serious	serious [c,w]	none	42	35	-	MD **3.25 lower** (8.61 lower to 2.12 higher)	⨁◯◯◯ VERY LOW	CRITICAL
SF-36 health transition (0-100) (follow up: 6 months; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,x]	none	22	15	-	MD **1 lower** (17.67 lower to 15.67 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Depression Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,y]	none	11	10	-	MD **5.49 lower** (2.17 lower to 13.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Beck Anxiety Inventory (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,z]	none	11	10	-	MD **0.35 higher** (3.39 lower to 4.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - Stroop colour word interference (attention/concentration) (follow up: 6 months)												
1	randomised trials	very serious [a]	not serious	not serious	serious [aa,c]	none	22	20	-	MD **1.4 lower** (4.7 lower to 1.9 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (MS exacerbation) (follow up: 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga	aerobic exercise	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [c,e]	none	1/23 (4.3%)	6.3%	**RR 0.70** (0.05 to 10.32)	**19 fewer per 1,000** (from 59 fewer to 583 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±0.69

e. MID used to assess imprecision was ±1.83

f. MID used to assess imprecision was ±2.03

g. MID used to assess imprecision was ±2.13

h. MID used to assess imprecision was ±1.53

i. MID used to assess imprecision was ±2.38

j. MID used to assess imprecision was ±0.76

k. MID used to assess imprecision was ±6.33

l. MID used to assess imprecision was ±5.90

m. MID used to assess imprecision was ±18.02

n. MID used to assess imprecision was ±8.32

o. MID used to assess imprecision was ±10.15

p. Downgraded by 1 increment as point estimates vary widely suggesting heterogeneity

q. MID used to assess imprecision was ±10.06

r. MID used to assess imprecision was ±7.87

s. MID used to assess imprecision was ±5.55

t. Heterogeneity present that cannot be explained by subgrouping strategies and I2 >75%

u. MID used to assess imprecision was ±7.17

v. MID used to assess imprecision was ±5.43

w. MID used to assess imprecision was ±6.82

x. MID used to assess imprecision was ±11.83

y. MID used to assess imprecision was ±3.87

z. MID used to assess imprecision was ±2.61

aa. MID used to assess imprecision was ±2.43

Table 78: Clinical evidence profile: Pilates vs. control (waitlist, no intervention) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pilates	control (waitlist, no intervention)	Relative (95% CI)	Absolute (95% CI)		
MFIS total (0-84) (follow up: 8 weeks; Scale from: 0 to 84)												
3	randomised trials	very serious [a]	very serious [b]	serious [c]	serious [d,e]	none	61	59	-	MD **10.4 lower** (18.98 lower to 1.82 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS physical (0-36) (follow up: 8 weeks; Scale from: 0 to 36)												
2	randomised trials	very serious [a]	not serious	serious [c]	serious [d,f]	none	48	47	-	MD **6.14 lower** (8.9 lower to 3.39 lower)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS cognitive (0-40) (follow up: 8 weeks; Scale from: 0 to 40)												
2	randomised trials	very serious [a]	serious [g]	serious [c]	serious [d,h]	none	48	47	-	MD **6.73 lower** (14.62 lower to 1.15 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS psychosocial (0-8) (follow up: 8 weeks; Scale from: 0 to 8)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pilates	control (waitlist, no intervention)	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	very serious [a]	serious [i]	serious [c]	serious [d,j]	none	48	47	-	MD **1.57 lower** (3.14 lower to 0)	⨁◯◯◯ VERY LOW	CRITICAL
STAY-Y1 - anxiety (20-80) (follow up: 8 weeks; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [k]	none	9	6	-	MD **18.5 lower** (24.85 lower to 12.15 lower)	⨁◯◯◯ VERY LOW	CRITICAL
STAY-Y2 - anxiety (20-80) (follow up: 8 weeks; Scale from: 20 to 80)												
2	randomised trials	very serious [a]	very serious [b]	serious [c]	very serious [d,l]	none	48	47	-	MD **7.44 lower** (21.22 lower to 6.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HADS - anxiety (0-21) (follow up: 8 weeks; Scale from: 0 to 21)												
2	randomised trials	very serious [a]	very serious [m]	serious [c]	very serious [d,n]	none	48	47	-	MD **0.64 higher** (2.29 lower to 3.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
HADS - depression (0-21) (follow up: 8 weeks; Scale from: 0 to 21)												
2	randomised trials	very serious [a]	serious [g]	serious [c]	serious [d,o]	none	48	47	-	MD **2.72 lower** (6.48 lower to 1.03 higher)	⨁◯◯◯ VERY LOW	CRITICAL
QIDS - depression (0-27) (follow up: 8 weeks; Scale from: 0 to 27)												
2	randomised trials	very serious [a]	not serious	serious [c]	serious [d,p]	none	48	47	-	MD **2.45 lower** (3.83 lower to 1.07 lower)	⨁◯◯◯ VERY LOW	CRITICAL
POMS-B total mood (scale unclear) (follow up: 8 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pilates	control (waitlist, no intervention)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,q]	none	9	6	-	MD **24.4 lower** (41.28 lower to 7.52 lower)	⨁◯◯◯ VERY LOW	CRITICAL
POMS-B depression subscale (scale unclear) (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,r]	none	9	6	-	MD **4.2 lower** (7.33 lower to 1.07 lower)	⨁◯◯◯ VERY LOW	CRITICAL
POMS-B fatigue subscale (scale unclear) (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,s]	none	9	6	-	MD **7.6 lower** (13.07 lower to 2.13 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events (follow up: 8 weeks)												
2	randomised trials	very serious [a]	not serious	serious [c]	serious [t]	none	0/48 (0.0%)	0.0%	**RD 0.00** (-0.06 to 0.06)	**-- per 1,000** (from -- to --)	⨁◯◯◯ VERY LOW	CRITICAL
Discontinuation possibly related to intervention (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [c]	very serious [d]	none	5/39 (12.8%)	14.6%	**RR 0.88** (0.29 to 2.64)	**18 fewer per 1,000** (from 104 fewer to 240 more)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 2 increments as there was heterogeneity present that could not be explained by subgrouping strategies. Point estimates vary widely across studies and I2 >75%

c. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±6.73

f. MID used to assess imprecision was ±3.63

g. Downgraded by 2 increments as there was heterogeneity present that could not be explained by subgrouping strategies, with I2 >60%

h. MID used to assess imprecision was ±3.73

i. Downgraded by 2 increments as there was heterogeneity present that could not be explained by subgrouping strategies, with I2 >80%

j. MID used to assess imprecision was ±0.95

k. MID used to assess imprecision was ±5.23

l. MID used to assess imprecision was ±5.55

m. Downgraded by 2 increments as there was heterogeneity present that could not be explained by subgrouping strategies. Point estimates vary widely across studies and I2 >70%

n. MID used to assess imprecision was ±1.63

o. MID used to assess imprecision was ±1.43

p. MID used to assess imprecision was ±2.23

q. MID used to assess imprecision was ±7.53

r. MID used to assess imprecision was ±1.60

s. MID used to assess imprecision was ±2.25

t. Imprecision assessed by sample size as zero events in both arms. Downgraded by 1 increment as sample size >70 and <350

Table 79: Clinical evidence profile: Pilates vs. resistance + balance exercises – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pilates	resistance + balance exercises	Relative (95% CI)	Absolute (95% CI)		
MFIS physical (0-36) (follow up: 8 weeks; Scale from: 0 to 36)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,d]	none	11	9	-	MD **0.26 lower** (4.32 lower to 3.8 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS cognitive (0-40) (follow up: 8 weeks; Scale from: 0 to 40)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pilates	resistance + balance exercises	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,e]	none	11	9	-	MD **1.51 lower** (6.75 lower to 3.73 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MFIS psychosocial (0-8) (follow up: 8 weeks; Scale from: 0 to 8)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,f]	none	11	9	-	MD **5.47 lower** (14.24 lower to 3.3 higher)	⨁◯◯◯ VERY LOW	CRITICAL
MusiQoL (0-100) (follow up: 8 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,g]	none	11	9	-	MD **16.23 lower** (28.78 lower to 3.68 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive - PASAT (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	not serious [h]	none	11	9	-	MD **19.93 higher** (9.07 higher to 30.79 higher)	⨁◯◯◯ VERY LOW	CRITICAL
BDI (0-63) (follow up: 8 weeks; Scale from: 0 to 63)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c,i]	none	11	9	-	MD **1.87 lower** (7.18 lower to 3.44 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±3.44

e. MID used to assess imprecision was ±4.06

f. MID used to assess imprecision was ±6.49

g. MID used to assess imprecision was ±6.28

h. MID used to assess imprecision was ±7.14

i. MID used to assess imprecision was ±2.94

Table 80: Clinical evidence profile: Pilates + balance training vs. relaxation – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pilates + balance training	relaxation	Relative (95% CI)	Absolute (95% CI)		
Adverse or harmful events (follow up: 8 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	very serious [c]	none	0/26 (0.0%)	0/13 (0.0%)	**RD 0.00** (-0.11 to 0.11)	**0 fewer per 1,000** (from 110 fewer to 110 more) [d]	⨁◯◯◯ VERY LOW	CRITICAL
Adherence - discontinuation due to work intensity												
1	randomised trials	very serious [a]	not serious	not serious	serious [e]	none	8/34 (23.5%)	0/13 (0.0%)	**OR 5.11** (0.95 to 27.46)	**235 more per 1,000** (from 63 more to 407 more) [d]	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of evidence had a follow-up less than the minimum 3 months in the protocol

c. Imprecision assessed using sample size as zero events in both arms of a single study. Downgraded by 2 increments as sample size <70.

d. Absolute effect was calculated manually using risk difference as zero events in at least one arm of at least one study

e. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 81: Clinical evidence profile: Relaxation vs. control (waitlist) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relaxation	control (waitlist)	Relative (95% CI)	Absolute (95% CI)		
MFIS - total (0-84) (follow up: 8 weeks; Scale from: 0 to 84)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,d]	none	22	23	-	MD **3.8 lower** (12.93 lower to 5.33 higher)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the minimum 3 months in the protocol

c. MID used to assess imprecision was ±7.88

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 82: Clinical evidence profile: Acupressure vs. control (touching only) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	control (touching only/sham)	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (scale unclear) (follow up: 4 weeks)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [c,d]	none	50	50	-	MD **30 lower** (58.23 lower to 1.77 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (scale 1-7) (follow up: 4 weeks; Scale from: 1 to 7)												
1	randomised trials	serious [a]	not serious	serious [b]	not serious [e]	none	44	42	-	MD **0.16 lower** (0.81 lower to 0.49 higher)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupressure	control (touching only/sham)	Relative (95% CI)	Absolute (95% CI)		
Depression - DASS-42 (scale 0-42) (follow up: 4 weeks; Scale from: 0 to 42)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,f]	none	44	42	-	MD **1.7 lower** (3.01 lower to 0.39 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up that was less than the minimum 3 months in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±27.25

e. MID used to assess imprecision was ±0.81

f. MID used to assess imprecision was ±1.67

Table 83: Clinical evidence profile: Reflexology/relaxation vs. control (usual care) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reflexology/relaxation	control (usual care)	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (1-7) - Foot reflexology vs. control (follow up: 8-12 weeks; Scale from: 1 to 7)												
2	randomised trials	very serious [a]	not serious	serious [b]	not serious [c]	none	55	55	-	MD **1.99 lower** (2.41 lower to 1.56 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Severity Scale (1-7) - Relaxation vs. control (follow up: 8 weeks; Scale from: 1 to 7)												
1	randomised trials	very serious [a]	not serious	serious [b]	serious [d,e]	none	25	25	-	MD **0.47 lower** (0.93 lower to 0.01 lower)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reflexology/relaxation	control (usual care)	Relative (95% CI)	Absolute (95% CI)		
MSQoL-54 physical composite (0-100 usually) - Foot reflexology vs. control (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [f]	none	30	30	-	MD **24.43 higher** (15.66 higher to 33.2 higher)	⨁⨁◯◯ LOW	CRITICAL
MSQoL-54 mental composite (0-100 usually) - Foot reflexology vs. control (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [g]	none	30	30	-	MD **28.83 higher** (18.85 higher to 37.81 higher)	⨁⨁◯◯ LOW	CRITICAL
MSQoL-54 health change (0-100 usually) - Foot reflexology vs. control (follow up: 12 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious [a]	not serious	not serious	not serious [h]	none	30	30	-	MD **39.17 higher** (28.82 higher to 49.52 higher)	⨁⨁◯◯ LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the 3 months minimum in the protocol

c. MID used to assess imprecision was ±0.53

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±0.46

f. MID used to assess imprecision was ±8.36

g. MID used to assess imprecision was ±9.06

h. MID used to assess imprecision was ±11.03

Table 84: Clinical evidence profile: Massage vs. control (usual care) – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Massage	control (usual care/no intervention)	Relative (95% CI)	Absolute (95% CI)		
Fatigue Severity Scale (9-63) mix of change from BL and final values (follow up: 4-7 weeks; Scale from: 9 to 63)												
3	randomised trials	very serious [a]	very serious [b]	serious [c]	serious [d,e]	none	82	82	-	MD **11.38 lower** (22.08 lower to 0.68 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue relief and effectiveness of fatigue reduction VAS (scale 0-10) (follow up: 4 weeks; Scale from: 0 to 10)												
1	randomised trials	very serious [a]	not serious	serious [c]	serious [d,f]	none	40	40	-	MD **1.3 higher** (0.11 higher to 2.49 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Spielberger Overt Anxiety Questionnaire (scale 20-80) (follow up: 7 weeks; Scale from: 20 to 80)												
1	randomised trials	very serious [a]	not serious	serious [c]	not serious [g]	none	30	30	-	MD **13.48 lower** (15.97 lower to 10.99 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 2 increments as heterogeneity present that could not be explained by subgroup analyses, based on wide variation in point estimates across studies and I2 >90%

c. Downgraded by 1 increment as the majority of the evidence had a follow-up of less than the 3 months minimum in the protocol

d. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

e. MID used to assess imprecision was ±5.01

f. MID used to assess imprecision was ±1.42

g. MID used to assess imprecision was ±2.37

Table 85: Clinical evidence profile: Reflexology vs. non-specialised foot massage – up to 6 months outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reflexology	non-specialised foot massage	Relative (95% CI)	Absolute (95% CI)		
Fatigue Impact scale - Total score (0-160) (follow up: 4 weeks; Scale from: 0 to 160)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,d]	none	33	30	-	MD **13.57 lower** (31.22 lower to 4.08 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact scale - Physical subscale (0-40) (follow up: 4 weeks; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,e]	none	33	30	-	MD **5.06 lower** (9.89 lower to 0.23 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact scale - Cognitive subscale (0-40) (follow up: 4 weeks; Scale from: 0 to 40)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,f]	none	33	30	-	MD **1.98 lower** (7.05 lower to 3.09 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Fatigue Impact scale - Psychosocial scale (0-80) (follow up: 4 weeks; Scale from: 0 to 80)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,g]	none	33	30	-	MD **6.83 lower** (16.22 lower to 2.56 higher)	⨁◯◯◯ VERY LOW	CRITICAL
State trait anxiety inventory (20-80) (follow up: 4 weeks; Scale from: 20 to 80)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c,h]	none	33	30	-	MD **6.2 lower** (7.3 lower to 5.1 lower)	⨁◯◯◯ VERY LOW	CRITICAL

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b. Downgraded by 1 increment as the majority of the evidence had a follow-up less than the minimum of 3 months in the protocol

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

d. MID used to assess imprecision was ±17.09

e. MID used to assess imprecision was ±4.02

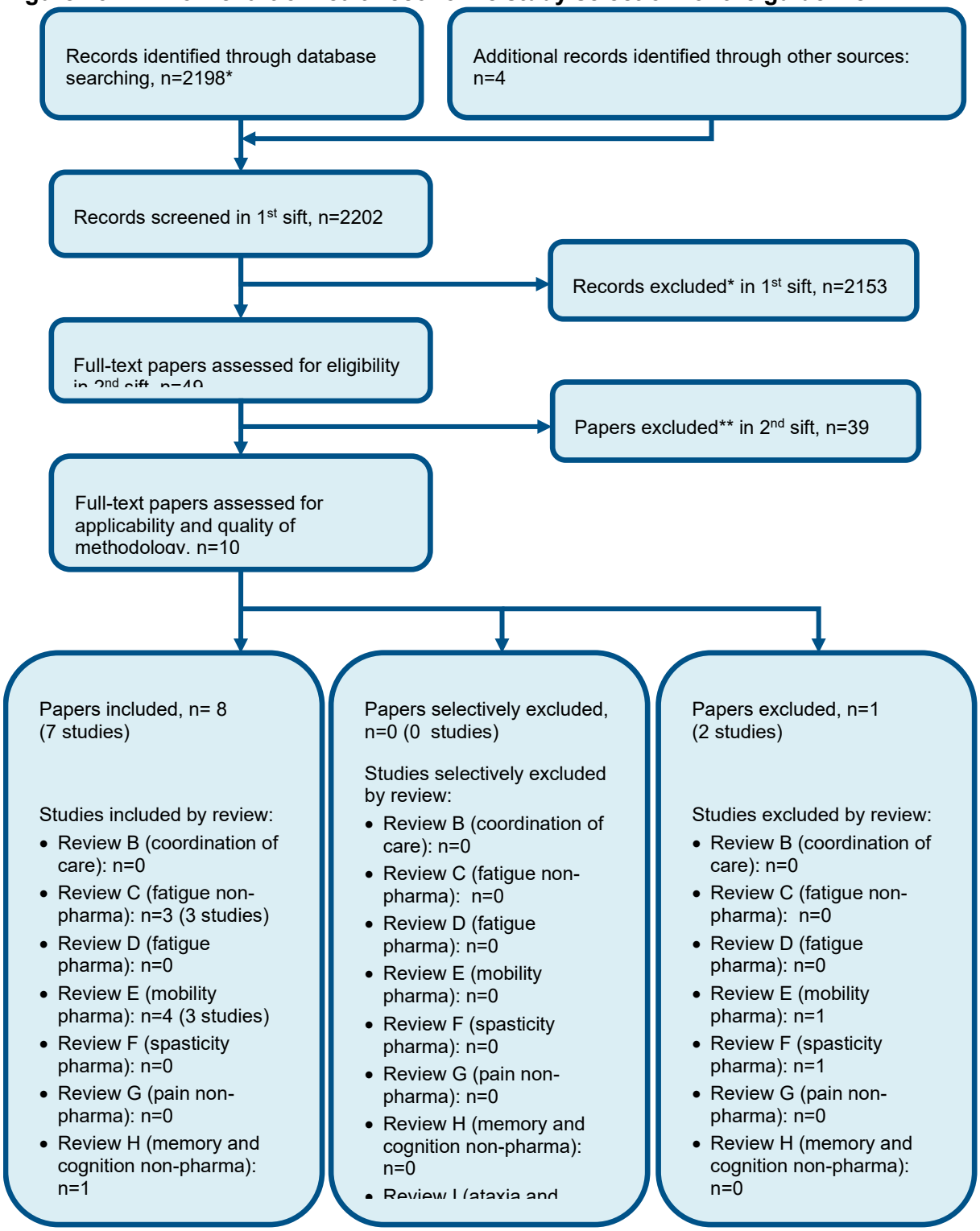
f. MID used to assess imprecision was ±4.70

g. MID used to assess imprecision was ±8.95

h. MID used to assess imprecision was ±6.46

Appendix G – Economic evidence study selection

Figure 434: Flow chart of health economic study selection for the guideline



* Excluding conference abstracts.

**Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Moss-Morris 2012[3]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Within trial analysis (pilot RCT: Moss-Morris 2012[3]) **Approach to analysis:** Analysis of individual level data for health outcomes, EQ-5D and service use during the 10-week follow-up period. **Perspective:** UK NHS **Time horizon:** 10 weeks **Treatment effect duration:**[(a)] NA	**Population:** Adults with mixed types MS and fatigue **Cohort settings:** Median age: 40.1 years Male: 80% Mean EDSS: NR N = 40 **Intervention 1:** Waitlist (Able to access MSInvigor8 website once they had completed the 10-week questionnaire; did not receive telephone support) **Intervention 2:** Online CBT program (MSInvigor8 website developed based on RCT for CBT for MS fatigue (Van Kessel 2008[8]) Eight weekly sessions that took 25 to 50 minutes to complete)	**Total costs (mean change):** Intervention 1: £214 Intervention 2: £211 Incremental (2−1): saves £4 (95% CI: NR; p=NR) **Currency & cost year:** 2008 UK pounds **Cost components incorporated:** Outpatient appointments (neurology and other), inpatient care (urology, intensive care unit, other), residential care, general practitioner, specialists (neurologist, other), physiotherapist, social worker, nurse, home help, other.	**QALYs (mean change):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.015 (95% CI: NR; p=0.038) **Fatigue Scale (mean change):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 15.55 (95% CI: NR; p<0.001) **Modified Fatigue Impact Scale (mean change):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 14.67 (95% CI: NR; p<0.001)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates intervention 1 95% CI: NR Probability that Intervention 2 was cost effective (£20k/30k threshold): NA Mean costs were similar between groups with a small but non-significant improvement in quality of life. **Analysis of uncertainty:** The results retained their significance levels for all outcomes when the analysis was rerun controlling for gender, ambulation status and completion.

Discounting: Costs: NA Outcomes: NA				
Data sources				
Health outcomes: Participants provided demographic data and information on their MS type and duration. Questions to quantify MS type were drawn from previous research by Skerrett 2006. Ambulation ability was measured using the ambulation questions from the self-report Expanded Disability Status Scale. Primary outcomes were fatigue severity, measured by the ordinal version of the Fatigue Scale and fatigue impact assessed by the Modified Fatigue Impact Scale. Secondary outcomes were anxiety and depression measured by the Hospital Anxiety and Depression Scale. **Quality-of-life weights:** QALYs were calculated by adding the baseline and follow-up EQ-5D scores and dividing by 2, assuming a linear change over time and multiplying by 10/52, which is the maximum QALY gain attainable in the follow-up period. **Cost sources:** Costs were calculated by combining service use data with unit costs obtained from the Personal Social Services Research Unit 2006 and 2008.				
Comments				
Source of funding: Multiple Sclerosis Society UK **Limitations:** Does not include all relevant comparators for this question. EQ-5D scoring tariff was not reported. Cost utility model based on a pilot RCT (Moss-Morris 2012[3] Sample size was small (n=40) with a high non-completion rate. The study was a small feasibility trial with no long-term follow-up data; cost-effectiveness would be heavily influenced by the maintenance of treatment gains. 10 weeks may be too short to show much change in healthcare resource use between groups. Intervention effects were obtained from the current trial, which was a pilot trial and not designed to evaluate intervention effects with certainty nor long enough to estimate the duration of treatment effect. Costs did not include development or administration of the intervention, which would depend on how many people used it. Medication costs were not included. Resource use was self-reported by trial participants at 10 weeks, which may be unreliable. The only reference for unit costs was Personal Social Services Research Unit. However, for some unit costs the NHS Tariff may have been a more appropriate source. The analysis was rerun controlling for gender, ambulation status and completion but detailed results of these analyses were not reported. No probabilistic sensitivity analysis conducted. **Other:** The authors reported that to achieve a cost per QALY of £20,000 the intervention costs would need to be no more than £300 per person (£20,000 / 0.015) or approximately £50 per session. If used by 300 people, this would cover a £90,000 development cost which was above the actual cost accrued.				
Overall applicability:(b) Partially applicable	**Overall quality:**(c) Very serious limitations			

Abbreviations: 95% CI= 95% confidence interval; CBT = cognitive behavioural therapy; CUA= cost utility analysis; da= deterministic analysis; EDSS = Expanded Disability Status Scale; *ICER= incremental cost-effectiveness ratio; MS = multiple sclerosis; NA = not applicable; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years.*

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Tosh (2014)[7]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome = QALY). **Study design:** Within-trial analysis (RCT) (Carter 2014[2]) **Approach to analysis:** Analysis of individual level data for health outcomes, EQ-5D and resource use. Unit costs applied. **Perspective:** UK NHS and Personal Social Services **Follow-up:** 9 months (6 months after final session) **Treatment effect duration:** 9 months (6 months after final	**Population:** Clinically definite MS diagnosis; EDSS score 1.0– 6.5; able to walk a 10-metre distance and physically able to participate in exercise three times per week. **Patient characteristics:** Age: Mean 46 Male: 28.3% Mean EDSS: 3.8 N = 60 **Intervention 1:** Current local practice **Intervention 2:** Programme incorporating aerobic and resistance exercise and CBT (EXIMS) for 12 weeks and current local practice	**Total costs (mean per patient):** Intervention 1: £932 Intervention 2: £1,398 Incremental (2-1): £466 (95% CI -237 to 1,310; p = NR) **Currency & cost year:** 2011 UK pounds for all costs except for intervention costs which were reported in 2012 UK pounds. **Cost components incorporated:** EXIMS programme (£408 per person) includes staff (physiotherapists and exercise specialists), equipment, and overheads. Estimated costs for NHS and social care services over 9-month period (intervention start to end of follow-up) assessed for both interventions. These	**QALYs (mean per patient):** Intervention 1: 0.492 Intervention 2: 0.538 Incremental (2-1): 0.046 (95% CI -0.022 to 0.115; p = NR) From RCT: **Total MFIS 9 months [lower better]** Intervention 1: 41.3 Intervention 2: 39.6 **MSQoL-54 9 months [higher better]** Intervention 1: 60.4 Intervention 2: 65.9	**ICER (Intervention 2 versus Intervention 1):** £10,137 per QALY gained (pa) Probability intervention 2 cost-effective (£20K/30K threshold): 75%/78% Analysis of uncertainty: Scenario analyses conducted: • Scenario 1 (EDSS score): 14 = £9,558 per QALY • Scenario 2 (GLTEQ score): >14 = £9,558 per QALY • Scenario 3 (private provision of intervention): £11,938 per QALY gained • Scenario 4 (SF-6D utility score): £19,783 per QALY gained

session) **Discounting:** Costs =n/a; Outcomes = n/a		costs are estimated using self-reported and health care professional resource utilisation and published unit costs. Services included GP, community health, specialist, and social care visits.		
Data sources				
Health outcomes: The exercise intervention increased self-reported physical activity, improved fatigue symptoms and led to a sustained enhancement of health-related quality of life (HRQoL). QALYs calculated using the trapezium rule to estimate the area under the curve. In the base case using EQ-5D (from patients) and in the scenario analysis using SF-6D (extracting SF-36 items from MSQOL-54 instrument and mapping SF-36 to SF-6D). **Quality-of-life weights:** Within-RCT analysis: EQ-5D (from patients), tariff used not stated. **Cost sources:** Does not include all relevant comparators for this question. Resource use from within RCT. Source of costs PSSRU, NHS reference costs and retail prices for equipment. No intervention costs were included for the current local practice as this was included in both arms				
Comments				
Source of funding: Supported by Multiple Sclerosis Society in UK. **Limitations:** Cost utility model based on a single RCT. Short follow-up, participants asked to complete questionnaires with a three-month recall period on their resource use which could have introduced potential recall bias.				
Overall applicability:[a] Partially applicable **Overall quality:**[b] Potentially serious limitations				

Abbreviations: CBT = cognitive behavioural therapy; CI = 95% confidence interval; CUA = cost-utility analysis; EDSS = Expanded Disability Status Scale; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; EXIMS = EXercise Intervention for people with MS; GLTEQ = Godin Leisure Time Exercise Questionnaire; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; PSA = probabilistic sensitivity analysis; PSSRU = Personal and Social Services Research Unit; QALYs = quality-adjusted life years; RCT = randomised control trial; SF-6D = Short form 6 dimension.

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Thomas (2013)[6]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: CUA (health outcome = QALY). **Study design:** Within trial analysis (RCT) Thomas 2013[6] **Approach to analysis:** Analysis of individual level data for health outcomes, EQ-5D and resource use. Unit costs applied. **Perspective:** UK NHS Follow-up: 5.5 months (4 months after final session) **Treatment effect duration:** 5.5 months (4 months after final session) **Discounting:** Costs = n/a; Outcomes = n/a	**Population:** Clinically definite MS diagnosis; FSS total score >4; ambulant. **Patient characteristics:** Age: Intervention 1: 50.1 Intervention 2: 48 Male: 27% **Intervention 1:** Current local practice **Intervention 2:** Group based fatigue management programme (FACETS) for 6 weeks and current local practice	**Total costs** (mean per patient): Intervention 1: £190.37 Intervention 2: £678.36 Incremental (2-1): £487.99 (95% CI NR; p = NR) **Currency & cost year:** 2010 UK pounds **Cost components incorporated:** FACETS programme (£453) which includes training, equipment, session facilitators (two band 7 therapists), venue hire, refreshments, printing, administrative support and psychology support. Estimated costs for NHS and social care services (over a 3-month period) assessed at 4-month follow up for both interventions. These costs are estimated using self-reported resource utilisation and published unit costs. Services included GP, nurse and specialist appointments.	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): -0.02 (95% CI -0.05 to 0.02; p = 0.31) **Global Fatigue Severity (GFS) (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2-1): -0.36 (CI = -0.63 to -0.08; p = 0.01) **Fatigue self-efficacy scale (+ve indicates benefit to FACETS) at 5.5 months:** Intervention 1: NR Intervention 2: NR Incremental (2-1): 6 (0-12) (95% CIs n=164)	**ICER (Intervention 2 versus Intervention 1), QALY:** Intervention 1 dominates intervention 2 (da) **ICER (Intervention 2 versus Intervention 1), GFS**: £1259 per 1-point improvement in fatigue (da) **Analysis of uncertainty:** No PSA for ICER. A PSA was undertaken to analyse the impact of uncertainty in the level of staff input for FACETS programme delivery on costs. The mean cost of the intervention was £453 with 95% of estimates in the range of £331 to £585 per participant.
Data sources				

Health outcomes: QALYs derived from EQ5D (from patients) with maximum QALY equalling 0.46, assuming full health over 24 weeks. **Quality-of-life weights:** Within RCT analysis: EQ5D (from patients), tariff used not stated. **Cost sources:** Resource use from within RCT. Source of costs PSSRU, NHS reference costs and local NHS Trust cost data. No intervention costs were included for the current local practice.
Comments
Source of funding: Multiple Sclerosis Society of Great Britain and Northern Ireland. **Limitations:** Does not include all relevant comparators for this question. Cost utility model based on a single RCT. Probabilistic sensitivity analysis for ICER not undertaken and follow-up short. **Other:** Authors suggest that a longer-term follow-up may be required for improvements as a result of changes in attitudes and lifestyle (central to the FACETS programme) to impact on quality of life.
Overall applicability:(a) Partially applicable **Overall quality:**(b) Potentially serious limitations

Abbreviations: CUA = cost-utility analysis; CI = 95% confidence interval; da = deterministic analysis; EQ5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; FACETS: Fatigue Applying Cognitive behavioural and Energy effectiveness Techniques to lifeStyle; FSS = Fatigue Severity Scale; ICER = incremental cost-effectiveness ratio; GFS = global fatigue scale; NR = not reported; PSA = probabilistic sensitivity analysis; PSSRU = Personal and Social Services Research Unit; QALYs = quality-adjusted life years; RCT = randomised control trial.

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**National Institute for Health and Care Excellence, P.421, 2014[5] (UK)**							
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**				
Economic analysis: CUA (health outcome = QALY). **Study design:** Within trial analysis (RCT from Cakit, 2010[1]) **Approach to analysis:**	**Population:** Adults with MS; either relapsing-remitting or secondary progressive MS, EDSS ≤6.0, and the ability to stand independently for > 3 secs and if they had been without steroid and immunosuppressive therapy within the past 4 weeks.	**Total costs** (mean per patient): Intervention 1: £0 Intervention 2: £52 Intervention 3: £450 (a) **Currency & cost year:** 2010 UK pounds	**QALYs (mean per patient):** Intervention 1: 0.079 QALYs Intervention 2: 0.090 QALY Intervention 3: 0.142 QALY (b)	Full incremental analysis	Cost	QALY	Inc Cost	Inc QALY	ICER

Perspective: UK NHS
Time horizon: 1 year

Treatment effect duration: 8 weeks, extrapolated to 1 year

Discounting:
Costs = n/a
Outcomes = n/a

Patient characteristics:
Mean age:
Intervention 1: 35.5
Intervention 2: 43
Intervention 3: 36.4

Comparators:
Intervention 1: Control
Intervention 2: Homebased resistance and balance
Intervention 3: Supervised resistance and balance
Based on an RCT included in the clinical review (Cakit 2010[1])

Cost components incorporated:
Staff costs to observe group sessions and phone calls conducted by community physiotherapists. Cost of cycling machine and downstream costs were not incorporated.

(da): (c) (d) Int					
1	£0	0.079	Baseline		
2	£52	0.090	£52	0.011	£4,867
3	£450	0.142	£398	0.052	£7,619

Intervention 3 is the most cost-effective intervention at £20,000 per QALY

Analysis of uncertainty:
Sensitivity analysis was conducted with a shorter time horizon of 8 weeks. Assuming the improvement in quality of life is not maintained beyond the 8-week intervention duration, the ICER increased to £31,633 per QALY and £49,526 per QALY for comparison 1 and 2 respectively.

Data sources

Health outcomes: Effectiveness was expressed as quality adjusted life years (QALYs). QALY gains for each intervention were estimated by assuming the effectiveness throughout the year is similar to the effectiveness observed at 8 weeks. **Quality-of-life weights:** Direct EQ-5D data was not available, therefore, QALYs were estimated through the mapping of changes in SF-36 scores obtained from the RCT using algorithm by Ara and Brazier (2008). **Cost sources:** Costs of each intervention were estimated based on published unit costs (PSSRU) and within trial resource use. The cost of a cycling machine was not included; however, when the cost of the machine is spread over the lifetime of the equipment and the amount of usage, the cost per patient per session is expected to be low. Downstream costs were not incorporated as it is unclear what these would be.

Comments

Source of funding: National Institute for Health and Care Excellence (NICE). **Limitations:** Does not include all relevant comparators for this question. Cost utility model based on a single RCT. The results were sensitive to the assumption of a continued treatment effect beyond the trial follow-up. This analysis does not include all intervention costs, for example the cost of the cycling machine. However, when the cost of the machine is spread over the lifetime of the equipment and the amount of usage, the cost per patient per session is expected to be low. Downstream costs were not included in the analysis as they were unclear from the clinical evidence. The regression models by Ara and Brazier (2008) have not been validated in people with MS specifically and model selected to map the SF-36 to EQ-5D score does not utilise the score from the physical role domain or the vitality (energy/fatigue) dimensions. **Other:** Potential for cost-savings in terms of reduced healthcare visits related to fatigue and mobility issues but there was no clinical evidence to support this.

Overall applicability:[e] Directly applicable **Overall quality:**[f] Potentially serious limitations

Abbreviations: CUA = cost-utility analysis; CI = 95% confidence interval; da = deterministic analysis; EQ5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health]; FACETS: Fatigue Applying Cognitive behavioural and Energy effectiveness Techniques to lifeStyle; FSS = Fatigue Severity Scale; ICER = incremental cost-effectiveness ratio; GFS = global fatigue scale; NR = not reported; PSA = probabilistic sensitivity analysis; PSSRU = Personal and Social Services Research Unit; QALYs = quality-adjusted life years; RCT = randomised control trial.

(a) Cost of staff time only.

(b) *Difference in QALY calculated as the incremental change in EQ-5D score between baseline and follow-up using an algorithm that mapped SF-36 scores to EQ-5D scores. The improvement in EQ-5D was assumed to be maintained, beyond the 8-week intervention period, over 1 year.*

(c) Intervention number in order of least to most effective (in terms of QALYs)

(s) Full incremental analysis of available strategies: first strategies are ruled out that are dominated (another strategy is more effective and has lower costs) or subject to extended dominance (the strategy is more effective and more costly but the incremental cost effectiveness ratio is higher than the next most effective option and so it would never be the most cost effective option); incremental costs, incremental effects and incremental cost effectiveness ratios are calculated for the remaining strategies by comparing each to the next most effective option

(e)Directly applicable / Partially applicable / Not applicable

(f)Minor limitations / Potentially serious limitations / Very serious limitations

Appendix H – Health economic model

No original economic modelling was undertaken.

Appendix I – Excluded studies

I.1 Clinical studies

Table 86: Studies excluded from the clinical review

Study	Code [Reason]
Aidar, Felipe J., Carneiro, André L., Costa Moreira, Osvaldo et al. (2018) Effects of resistance training on the physical condition of people with multiple sclerosis. Journal of Sports Medicine & Physical Fitness 58(78): 1127-1134	- No fatigue outcomes reported
Akbar, N., Sandroff, B. M., Wylie, G. R. et al. (2020) Progressive resistance exercise training and changes in resting-state functional connectivity of the caudate in persons with multiple sclerosis and severe fatigue: A proof-of-concept study. Neuropsychological Rehabilitation 30(1): 54-66	- Non-randomised study
Akbarfahimi, M., Nabavi, S. M., Kor, B. et al. (2020) The Effectiveness of Occupational Therapy-Based Sleep Interventions on Quality of Life and Fatigue in Patients with Multiple Sclerosis: A Pilot Randomized Clinical Trial Study. Neuropsychiatric Disease & Treatment 16: 1369-1379	- Treatment of fatigue was not one of the main aims of the study
Al-Sharman, A., Khalil, H., El-Salem, K. et al. (2019) The effects of aerobic exercise on sleep quality measures and sleep-related biomarkers in individuals with Multiple Sclerosis: A pilot randomised controlled trial. Neurorehabilitation 45(1): 107-115	- No fatigue outcomes reported
Alam, M. M.; Khan, A. A.; Farooq, M. (2020) Effects of whole-body vibration on muscle strength, balance and functional mobility in patients with multiple sclerosis: a systematic review and meta-analysis. Journal of Musculoskeletal Research 23 (4): 2050019	- Systematic review used as source of primary studies
Alashram, A. R.; Padua, E.; Annino, G. (2019) Effects of Whole-Body Vibration on Motor Impairments in Patients With Neurological Disorders: A Systematic Review. American Journal of Physical Medicine & Rehabilitation 98(12): 1084-1098	- Systematic review used as source of primary studies

Study	Code [Reason]
Alguacil Diego, I. M., Pedrero Hernández, C., Molina Rueda, F. et al. (2012) Effects of vibrotherapy on postural control, functionality and fatigue in multiple sclerosis patients. A randomised clinical trial. Neurologia (Barcelona, Spain) 27(3): 143-153	- Study not reported in English
Alschuler, K. N., Arewasikporn, A., Nelson, I. K. et al. (2018) Promoting resilience in individuals aging with multiple sclerosis: Results from a pilot randomized controlled trial. Rehabilitation Psychology 63(3): 338-348	- Treatment of fatigue was not one of the main aims of the study
Amato, M. P., Goretti, B., Viterbo, R. G. et al. (2014) Computer-assisted rehabilitation of attention in patients with multiple sclerosis: results of a randomized, double-blind trial. Multiple Sclerosis 20(1): 91-8	- No fatigue outcomes reported - Treatment of fatigue was not one of the main aims of the study
Amatya, B., Galea, M. P., Kesselring, J. et al. (2015) Effectiveness of telerehabilitation interventions in persons with multiple sclerosis: A systematic review. Multiple Sclerosis and Related Disorders 4(4): 358-69	- Systematic review used as source of primary studies
Amatya, B.; Khan, F.; Galea, M. (2019) Rehabilitation for people with multiple sclerosis: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Amatya, B.; Young, J.; Khan, F. (2018) Non-pharmacological interventions for chronic pain in multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Amedoro, A., Berardi, A., Conte, A. et al. (2020) The effect of aquatic physical therapy on patients with multiple sclerosis: A systematic review and meta-analysis. Mult. Scler. Relat. Disord. 41: 102022	- Systematic review used as source of primary studies
Andreu-Caravaca, L., Ramos-Campo, D. J., Chung, L. H. et al. (2021) Dosage and effectiveness of aerobic training on cardiorespiratory fitness, functional capacity, balance, and fatigue in people with Multiple Sclerosis: a systematic review and meta-analysis. Archives of Physical Medicine & Rehabilitation 102(9):1826-1839	- Systematic review used as source of primary studies

Study	Code [Reason]
Arazi, H., Samami, N., Dehghan, M. et al. (2016) The effect of eight-week concurrent aerobic-resistance training on aerobic power and functional capacity on young female patients with multiple sclerosis. Journal of Zanjan University of Medical Sciences and Health Services 24(105): 31-42	- Study not reported in English
Asano, M., Berg, E., Johnson, K. et al. (2015) A scoping review of rehabilitation interventions that reduce fatigue among adults with multiple sclerosis. Disability & Rehabilitation 37(9): 729-38	- Systematic review used as source of primary studies
Asano, M. and Finlayson, M. L. (2014) Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Multiple Sclerosis International 2014: 798285	- Systematic review used as source of primary studies
Ashrafi, A.; Mohseni-Bandpei, M. A.; Seydi, M. (2020) The effect of tDCS on the fatigue in patients with multiple sclerosis: A systematic review of randomized controlled clinical trials. Journal of Clinical Neuroscience 78: 277-283	- Systematic review used as source of primary studies
Ayache, S. S., Palm, U., Chalah, M. A. et al. (2016) Prefrontal tDCS Decreases Pain in Patients with Multiple Sclerosis. Frontiers in Neuroscience 10: 147 DOI: 10.3389/fnins.2016.00147	- Treatment of fatigue was not one of the main aims of the study
Aydin, T., Akif Sariyildiz, M., Guler, M. et al. (2014) Evaluation of the effectiveness of home based or hospital based calisthenic exercises in patients with multiple sclerosis. European Review for Medical & Pharmacological Sciences 18(8): 1189-98	- Comparator in study does not match that specified in this review protocol
Azari-Barzandig, R., Sattarzadeh-Jahdi, N., Nourizadeh, R. et al. (2020) The Effect of Counseling Based on EX-PLISSIT Model on Sexual Dysfunction and Quality of Sexual Life of Married Women with Multiple Sclerosis: A Randomized Controlled Clinical Trial. Sexuality and Disability 38(2): 271-284	- Study does not contain an intervention relevant to this review protocol
Bahr, L. S., Bock, M., Liebscher, D. et al. (2020) Ketogenic diet and fasting diet as Nutritional Approaches in Multiple Sclerosis (NAMS):	- Protocol only

Study	Code [Reason]
protocol of a randomized controlled study. Trials [Electronic Resource] 21(1): 3	
Bansi, J., Bloch, W., Gamper, U. et al. (2013) Endurance training in MS: short-term immune responses and their relation to cardiorespiratory fitness, health-related quality of life, and fatigue. Journal of Neurology 260(12): 2993-3001	- Compares two similar forms of exercise
Baquet, L., Hasselmann, H., Patra, S. et al. (2018) Short-term interval aerobic exercise training does not improve memory functioning in relapsing-remitting multiple sclerosis-a randomized controlled trial. PeerJ 6: e6037	- Treatment of fatigue was not one of the main aims of the study
Bayraktar, D., Guclu-Gunduz, A., Yazici, G. et al. (2013) Effects of Ai-Chi on balance, functional mobility, strength and fatigue in patients with multiple sclerosis: a pilot study. Neurorehabilitation 33(3): 431-7	- Non-randomised study
Beckerman, H., Blikman, L. J., Heine, M. et al. (2013) The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE programme. Trials 14: 250	- Protocol only
Bellmann-Strobl, J., Pach, D., Chang, Y. et al. (2018) The effectiveness of acupuncture and mindfulness-based stress reduction (MBSR) for patients with multiple sclerosis associated fatigue - A study protocol and its rationale for a randomized controlled trial. European Journal of Integrative Medicine 20: 6-15	- Protocol only
Berriozabalgoitia, R., Bidaurrazaga-Letona, I., Otxoa, E. et al. (2021) Overground Robotic Program Preserves Gait in Individuals With Multiple Sclerosis and Moderate to Severe Impairments: A Randomized Controlled Trial. Archives of Physical Medicine & Rehabilitation 102(5): 932-939	- Treatment of fatigue was not one of the main aims of the study
Berriozabalgoitia, R., Sanz, B., Fraile-Bermudez, A. B. et al. (2020) An Overground Robotic Gait Training Program for People With Multiple Sclerosis: A Protocol for a Randomized Clinical Trial. Frontiers in Medicine 7: 238	- Protocol only

Study	Code [Reason]
Blikman, L. J. M., van Meeteren, J., Twisk, J. W. R. et al. (2019) Energy Conservation Management for People With Multiple Sclerosis-Related Fatigue: Who Benefits?. American Journal of Occupational Therapy 73(4): 7304205040p1-7304205040p9	- Secondary publication of an included study that does not provide any additional relevant information
Boeschoten, R. E., Dekker, J., Uitdehaag, B. M. J. et al. (2012) Internet-based self-help treatment for depression in multiple sclerosis: Study protocol of a randomized controlled trial. BMC Psychiatry 11;12:137	- Protocol only
Boffa, G., Tacchino, A., Sbragia, E. et al. (2020) Preserved brain functional plasticity after upper limb task-oriented rehabilitation in progressive multiple sclerosis. European Journal of Neurology 27(1): 77-84	- Treatment of fatigue was not one of the main aims of the study
Bogosian, A., Chadwick, P., Windgassen, S. et al. (2015) Distress improves after mindfulness training for progressive MS: A pilot randomised trial. Multiple Sclerosis 21(9): 1184-94	- Treatment of fatigue was not one of the main aims of the study
Boldt, I., Eriks-Hoogland, I., Brinkhof, M. W. G. et al. (2014) Non-pharmacological interventions for chronic pain in people with spinal cord injury. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Brichetto, G., Piccardo, E., Pedulla, L. et al. (2015) Tailored balance exercises on people with multiple sclerosis: A pilot randomized, controlled study. Multiple Sclerosis 21(8): 1055-63	- Treatment of fatigue was not one of the main aims of the study
Brichetto, G., Spallarossa, P., de Carvalho, M. L. et al. (2013) The effect of Nintendo R Wii R on balance in people with multiple sclerosis: a pilot randomized control study. Multiple Sclerosis 19(9): 1219-21	- Treatment of fatigue was not one of the main aims of the study
Briken, S., Gold, S. M., Patra, S. et al. (2014) Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial. Multiple Sclerosis 20(3): 382-90	- Treatment of fatigue was not one of the main aims of the study
Byrnes, K. L. and Whillier, S. (2019) Effects of Nonpharmaceutical Treatments on Symptom Management in Adults With Mild or Moderate Multiple Sclerosis: A Meta-analysis. Journal of	- Systematic review used as source of primary studies

Study	Code [Reason]
Manipulative & Physiological Therapeutics 42(7): 514-531	
Callesen, J., Cattaneo, D., Brincks, J. et al. (2018) How does strength training and balance training affect gait and fatigue in patients with Multiple Sclerosis? A study protocol of a randomized controlled trial. Neurorehabilitation 42(2): 131-142	- Protocol only
Campbell, E.; Coulter, E. H.; Paul, L. (2018) High intensity interval training for people with multiple sclerosis: A systematic review. Multiple sclerosis and related disorders 24: 55-63	- Systematic review used as source of primary studies
Cancelli, A., Cottone, C., Giordani, A. et al. (2018) Personalized, bilateral whole-body somatosensory cortex stimulation to relieve fatigue in multiple sclerosis. Multiple Sclerosis 24(10): 1366-1374	- Study does not contain an intervention relevant to this review protocol
Canning, K. L. and Hicks, A. L. (2020) Benefits of Adhering to the Canadian Physical Activity Guidelines for Adults with Multiple Sclerosis Beyond Aerobic Fitness and Strength. International Journal of Ms Care 22(1): 15-21	- Insufficient reporting of fatigue outcomes
Canning, K. L. and Hicks, A. L. (2020) Physician referral improves adherence to the physical activity guidelines for adults with MS: A randomized controlled trial. Multiple Sclerosis and Related Disorders 37: 101441	- Order cancelled as difficulty ordering and deemed to be less relevant upon review of the abstract
Carletto, S., Borghi, M., Francone, D. et al. (2016) The efficacy of a Mindfulness Based Intervention for depressive symptoms in patients with Multiple Sclerosis and their caregivers: study protocol for a randomized controlled clinical trial. BMC Neurology 16: 7	- Protocol only
Carletto, S., Tesio, V., Borghi, M. et al. (2017) The Effectiveness of a Body-Affective Mindfulness Intervention for Multiple Sclerosis Patients with Depressive Symptoms: A Randomized Controlled Clinical Trial. Frontiers in Psychology 8: 2083	- Treatment of fatigue was not one of the main aims of the study
Case, L. K., Jackson, P., Kinkel, R. et al. (2018) Guided Imagery Improves Mood, Fatigue, and Quality of Life in Individuals With Multiple Sclerosis: An Exploratory Efficacy Trial of Healing Light Guided Imagery. Journal of	- Insufficient reporting of fatigue outcomes

Study	Code [Reason]
Evidence-based Integrative Medicine 23: 2515690x17748744	
Castillo-Bueno, I.; Ramos-Campo, D. J.; Rubio-Arias, J. A. (2018) Effects of whole-body vibration training in patients with multiple sclerosis: A systematic review. Neurologia 33(8): 534-548	- Systematic review used as source of primary studies
Castro-Sanchez, A. M., Mataran-Penarrocha, G. A., Lara-Palomo, I. et al. (2012) Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. Evidence-based complementary and alternative medicine 2012: 473963	- Treatment of fatigue was not one of the main aims of the study
Cavalera, C., Pagnini, F., Rovaris, M. et al. (2016) A telemedicine meditation intervention for people with multiple sclerosis and their caregivers: study protocol for a randomized controlled trial. Trials 17: 4	- Protocol only
Cavalera, C., Rovaris, M., Mendozzi, L. et al. (2019) Online meditation training for people with multiple sclerosis: A randomized controlled trial. Multiple Sclerosis 25(4): 610-617	- Insufficient reporting of fatigue outcomes
Chalah, M. A. and Ayache, S. S. (2018) Cognitive behavioral therapies and multiple sclerosis fatigue: A review of literature. Journal of Clinical Neuroscience 52: 1-4	- Review article but not a systematic review
Chalah, M. A., Grigorescu, C., Padberg, F. et al. (2020) Bifrontal transcranial direct current stimulation modulates fatigue in multiple sclerosis: a randomized sham-controlled study. J Neural Transm (Vienna) 127(6): 953-961	- Study does not contain an intervention relevant to this review protocol
Chalah, M. A., Riachi, N., Ahdab, R. et al. (2017) Effects of left DLPFC versus right PPC tDCS on multiple sclerosis fatigue. J Neurol Sci 372: 131-137	- Study does not contain an intervention relevant to this review protocol
Charvet, L. E., Dobbs, B., Shaw, M. T. et al. (2018) Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: Results from a randomized, sham-controlled trial. Multiple Sclerosis 24(13): 1760-1769	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
Chen, Y., Xu, S., Shen, J. et al. (2021) Effect of Exercise on Fatigue in Multiple Sclerosis Patients: A Network Meta-analysis. International Journal of Sports Medicine DOI: 10.1055/a-1524-1935	- Systematic review used as source of primary studies
Choobforoushzadeh, A., Neshat-Doost, H. T., Molavi, H. et al. (2015) Effect of neurofeedback training on depression and fatigue in patients with multiple sclerosis. Applied Psychophysiology & Biofeedback 40(1): 1-8	- Study does not contain an intervention relevant to this review protocol
Choudhary, A. and Singh, A. (2020) Need of comprehensive physiotherapy in multiple sclerosis: A narrative review. European Journal of Molecular and Clinical Medicine 7(7): 4754-4761	- Review article but not a systematic review
Clarke, R. and Coote, S. (2015) Perceptions of Participants in a Group, Community, Exercise Programme for People with Multiple Sclerosis. Rehabilitation Research and Practice 2015: 123494	- Non-randomised study
Coghe, G., Corona, F., Marongiu, E. et al. (2018) Fatigue, as measured using the Modified Fatigue Impact Scale, is a predictor of processing speed improvement induced by exercise in patients with multiple sclerosis: data from a randomized controlled trial. Journal of Neurology 265(6): 1328-1333	- Data not reported in an extractable format or a format that can be analysed
Coote, S., Gallagher, S., Msetfi, R. et al. (2014) A randomised controlled trial of an exercise plus behaviour change intervention in people with multiple sclerosis: the step it up study protocol. BMC Neurology 14: 241	- Protocol only
Coote, S., Hughes, L., Rainsford, G. et al. (2015) Pilot randomized trial of progressive resistance exercise augmented by neuromuscular electrical stimulation for people with multiple sclerosis who use walking aids. Archives of Physical Medicine & Rehabilitation 96(2): 197-204	- Treatment of fatigue was not one of the main aims of the study
Coote, S., Uszynski, M., Herring, M. P. et al. (2017) Effect of exercising at minimum recommendations of the multiple sclerosis exercise guideline combined with structured education or attention control education -	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
secondary results of the step it up randomised controlled trial. BMC Neurology 17(1): 119	
Corvillo, I., Varela, E., Armijo, F. et al. (2017) Efficacy of aquatic therapy for multiple sclerosis: a systematic review. European journal of physical & rehabilitation medicine. 53(6): 944-952	- Systematic review used as source of primary studies
Cramer, H., Lauche, R., Azizi, H. et al. (2014) Yoga for multiple sclerosis: a systematic review and meta-analysis. PLoS ONE 9(11): e112414	- Systematic review used as source of primary studies
Criado, M. B., Santos, M. J., Machado, J. et al. (2017) Effects of Acupuncture on Gait of Patients with Multiple Sclerosis. Journal of Alternative & Complementary Medicine 23(11): 852-857	- No fatigue outcomes reported - Systematic review used as source of primary studies
Cruickshank, T. M.; Reyes, A. R.; Ziman, M. R. (2015) A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. Medicine 94(4): e411	- Systematic review used as source of primary studies
Cuesta-Gomez, A., Sanchez-Herrera-Baeza, P., Ona-Simbana, E. D. et al. (2020) Effects of virtual reality associated with serious games for upper limb rehabilitation inpatients with multiple sclerosis: randomized controlled trial. Journal of Neuroengineering & Rehabilitation 17(1): 90	- Study does not contain an intervention relevant to this review protocol
Dahmardeh, H., Bahador, R. S., Barati, F. et al. (2017) Effect of self-care program based on Orem's model on complications of disease in patients with multiple sclerosis. Indian Journal of Public Health Research and Development 8(1): 337-341	- Fatigue reported but not as a patient-reported outcome scale
Daneshfar, F., Behboodi-Moghadam, Z., Khakbazan, Z. et al. (2017) The Influence of Ex-PLISSIT (Extended Permission, Limited Information, Specific Suggestions, Intensive Therapy) Model on Intimacy and Sexuality of Married Women with Multiple Sclerosis. Sexuality and Disability 35(4): 399-414	- Study does not contain an intervention relevant to this review protocol
Darwish, M. H., El-Tamawy, M. S., Basheer, M. A. et al. (2019) Effect of repetitive transcranial magnetic stimulation on motor functions in multiple sclerosis patients: A randomized	- No fatigue outcomes reported

Study	Code [Reason]
controlled trial. Indian Journal of Public Health Research and Development 10(11): 3368-3373	
de Carvalho, M. L., Motta, R., Konrad, G. et al. (2012) A randomized placebo-controlled cross-over study using a low frequency magnetic field in the treatment of fatigue in multiple sclerosis. Multiple sclerosis 18(1): 82-89	- Insufficient reporting of fatigue outcomes
De Giglio, L., De Luca, F., Prosperini, L. et al. (2015) A low-cost cognitive rehabilitation with a commercial video game improves sustained attention and executive functions in multiple sclerosis: a pilot study. Neurorehabilitation & Neural Repair 29(5): 453-61	- Study does not contain an intervention relevant to this review protocol
De-Bernardi-Ojuel, L.; Torres-Collado, L.; Garcia-de-la-Hera, M. (2021) Occupational Therapy Interventions in Adults with Multiple Sclerosis or Amyotrophic Lateral Sclerosis: A Scoping Review. International Journal of Environmental Research & Public Health [Electronic Resource] 18(4): 1432	- Systematic review used as source of primary studies
Di Fabio, R. P., Choi, T., Soderberg, J. et al. (1997) Health-related quality of life for patients with progressive multiple sclerosis: influence of rehabilitation. Phys Ther 77(12): 1704-16	- Non-randomised study
Dunne, J., Chih, H. J., Begley, A. et al. (2020) A randomised controlled trial to test the feasibility of online mindfulness programs for people with multiple sclerosis. Multiple Sclerosis and Related Disorders 48: 102728	- No fatigue outcomes reported
Dwyer, C. P., Alvarez-Iglesias, A., Joyce, R. et al. (2020) Evaluating the feasibility and preliminary efficacy of a Cognitive Occupation-Based programme for people with Multiple Sclerosis (COB-MS): protocol for a feasibility cluster-randomised controlled trial. Trials [Electronic Resource] 21(1): 269	- Protocol only
Ebrahimi, A.; Eftekhari, E.; Etemadifar, M. (2015) Effects of whole body vibration on hormonal & functional indices in patients with multiple sclerosis. Indian Journal of Medical Research 142(4): 450-8	- Study does not contain an intervention relevant to this review protocol
Edwards, T. and Pilutti, L. A. (2017) The effect of exercise training in adults with multiple sclerosis with severe mobility disability: A	- Systematic review used as source of primary studies

Study	Code [Reason]
systematic review and future research directions. Multiple Sclerosis and Related Disorders 16: 31-39	
Ehde, D. M., Alschuler, K. N., Day, M. A. et al. (2019) Mindfulness-based cognitive therapy and cognitive behavioral therapy for chronic pain in multiple sclerosis: a randomized controlled trial protocol. Trials [Electronic Resource] 20(1): 774	- Protocol only
Ehde, D. M., Alschuler, K. N., Sullivan, M. D. et al. (2018) Improving the quality of depression and pain care in multiple sclerosis using collaborative care: The MS-care trial protocol. Contemporary Clinical Trials 64: 219-229	- Protocol only
Ehde, D. M., Arewasikporn, A., Alschuler, K. N. et al. (2018) Moderators of Treatment Outcomes After Telehealth Self-Management and Education in Adults With Multiple Sclerosis: A Secondary Analysis of a Randomized Controlled Trial. Archives of Physical Medicine & Rehabilitation 99(7): 1265-1272	- Secondary publication of an included study that does not provide any additional relevant information
Ellis, B.; Blackburn, M.; Bath-Hextall, F. (2013) Balance training interventions for balance impairment and function in people with multiple sclerosis: A systematic review protocol. JBI Library of Systematic Reviews 11(10): 55-67	- Protocol only
Ensari, I.; Sandroff, B. M.; Motl, R. W. (2017) Intensity of treadmill walking exercise on acute mood symptoms in persons with multiple sclerosis. Anxiety, Stress, & Coping 30(1): 15-25	- Treatment of fatigue was not one of the main aims of the study
Ensari, I.; Sandroff, B. M.; Motl, R. W. (2016) Effects of Single Bouts of Walking Exercise and Yoga on Acute Mood Symptoms in People with Multiple Sclerosis. International Journal of Ms Care 18(1): 1-8	- Treatment of fatigue was not one of the main aims of the study
Escudero-Uribe, S., Hochsprung, A., Heredia-Camacho, B. et al. (2017) Effect of Training Exercises Incorporating Mechanical Devices on Fatigue and Gait Pattern in Persons with Relapsing-Remitting Multiple Sclerosis. Physiotherapy Canada 69(4): 292-302	- Study does not contain an intervention relevant to this review protocol
Farragher, Janine F., Jassal, Sarbjit V., McEwen, Sara et al. (2020) Energy management education and occupation-related outcomes in adults with chronic diseases: A	- Systematic review used as source of primary studies

Study	Code [Reason]
scoping review. British Journal of Occupational Therapy 83(9): 561-575	
Ferrucci, R., Vergari, M., Cogiamanian, F. et al. (2014) Transcranial direct current stimulation (tDCS) for fatigue in multiple sclerosis. NeuroRehabilitation 34(1): 121-7	- Study does not contain an intervention relevant to this review protocol
Fiene, M., Rufener, K. S., Kuehne, M. et al. (2018) Electrophysiological and behavioral effects of frontal transcranial direct current stimulation on cognitive fatigue in multiple sclerosis. J Neurol 265(3): 607-617	- Study does not contain an intervention relevant to this review protocol
Finlayson, M. (2005) Pilot study of an energy conservation education program delivered by telephone conference call to people with multiple sclerosis. Neurorehabilitation 20(4): 267-277	- Non-comparative study
Finlayson, M., Akbar, N., Turpin, K. et al. (2019) A multi-site, randomized controlled trial of MS INFoRm, a fatigue self-management website for persons with multiple sclerosis: rationale and study protocol. BMC Neurology 19(1): 142	- Protocol only
Finlayson, M.; Preissner, K.; Cho, C. (2013) Impact of comorbidity on fatigue management intervention outcomes among people with multiple sclerosis: an exploratory investigation. International Journal of Ms Care 15(1): 21-6	- Non-randomised study
Fitzgerald, K. C., Vizthum, D., Henry-Barron, B. et al. (2018) Effect of intermittent vs. daily calorie restriction on changes in weight and patient-reported outcomes in people with multiple sclerosis. Mult Scler Relat Disord 23: 33-39	- Treatment of fatigue was not one of the main aims of the study
Flachenecker, P., Meissner, H., Frey, R. et al. (2017) Neuropsychological Training of Attention Improves MS-Related Fatigue: Results of a Randomized, Placebo-Controlled, Double-Blind Pilot Study. European Neurology 78(56): 312-317	- Study does not contain an intervention relevant to this review protocol - Comparator in study does not match that specified in this review protocol
Fleming, K. M.; Coote, S. B.; Herring, M. P. (2020) An eight-week randomised controlled trial of home-based pilates for symptoms of anxiety, depression, and fatigue among people with MS with minimal-to-mild mobility disability:	- Protocol only

Study	Code [Reason]
Study protocol. Mental Health and Physical Activity 19: 100341	
Fleming, K. M., Herring, M. P., Coote, S. B. et al. (2021) Participant experiences of eight weeks of supervised or home-based Pilates among people with multiple sclerosis: a qualitative analysis. Disability & Rehabilitation: DOI: 10.1080/09638288.2021.1939446	- Secondary publication of an included study that does not provide any additional relevant information
Frevel, D. and Maurer, M. (2015) Internet-based home training is capable to improve balance in multiple sclerosis: a randomized controlled trial. European journal of physical & rehabilitation medicine. 51(1): 23-30	- Treatment of fatigue was not one of the main aims of the study
Gaede, G., Tiede, M., Lorenz, I. et al. (2018) Safety and preliminary efficacy of deep transcranial magnetic stimulation in MS-related fatigue. Neurol Neuroimmunol Neuroinflamm 5(1): e423	- Study does not contain an intervention relevant to this review protocol
Gandolfi, M., Geroin, C., Picelli, A. et al. (2014) Robot-assisted vs. sensory integration training in treating gait and balance dysfunctions in patients with multiple sclerosis: a randomized controlled trial. Frontiers in Human Neuroscience 8: 318	- Treatment of fatigue was not one of the main aims of the study
Gandolfi, M., Munari, D., Geroin, C. et al. (2015) Sensory integration balance training in patients with multiple sclerosis: A randomized, controlled trial. Multiple Sclerosis 21(11): 1453-62	- Treatment of fatigue was not one of the main aims of the study
Garcia Jalon, E.G., Lennon, S., Hannan, J. et al. (2008) Energy conservation for people with MS-related fatigue: a pilot randomized controlled trial [corrected] [published erratum appears in PHYSIOTHER RES INT 2008 Dec;13(4):217]. Physiotherapy research international 13(3): 139-140	- Abstract only
Garcia-Munoz, C., Cortes-Vega, M. D., Heredia-Rizo, A. M. et al. (2020) Effectiveness of vestibular training for balance and dizziness rehabilitation in people with multiple sclerosis: A systematic review and meta-analysis. Journal of Clinical Medicine 9 (2): 590	- Systematic review used as source of primary studies
Genova, Helen, Dacosta-Aguayo, Rosalia, Goverover, Yael et al. (2020) Effects of a Single Bout of Aquatic Exercise on Mood in Multiple	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
Sclerosis: A Pilot Study. International Journal of MS Care 22(4): 173-177	
Gervasoni, E., Cattaneo, D., Bertoni, R. et al. (2019) Effect of arm cycling and task-oriented exercises on fatigue and upper limb performance in multiple sclerosis: a randomized crossover study. International Journal of Rehabilitation Research 42(4): 300-308	- Insufficient reporting of fatigue outcomes
Gil-Bermejo-Bernardez-Zerpa, A., Moral-Munoz, J. A., Lucena-Anton, D. et al. (2021) Effectiveness of Motor Imagery on Motor Recovery in Patients with Multiple Sclerosis: Systematic Review. International Journal of Environmental Research & Public Health 18(2): 498	- Systematic review used as source of primary studies
Graham, J. E. (2006) Effects of exercise rehabilitation on fatigue in multiple sclerosis. Dissertation/ thesis: 114p	- Full text paper not available
Grazioli, E., Tranchita, E., Borriello, G. et al. (2019) The Effects of Concurrent Resistance and Aerobic Exercise Training on Functional Status in Patients with Multiple Sclerosis. Current Sports Medicine Reports 18(12): 452-457	- Treatment of fatigue was not one of the main aims of the study
Guclu-Gunduz, A., Citaker, S., Irkec, C. et al. (2014) The effects of pilates on balance, mobility and strength in patients with multiple sclerosis. Neurorehabilitation 34(2): 337-42	- No fatigue outcomes reported
Guijarro-Castro, C., Aladro-Benito, Y., Sanchez-Musulim, A. et al. (2017) Face-to-Face or Telematic Cognitive Stimulation in Patients with Multiple Sclerosis and Cognitive Impairment: Why Not Both?. Behavioural Neurology 2017: DOI: 10.1155/2017/5713934	- Protocol only
Gungor, F., Tarakci, E., Ozdemir-Acar, Z. et al. (2021) The effects of supervised versus home Pilates-based core stability training on lower extremity muscle strength and postural sway in people with multiple sclerosis. Multiple Sclerosis. 13524585211012202	- Treatment of fatigue was not one of the main aims of the study
Han, A. (2021) Mindfulness- and Acceptance-Based Interventions for Symptom Reduction in Individuals With Multiple Sclerosis: A Systematic Review and Meta-Analysis. Archives of Physical	- Systematic review used as source of primary studies

Study	Code [Reason]
Medicine & Rehabilitation DOI: https://doi.org/10.1016/j.apmr.2021.03.011	
Hanken, K., Bosse, M., Mohrke, K. et al. (2016) Counteracting Fatigue in Multiple Sclerosis with Right Parietal Anodal Transcranial Direct Current Stimulation. Frontiers in neurology [electronic resource]. 7: 154	- Study does not contain an intervention relevant to this review protocol
Harand, C., Daniel, F., Mondou, A. et al. (2019) Neuropsychological management of multiple sclerosis: evaluation of a supervised and customized cognitive rehabilitation program for self-used at home (SEPIA): protocol for a randomized controlled trial. Trials 20(1): 614	- Protocol only
Harrison, A. M., Safari, R., Mercer, T. et al. (2021) Which exercise and behavioural interventions show most promise for treating fatigue in multiple sclerosis? A network meta-analysis. Multiple Sclerosis: 1352458521996002	- Systematic review used as source of primary studies
Hasanpour-Dehkordi, A.; Jivad, N.; Solati, K. (2016) Effects of Yoga on Physiological Indices, Anxiety and Social Functioning in Multiple Sclerosis Patients: A Randomized Trial. Journal of Clinical and Diagnostic Research JCDR 10(6): VC01-VC05	- Insufficient reporting of fatigue outcomes
Hassanpour-Dehkordi, A. and Jivad, N. (2014) Comparison of regular aerobic and yoga on the quality of life in patients with multiple sclerosis. Medical Journal of the Islamic Republic of Iran 28: 141	- No fatigue outcomes reported
Hebert, J. R. (2009) Effects of vestibular rehabilitation on MS-related fatigue: randomized control trial. Dissertation/ thesis: 221p	- Full text paper not available
Heine, M., van de Port, I., Rietberg, M. B. et al. (2015) Exercise therapy for fatigue in multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Hempel, S., Graham, G. D., Fu, N. et al. (2017) A systematic review of the effects of modifiable risk factor interventions on the progression of multiple sclerosis. Multiple Sclerosis 23(4): 513-524	- Systematic review used as source of primary studies

Study	Code [Reason]
Herring, M. P., Fleming, K. M., Hayes, S. P. et al. (2017) Moderators of Exercise Effects on Depressive Symptoms in Multiple Sclerosis: A Meta-regression. American Journal of Preventive Medicine 53(4): 508-518	- Systematic review used as source of primary studies
Hochsprung, A., Escudero-Uribe, S., Ibanez-Vera, A. J. et al. (2021) Effectiveness of monopolar dielectric transmission of pulsed electromagnetic fields for multiple sclerosis-related pain: A pilot study. Neurologia 36(6): 433-439	- Treatment of fatigue was not one of the main aims of the study
Hogan, N., Kehoe, M., Larkin, A. et al. (2014) The Effect of Community Exercise Interventions for People with MS Who Use Bilateral Support for Gait. Mult Scler Int 2014: 109142	- Treatment of fatigue was not one of the main aims of the study
Hosseini, Seyedeh Shelir, Rajabi, Hamid, Sahraian, Mohammad Ali et al. (2018) Effects of 8-Week Home-Based Yoga and Resistance Training on Muscle Strength, Functional Capacity and Balance in Patients with Multiple Sclerosis: A Randomized Controlled Study. Asian Journal of Sports Medicine 9(3): 1-7	- No fatigue outcomes reported
Houniet-de Gier, M., Beckerman, H., van Vliet, K. et al. (2020) Testing non-inferiority of blended versus face-to-face cognitive behavioural therapy for severe fatigue in patients with multiple sclerosis and the effectiveness of blended booster sessions aimed at improving long-term outcome following both therapies: study protocol for two observer-blinded randomized clinical trials. Trials [Electronic Resource] 21(1): 98	- Protocol only
Hsu, W. Y., Cheng, C. H., Zanto, T. P. et al. (2021) Effects of Transcranial Direct Current Stimulation on Cognition, Mood, Pain, and Fatigue in Multiple Sclerosis: A Systematic Review and Meta-Analysis. Frontiers in Neurology. 12: 626113	- Study does not contain an intervention relevant to this review protocol
Hugos, C. L., Bourdette, D., Chen, Y. et al. (2017) A group-delivered self-management program reduces spasticity in people with multiple sclerosis: A randomized, controlled pilot trial. Multiple Sclerosis Journal Experimental Translational & Clinical 3(1): 2055217317699993	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
Hugos, C. L. and Cameron, M. H. (2020) MS Spasticity: Take Control (STC) for ambulatory adults: Protocol for a randomized controlled trial. BMC Neurology 20 (1): 368	- Protocol only
Ibrahim, F. A., Al Sebaee, H. A., El Deen, D. S. et al. (2020) Effect of acupressure pain and fatigue among patients with multiple sclerosis. Indian Journal of Public Health Research and Development 11(3): 1973-1978	- Length of follow-up <1 month - Non-randomised study
Jensen, M. P., Battalio, S. L., Chan, J. F. et al. (2018) Use of neurofeedback and mindfulness to enhance response to hypnosis treatmenet in individuals with multiple sclerosis: Results From a Pilot Randomized Clinical Trial. International Journal of Clinical & Experimental Hypnosis 66(3): 231-264	- Study does not contain an intervention relevant to this review protocol
Joisten, N., Rademacher, A., Bloch, W. et al. (2019) Influence of different rehabilitative aerobic exercise programs on (anti-) inflammatory immune signalling, cognitive and functional capacity in persons with MS - study protocol of a randomized controlled trial. BMC Neurology 19(1): 37	- Protocol only
Jolk, C., Alcantara, R., Bernhardt, L. et al. (2015) Improvements on walking distance in patients with multiple sclerosis. Nervenheilkunde 34(11): 906-914	- Study not reported in English
Kahraman, T., Savci, S., Ozdogar, A. T. et al. (2020) Physical, cognitive and psychosocial effects of telerehabilitation-based motor imagery training in people with multiple sclerosis: A randomized controlled pilot trial. Journal of Telemedicine & Telecare 26(5): 251-260	- Treatment of fatigue was not one of the main aims of the study
Kalron, A., Rosenblum, U., Frid, L. et al. (2017) Pilates exercise training vs. physical therapy for improving walking and balance in people with multiple sclerosis: a randomized controlled trial. Clinical Rehabilitation 31(3): 319-328	- Treatment of fatigue was not one of the main aims of the study
Kara, B., Kucuk, F., Poyraz, E. C. et al. (2017) Different types of exercise in Multiple Sclerosis: Aerobic exercise or Pilates, a single-blind clinical study. Journal of Back and Musculoskeletal Rehabilitation 30(3): 565-573	- Non-randomised study

Study	Code [Reason]
Karpatkin, H. I., Cohen, E. T., DiCarrado, S. et al. (2016) The effect of intermittent vs. continuous training on walking endurance and fatigue in people with multiple sclerosis: A randomized, crossover trial. Critical Reviews in Physical and Rehabilitation Medicine 28(12): 33-45	- Comparator in study does not match that specified in this review protocol
Karpatkin, H. I.; Napolione, D.; Siminovich-Blok, B. (2014) Acupuncture and multiple sclerosis: a review of the evidence. Evidence-Based Complementary & Alternative Medicine: 2014: 972935	- Systematic review used as source of primary studies
Karpatkin, H., Cohen, E. T., Rzetelny, A. et al. (2015) Effects of Intermittent Versus Continuous Walking on Distance Walked and Fatigue in Persons With Multiple Sclerosis: A Randomized Crossover Trial. Journal of Neurologic Physical Therapy 39(3): 172-8	- Comparator in study does not match that specified in this review protocol
Kehoe, M., Saunders, J., Jakeman, P. et al. (2015) Predictors of the physical impact of Multiple Sclerosis following community-based, exercise trial. Multiple Sclerosis 21(5): 590-8	- Secondary publication of an included study that does not provide any additional relevant information
Kerling, A., Keweloh, K., Tegtbur, U. et al. (2015) Effects of a Short Physical Exercise Intervention on Patients with Multiple Sclerosis (MS). International Journal of Molecular Sciences 16(7): 15761-75	- Treatment of fatigue was not one of the main aims of the study
Kern, C.; Elmenhorst, J.; Oberhoffer, R. (2013) Effect of sport climbing on patients with multiple sclerosis - Hints or evidence?. Neurologie und rehabilitation 19(4): 247-256	- Study not reported in English
Keytsman, C., Van Noten, P., Verboven, K. et al. (2021) Periodized versus classic exercise therapy in Multiple Sclerosis: a randomized controlled trial. Multiple Sclerosis and Related Disorders 49: 102782	- No fatigue outcomes reported - Comparator in study does not match that specified in this review protocol
Khadke, S. and Siddique, T. (2019) Diverse mechanisms and treatment strategies to confront fatigue in multiple sclerosis: A systematic review. F1000Research 8: 563	- Systematic review used as source of primary studies
Khalil, H., Al-Sharman, A., El-Salem, K. et al. (2018) The development and pilot evaluation of virtual reality balance scenarios in people with	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
multiple sclerosis (MS): A feasibility study. Neurorehabilitation 43(4): 473-482	
Khan, F. and Amatya, B. (2017) Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews. Archives of Physical Medicine & Rehabilitation 98(2): 353-367	- Systematic review used as source of primary studies
Khan, F.; Amatya, B.; Galea, M. (2014) Management of fatigue in persons with multiple sclerosis. Frontiers in Neurology. 5: 177	- Systematic review used as source of primary studies
Khan, F., Amatya, B., Kesselring, J. et al. (2015) Telerehabilitation for persons with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Kiropoulos, L. A., Kilpatrick, T., Holmes, A. et al. (2016) A pilot randomized controlled trial of a tailored cognitive behavioural therapy based intervention for depressive symptoms in those newly diagnosed with multiple sclerosis. BMC Psychiatry 16(1): 435	- Treatment of fatigue was not one of the main aims of the study
Kiropoulos, L., Kilpatrick, T., Kalincik, T. et al. (2020) Comparison of the effectiveness of a tailored cognitive behavioural therapy with a supportive listening intervention for depression in those newly diagnosed with multiple sclerosis (the ACTION-MS trial): protocol of an assessor-blinded, active comparator, randomised controlled trial. Trials 21(1): 100	- Protocol only
Klefbeck, B. and Hamrah Nedjad, J. (2003) Effect of inspiratory muscle training in patients with multiple sclerosis. Arch Phys Med Rehabil 84(7): 994-9	- Study does not contain an intervention relevant to this review protocol
Knowles, L. M., Hugos, C. L., Cameron, M. H. et al. (2021) Moderators of Improvements in Fatigue Impact Following a Self-Management Intervention in Multiple Sclerosis: A Secondary Analysis of a Randomized Controlled Trial. American Journal of Physical Medicine & Rehabilitation DOI: 10.1097/phm.0000000000001861	- Secondary publication of an included study that does not provide any additional relevant information
Korzhova, J. E., Chervyakov, A. V., Poydasheva, A. G. et al. (2016) The application of high-frequency and iTBS transcranial magnetic stimulation for the treatment of spasticity in the patients presenting with	- Study not reported in English

Study	Code [Reason]
secondary progressive multiple sclerosis. Voprosy Kurortologii, Fizioterapii, i Lechebnoi Fizicheskoi Kultury 93(5): 8-13	
Korzhova, J., Bakulin, I., Sinitsyn, D. et al. (2019) High-frequency repetitive transcranial magnetic stimulation and intermittent theta-burst stimulation for spasticity management in secondary progressive multiple sclerosis. European Journal of Neurology 26(4): 680-e44	- Treatment of fatigue was not one of the main aims of the study
Kratz, A. L., Alschuler, K. N., Ehde, D. M. et al. (2019) A randomized pragmatic trial of telephone-delivered cognitive behavioral-therapy, modafinil, and combination therapy of both for fatigue in multiple sclerosis: The design of the "COMBO-MS" trial. Contemporary Clinical Trials 84: 105821	- Protocol only
Kratz, A. L., Atalla, M., Whibley, D. et al. (2020) Calling Out MS Fatigue: Feasibility and Preliminary Effects of a Pilot Randomized Telephone-Delivered Exercise Intervention for Multiple Sclerosis Fatigue. Journal of Neurologic Physical Therapy 44(1): 23-31	- Comparator in study does not match that specified in this review protocol
Kratz, A. L.; Ehde, D. M.; Bombardier, C. H. (2014) Affective mediators of a physical activity intervention for depression in multiple sclerosis. Rehabilitation Psychology 59(1): 57-67	- No fatigue outcomes reported
Köpke, S., Solari, A., Rahn, A. et al. (2018) Information provision for people with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Lamberti, N., Straudi, S., Donadi, M. et al. (2020) Effectiveness of blood flow-restricted slow walking on mobility in severe multiple sclerosis: A pilot randomized trial. Scandinavian Journal of Medicine & Science in Sports 30(10): 1999-2009	- Comparator in study does not match that specified in this review protocol
Lamers, I., Raats, J., Spaas, J. et al. (2019) Intensity-dependent clinical effects of an individualized technology-supported task-oriented upper limb training program in Multiple Sclerosis: A pilot randomized controlled trial. Multiple Sclerosis and Related Disorders 34: 119-127	- No fatigue outcomes reported

Study	Code [Reason]
Lampit, A., Heine, J., Finke, C. et al. (2019) Computerized Cognitive Training in Multiple Sclerosis: A Systematic Review and Meta-analysis. Neurorehabilitation & Neural Repair 33(9): 695-706	- Systematic review used as source of primary studies
Lappin, M.S., Lawrie, F.W., Richards, T.L. et al. (2003) Effects of a pulsed electromagnetic therapy on multiple sclerosis fatigue and quality of life: A double-blind, placebo controlled trial. Alternative therapies in health and medicine 9(4): 38-48	- Study does not contain an intervention relevant to this review protocol
Latorraca, C. O. C., Martimbianco, A. L. C., Pachito, D. V. et al. (2019) Palliative care interventions for people with multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Learmonth, Y. C., Adamson, B. C., Kinnett-Hopkins, D. et al. (2017) Results of a feasibility randomised controlled study of the guidelines for exercise in multiple sclerosis project. Contemp Clin Trials 54: 84-97	- Treatment of fatigue was not one of the main aims of the study
Lee, J. E., Titcomb, T. J., Bisht, B. et al. (2021) A Modified MCT-Based Ketogenic Diet Increases Plasma beta-Hydroxybutyrate but Has Less Effect on Fatigue and Quality of Life in People with Multiple Sclerosis Compared to a Modified Paleolithic Diet: A Waitlist-Controlled, Randomized Pilot Study. Journal of the American College of Nutrition 40(1): 13-25	- Insufficient reporting of fatigue outcomes
Lincoln, N. B., Bradshaw, L. E., Constantinescu, C. S. et al. (2020) Group cognitive rehabilitation to reduce the psychological impact of multiple sclerosis on quality of life: the CRAMMS RCT. Health Technology Assessment 24(4): 1-182	- Study does not contain an intervention relevant to this review protocol
Lincoln, N. B., Bradshaw, L. E., Constantinescu, C. S. et al. (2020) Cognitive rehabilitation for attention and memory in people with multiple sclerosis: a randomized controlled trial (CRAMMS). Clinical Rehabilitation 34(2): 229-241	- Study does not contain an intervention relevant to this review protocol
Liu, M., Fan, S., Xu, Y. et al. (2019) Non-invasive brain stimulation for fatigue in multiple sclerosis patients: A systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 36: 101375	- Systematic review used as source of primary studies

Study	Code [Reason]
Longley, W. A.; Tate, R. L.; Brown, R. F. (2012) A protocol for measuring the direct psychological benefit of neuropsychological assessment with feedback in multiple sclerosis. Brain impairment 13(2): 238-255	- Protocol only
Loyd, B. J., Fangman, A., Peterson, D. S. et al. (2019) Rehabilitation to improve gaze and postural stability in people with multiple sclerosis: study protocol for a prospective randomized clinical trial. BMC Neurology 19(1): 119	- Protocol only
Mackay, A. M., Buckingham, R., Schwartz, R. S. et al. (2015) The Effect of Biofeedback as a Psychological Intervention in Multiple Sclerosis: A Randomized Controlled Study. International Journal of Ms Care 17(3): 101-8	- Study does not contain an intervention relevant to this review protocol
Maggio, M. G., Russo, M., Cuzzola, M. F. et al. (2019) Virtual reality in multiple sclerosis rehabilitation: A review on cognitive and motor outcomes. Journal of Clinical Neuroscience 65: 106-111	- Systematic review used as source of primary studies
Mahler, A., Balogh, A., Csizmadia, I. et al. (2018) Metabolic, mental and immunological effects of normoxic and hypoxic training in multiple sclerosis patients: A pilot study. Frontiers in Immunology DOI: 10.3389/fimmu.2018.02819	- Treatment of fatigue was not one of the main aims of the study - Insufficient reporting of fatigue outcomes
Malekzadeh, A., Bader, I., van Dieteren, J. et al. (2019) Diurnal Cortisol Secretion Is Not Related to Multiple Sclerosis-Related Fatigue. Frontiers in Neurology. 10: 1363	- Secondary publication of an included study that does not provide any additional relevant information
Mantynen, A., Rosti-Otajarvi, E., Koivisto, K. et al. (2014) Neuropsychological rehabilitation does not improve cognitive performance but reduces perceived cognitive deficits in patients with multiple sclerosis: A randomised, controlled, multi-centre trial. Multiple Sclerosis 20(1): 99-107	- Treatment of fatigue was not one of the main aims of the study
Mateen, F. J., Manalo, N. C., Grundy, S. J. et al. (2017) Light therapy for multiple sclerosis-associated fatigue: Study protocol for a randomized controlled trial. Medicine 96(36): e8037	- Protocol only

Study	Code [Reason]
Mateen, F. J., Vogel, A. C., Kaplan, T. B. et al. (2020) Light therapy for multiple sclerosis-associated fatigue: a randomized, controlled phase II trial. Journal of Neurology 267(8): 2319-2327	- Study does not contain an intervention relevant to this review protocol
Mayo, N. E., Bayley, M., Duquette, P. et al. (2013) The role of exercise in modifying outcomes for people with multiple sclerosis: a randomized trial. BMC neurology 13: 69	- Protocol only
Mayo, N. E., Mate, K. K., Reid, R. et al. (2020) Participation in and outcomes from a 12-month tailored exercise programme for people with multiple sclerosis (MSTEP©): a randomized trial. Clinical Rehabilitation 34(7): 927-937	- Treatment of fatigue was not one of the main aims of the study
Messinis, L., Kosmidis, M. H., Nasios, G. et al. (2020) Do Secondary Progressive Multiple Sclerosis patients benefit from Computer- based cognitive neurorehabilitation? A randomized sham controlled trial. Multiple Sclerosis and Related Disorders 39: 101932	- Order cancelled as difficulty ordering and deemed to be less relevant upon review of the abstract
Miller, L., Paul, L., Mattison, P. et al. (2011) Evaluation of a home-based physiotherapy programme for those with moderate to severe multiple sclerosis: a randomized controlled pilot study. Clinical rehabilitation 25(8): 720-730	- No fatigue outcomes reported
Miller, P. and Soundy, A. (2017) The pharmacological and non-pharmacological interventions for the management of fatigue related multiple sclerosis. Journal of the Neurological Sciences 381: 41-54	- Systematic review used as source of primary studies
Minen, M. T.; Schaubhut, K. B.; Morio, K. (2020) Smartphone based behavioral therapy for pain in multiple sclerosis (MS) patients: A feasibility acceptability randomized controlled study for the treatment of comorbid migraine and MS pain. Multiple Sclerosis and Related Disorders 46: 102489	- No fatigue outcomes reported
Mische, L. J. and Mowry, E. M. (2018) The Evidence for Dietary Interventions and Nutritional Supplements as Treatment Options in Multiple Sclerosis: a Review. Current Treatment Options in Neurology 20(4): 8	- Review article but not a systematic review

Study	Code [Reason]
Mitolo, M., Venneri, A., Wilkinson, I. D. et al. (2015) Cognitive rehabilitation in multiple sclerosis: A systematic review. Journal of the Neurological Sciences 354(12): 1-9	- Systematic review used as source of primary studies
Moghadasi, A., Ghasemi, G., Sadeghi-Demneh, E. et al. (2020) The Effect of Total Body Resistance Exercise on Mobility, Proprioception, and Muscle Strength of the Knee in People With Multiple Sclerosis. Journal of sport rehabilitation 29(2): 192-199	- No fatigue outcomes reported
Mokhtarzade, M., Ranjbar, R., Majdinasab, N. et al. (2017) Effect of aerobic interval training on serum IL-10, TNFalpha, and adipokines levels in women with multiple sclerosis: possible relations with fatigue and quality of life. Endocrine 57(2): 262-271	- Non-randomised study
Moradi, M., Sahraian, M. A., Aghsaie, A. et al. (2015) Effects of Eight-week Resistance Training Program in Men With Multiple Sclerosis. Asian Journal of Sports Medicine 6(2): e22838	- No fatigue outcomes reported
Moraes, A. G., Neri, S. G. R., Motl, R. W. et al. (2021) Effects of hippotherapy on postural balance, functional mobility, self-perceived fatigue, and quality of life in people with relapsing-remitting multiple sclerosis: Secondary results of an exploratory clinical trial. Multiple Sclerosis and Related Disorders 52: 102948	- Treatment of fatigue was not one of the main aims of the study
Mori, F., Ljoka, C., Magni, E. et al. (2011) Transcranial magnetic stimulation primes the effects of exercise therapy in multiple sclerosis. Journal of neurology 258(7): 1281-1287	- Treatment of fatigue was not one of the main aims of the study
Morrison, J. D. and Mayer, L. (2017) Physical activity and cognitive function in adults with multiple sclerosis: an integrative review. Disability & Rehabilitation 39(19): 1909-1920	- Systematic review used as source of primary studies
Morrow, S. A., Riccio, P., Vording, N. et al. (2021) A mindfulness group intervention in newly diagnosed persons with multiple sclerosis: A pilot study. Multiple Sclerosis and Related Disorders 52: 103016	- Treatment of fatigue was not one of the main aims of the study
Mortezanejad, Marzieh, Ehsani, Fatemeh, Masoudian, Nooshin et al. (2020) Comparing	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
the effects of multi-session anodal trans-cranial direct current stimulation of primary motor and dorsolateral prefrontal cortices on fatigue and quality of life in patients with multiple sclerosis: a double-blind, randomized, sham-controlled trial. Clinical Rehabilitation 34(8): 1103-1111	
Moss-Morris, R., Harrison, A. M., Safari, R. et al. (2021) Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. Behaviour Research & Therapy 137: 103464	- Systematic review used as source of primary studies
Motl, R. W., Backus, D., Neal, W. N. et al. (2019) Rationale and design of the STEP for MS Trial: Comparative effectiveness of Supervised versus Telerehabilitation Exercise Programs for Multiple Sclerosis. Contemporary Clinical Trials 81: 110-122	- Protocol only
Motl, R. W., Hubbard, E. A., Bollaert, R. E. et al. (2017) Randomized controlled trial of an e-learning designed behavioral intervention for increasing physical activity behavior in multiple sclerosis. Multiple Sclerosis Journal Experimental Translational & Clinical 3(4): 2055217317734886	- Treatment of fatigue was not one of the main aims of the study
Motl, R. W. and Sandroff, B. M. (2020) Randomized controlled trial of physical activity intervention effects on fatigue and depression in multiple sclerosis: Secondary analysis of data from persons with elevated symptom status. Contemporary Clinical Trials Communications 17: 100521	- Treatment of fatigue was not one of the main aims of the study
Motl, R. W., Sandroff, B. M., Wingo, B. C. et al. (2018) Phase-III, randomized controlled trial of the behavioral intervention for increasing physical activity in multiple sclerosis: Project BIPAMS. Contemporary Clinical Trials 71: 154-161	- Protocol only
Munoz San Jose, A., Oreja-Guevara, C., Cebolla Lorenzo, S. et al. (2016) Psychotherapeutic and psychosocial interventions for managing stress in multiple sclerosis: the contribution of mindfulness-based interventions. Neurologia 31(2): 113-20	- Review article but not a systematic review

Study	Code [Reason]
Nazari, F., Soheili, M., Hosseini, S. et al. (2016) A comparison of the effects of reflexology and relaxation on pain in women with multiple sclerosis. Journal of Complementary & Integrative Medicine 13(1): 65-71	- No fatigue outcomes reported
Nedeljkovic, U., Dubljanin Raspopovic, E., Ilic, N. et al. (2014) Endurance and resistance training in rehabilitation of patients with multiple sclerosis. Vojnosanitetski Pregled 71(10): 963-968	- Systematic review used as source of primary studies
Negaresh, R., Motl, R., Mokhtarzade, M. et al. (2019) Effect of Short-Term Interval Exercise Training on Fatigue, Depression, and Fitness in Normal Weight vs. Overweight Person With Multiple Sclerosis. Explore: The Journal of Science & Healing 15(2): 134-141	- Data not reported in an extractable format or a format that can be analysed
Nejati, S., Rajezi Esfahani, S., Rahmani, S. et al. (2016) The Effect of Group Mindfulness-based Stress Reduction and Consciousness Yoga Program on Quality of Life and Fatigue Severity in Patients with MS. Journal of Caring Sciences 5(4): 325-335	- Non-randomised study
Nicholas, R. and Chataway, J. (2007) Multiple sclerosis. Clinical Evidence 15: 15	- Systematic review used as source of primary studies
Nicholas, R. and Chataway, J. (2009) Multiple sclerosis. Clinical Evidence 14: 14	- Systematic review used as source of primary studies
Nicholas, R. and Rashid, W. (2012) Multiple sclerosis. Clinical Evidence 10: 10	- Systematic review used as source of primary studies
Omrani, S., Mirzaeian, B., Aghabagheri, H. et al. (2012) Investigating effectuality of cognitive-behavioral therapy (CBT) as group method on the basis of hope rate in patients suffering from multiple sclerosis (M.S). Journal of mazandaran university of medical sciences 22(93): 57-65	- Study not reported in English
Oral, A. and Yaliman, A. (2013) Revisiting the management of fatigue in multiple sclerosis in the context of rehabilitation: a narrative review of current evidence. International Journal of Rehabilitation Research 36(2): 97-104	- Review article but not a systematic review
Ozdelikara, A. and Agcadiken Alkan, S. (2018) The Effects of Reflexology on Fatigue and	- Non-comparative study

Study	Code [Reason]
Anxiety in Patients With Multiple Sclerosis. Altern Ther Health Med 24(4): 8-13	
Ozdogar, A. T., Ertekin, O., Kahraman, T. et al. (2020) Effect of video-based exergaming on arm and cognitive function in persons with multiple sclerosis: A randomized controlled trial. Multiple Sclerosis and Related Disorders 40: 101966	- Treatment of fatigue was not one of the main aims of the study
Ozkul, C., Guclu-Gunduz, A., Eldemir, K. et al. (2020) Combined exercise training improves cognitive functions in multiple sclerosis patients with cognitive impairment: A single-blinded randomized controlled trial. Multiple Sclerosis and Related Disorders 45: 102419	- Treatment of fatigue was not one of the main aims of the study
Ozkul, C., Guclu-Gunduz, A., Irkec, C. et al. (2018) Effect of combined exercise training on serum brain-derived neurotrophic factor, suppressors of cytokine signaling 1 and 3 in patients with multiple sclerosis. Journal of Neuroimmunology 316: 121-129	- Treatment of fatigue was not one of the main aims of the study
Pagnini, F., Bosma, C. M., Phillips, D. et al. (2014) Symptom changes in multiple sclerosis following psychological interventions: a systematic review. BMC Neurology 14: 222	- Systematic review used as source of primary studies
Panagopoulou, Z., Artemiadis, A. K., Chrousos, G. P. et al. (2021) Pythagorean Self-Awareness Intervention for Multiple Sclerosis Patients: A Quasi-Experimental Pragmatic Trial. Archives of Clinical Neuropsychology DOI: 10.1093/arclin/acab044	- Non-randomised study
Parks, N. E., Jackson-Tarlton, C. S., Vacchi, L. et al. (2020) Dietary interventions for multiple sclerosis-related outcomes. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Patt, N., Kool, J., Hersche, R. et al. (2021) High-intensity interval training and energy management education, compared with moderate continuous training and progressive muscle relaxation, for improving health-related quality of life in persons with multiple sclerosis: study protocol of a randomized controlled superiority trial with six months' follow-up. BMC Neurology 21(1): 65	- Protocol only
Pau, M., Corona, F., Coghe, G. et al. (2018) Quantitative assessment of the effects of 6	- No fatigue outcomes reported

Study	Code [Reason]
months of adapted physical activity on gait in people with multiple sclerosis: a randomized controlled trial. Disability & Rehabilitation 40(2): 144-151	
Payne, C.; Wiffen, P. J.; Martin, S. (2017) Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews 2017 (4)	- Full text paper not available
Perez-Martin, M. Y., Gonzalez-Platas, M., Eguia-Del Rio, P. et al. (2017) Efficacy of a short cognitive training program in patients with multiple sclerosis. Neuropsychiatric Disease & Treatment 13: 245-252	- Treatment of fatigue was not one of the main aims of the study
Petajan, J. H., Gappmaier, E., White, A. T. et al. (1996) Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 39(4): 432-41	- Insufficient reporting of fatigue outcomes
Phyo, A. Z. Z., Demaneuf, T., De Livera, A. M. et al. (2018) The Efficacy of Psychological Interventions for Managing Fatigue in People With Multiple Sclerosis: A Systematic Review and Meta-Analysis. Frontiers in neurology [electronic resource]. 9: 149	- Systematic review used as source of primary studies
Piatkowski, Joachim; Kern, Simone; Ziemssen, Tjalf (2009) Effect of BEMER magnetic field therapy on the level of fatigue in patients with multiple sclerosis: a randomized, double-blind controlled trial. Journal of Alternative and Complementary Medicine 15(5): 507-511	- Study does not contain an intervention relevant to this review protocol
Pilutti, L. A., Dlugonski, D., Sandroff, B. M. et al. (2014) Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. Multiple Sclerosis 20(5): 594-601	- Treatment of fatigue was not one of the main aims of the study
Pilutti, L. A., Edwards, T., Motl, R. W. et al. (2019) Functional Electrical Stimulation Cycling Exercise in People with Multiple Sclerosis: Secondary Effects on Cognition, Symptoms, and Quality of Life. International Journal of MS Care 21(6): 258-264	- Treatment of fatigue was not one of the main aims of the study
Pilutti, L. A., Greenlee, T. A., Motl, R. W. et al. (2013) Effects of exercise training on fatigue in	- Systematic review used as source of primary studies

Study	Code [Reason]
multiple sclerosis: a meta-analysis. Psychosomatic Medicine 75(6): 575-80	
Pilutti, L. A., Paulseth, J. E., Dove, C. et al. (2016) Exercise Training in Progressive Multiple Sclerosis: A Comparison of Recumbent Stepping and Body Weight-Supported Treadmill Training. International Journal of Ms Care 18(5): 221-229	- Treatment of fatigue was not one of the main aims of the study
Plow, M., Bethoux, F., Mai, K. et al. (2014) A formative evaluation of customized pamphlets to promote physical activity and symptom self-management in women with multiple sclerosis. Health Education Research 29(5): 883-96	- No fatigue outcomes reported
Plow, M., Motl, R. W., Finlayson, M. et al. (2020) Intervention Mediators in a Randomized Controlled Trial to Increase Physical Activity and Fatigue Self-management Behaviors Among Adults With Multiple Sclerosis. Annals of Behavioral Medicine 54(3): 213-221	- Secondary publication of an included study that does not provide any additional relevant information
Plow, M., Motl, R. W., Finlayson, M. et al. (2020) Response heterogeneity in a randomized controlled trial of telerehabilitation interventions among adults with multiple sclerosis. Journal of Telemedicine & Telecare: 1357633x20964693	- Secondary publication of an included study that does not provide any additional relevant information
Plow, M., Packer, T., Mathiowetz, V. G. et al. (2020) REFRESH protocol: a non-inferiority randomised clinical trial comparing internet and teleconference to in-person 'Managing Fatigue' interventions on the impact of fatigue among persons with multiple sclerosis. BMJ Open 10(8): e035470	- Protocol only
Plow, Matthew A.; Mathiowetz, Virgil; Lowe, Dawn A. (2009) Comparing individualized rehabilitation to a group wellness intervention for persons with multiple sclerosis. American journal of health promotion 24(1): 23-26	- Insufficient reporting of fatigue outcomes
Pommerich, U. M.; Brincks, J.; Christensen, M. E. (2018) Is there an effect of dietary intake on MS-related fatigue? - A systematic literature review. Multiple Sclerosis and Related Disorders 25: 282-291	- Systematic review used as source of primary studies
Pompa, A., Morone, G., Iosa, M. et al. (2017) Does robot-assisted gait training improve ambulation in highly disabled multiple sclerosis	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
people? A pilot randomized control trial. Multiple Sclerosis 23(5): 696-703	
Proctor, B. J., Moghaddam, N., Vogt, W. et al. (2018) Telephone psychotherapy in multiple sclerosis: A systematic review and meta-analysis. Rehabilitation Psychology 63(1): 16-28	- Systematic review used as source of primary studies
Prokopiusova, T., Pavlikova, M., Markova, M. et al. (2020) Randomized comparison of functional electric stimulation in posturally corrected position and motor program activating therapy: treating foot drop in people with multiple sclerosis. European journal of physical & rehabilitation medicine. 56(4): 394-402	- Treatment of fatigue was not one of the main aims of the study
Pusswald, G., Mildner, C., Zebenholzer, K. et al. (2014) A neuropsychological rehabilitation program for patients with Multiple Sclerosis based on the model of the ICF. Neurorehabilitation 35(3): 519-27	- Treatment of fatigue was not one of the main aims of the study
Quinn, E. and Hynes, S. M. (2021) Occupational therapy interventions for multiple sclerosis: A scoping review. Scandinavian Journal of Occupational Therapy. DOI: https://doi.org/10.1080/11038128.2020.1786160	- Systematic review used as source of primary studies
Razazian, N., Kazeminia, M., Moayedi, H. et al. (2020) The impact of physical exercise on the fatigue symptoms in patients with multiple sclerosis: a systematic review and meta-analysis. BMC Neurology 20(1): 93	- Systematic review used as source of primary studies
Rice, I. M.; Rice, L. A.; Motl, R. W. (2015) Promoting Physical Activity Through a Manual Wheelchair Propulsion Intervention in Persons With Multiple Sclerosis. Archives of Physical Medicine & Rehabilitation 96(10): 1850-8	- Study does not contain an intervention relevant to this review protocol - Treatment of fatigue was not one of the main aims of the study
Richards, T.L., Lappin, M.S., Acosta-Urquidi, J. et al. (1997) Double-blind study of pulsing magnetic field effects on multiple sclerosis. Journal of Alternative and Complementary Medicine 3(1): 21-29	- Study does not contain an intervention relevant to this review protocol
Rietberg, M. B., Veerbeek, J. M., Gosselink, R. et al. (2017) Respiratory muscle training for multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies

Study	Code [Reason]
Rimmer, J. H., Herman, C., Wingo, B. et al. (2018) Methodological and clinical implications of a three-in-one Russian doll design for tracking health trajectories and improving health and function through innovative exercise treatments in adults with disability. BMC Medical Research Methodology 18(1): 28	- Protocol only
Rimmer, J. H., Thirumalai, M., Young, H. J. et al. (2018) Rationale and design of the tele-exercise and multiple sclerosis (TEAMS) study: A comparative effectiveness trial between a clinic- and home-based telerehabilitation intervention for adults with multiple sclerosis (MS) living in the deep south. Contemporary Clinical Trials 71: 186-193	- Protocol only
Roman, S. N., Fitzgerald, K. C., Beier, M. et al. (2020) Safety and feasibility of various fasting-mimicking diets among people with multiple sclerosis. Multiple Sclerosis and Related Disorders 42: 102149	- Treatment of fatigue was not one of the main aims of the study
Rooney, S., Moffat, F., Wood, L. et al. (2019) Effectiveness of Fatigue Management Interventions in Reducing Severity and Impact of Fatigue in People with Progressive Multiple Sclerosis: A Systematic Review. International Journal of Ms Care 21(1): 35-46	- Systematic review used as source of primary studies
Rosti-Otajarvi, E., Mantynen, A., Koivisto, K. et al. (2013) Neuropsychological rehabilitation has beneficial effects on perceived cognitive deficits in multiple sclerosis during nine-month follow-up. Journal of the Neurological Sciences 334(12): 154-60	- Treatment of fatigue was not one of the main aims of the study
Rosti-Otajärvi, E. M. and Hämäläinen, P. I. (2014) Neuropsychological rehabilitation for multiple sclerosis. Cochrane Database of Systematic Reviews	- Systematic review used as source of primary studies
Ryan, J. M., Fortune, J., Stennett, A. et al. (2017) Changing physical activity behaviour for people with multiple sclerosis: protocol of a randomised controlled feasibility trial (iStep-MS). BMJ Open 7(11): e018875	- Protocol only
Ryan, J. M., Fortune, J., Stennett, A. et al. (2020) Safety, feasibility, acceptability and effects of a behaviour-change intervention to change physical activity behaviour among	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
people with multiple sclerosis: Results from the iStep-MS randomised controlled trial. Multiple Sclerosis 26(14): 1907-1918	
Sadeghi Bahmani, D., Motl, R. W., Razazian, N. et al. (2020) Aquatic exercising may improve sexual function in females with multiple sclerosis - an exploratory study. Multiple Sclerosis and Related Disorders 43: 102106	- Treatment of fatigue was not one of the main aims of the study
Sadeghi Bahmani, D., Razazian, N., Motl, R. W. et al. (2020) Physical activity interventions can improve emotion regulation and dimensions of empathy in persons with multiple sclerosis: An exploratory study. Multiple Sclerosis and Related Disorders 37: 101380	- Secondary publication of an included study that does not provide any additional relevant information
Safari, R.; Van der Linden, M. L.; Mercer, T. H. (2017) Effect of exercise interventions on perceived fatigue in people with multiple sclerosis: synthesis of meta-analytic reviews. Neurodegenerative Disease Management 7(3): 219-230	- Systematic review used as source of primary studies
Saiote, C., Goldschmidt, T., Timäus, C. et al. (2014) Impact of transcranial direct current stimulation on fatigue in multiple sclerosis. Restor Neurol Neurosci 32(3): 423-36	- Study does not contain an intervention relevant to this review protocol
Salarvand, S., Heidari, M. E., Farahi, K. et al. (2021) Effectiveness of massage therapy on fatigue and pain in patients with multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis Journal Experimental Translational & Clinical 7(2): 20552173211022779	- Systematic review used as source of primary studies
Salemi, G., Vazzoler, G., Ragonese, P. et al. (2019) Application of tRNS to improve multiple sclerosis fatigue: a pilot, single-blind, sham-controlled study. Journal of Neural Transmission 126(6): 795-799	- Study does not contain an intervention relevant to this review protocol
Salome, A., Sasso D'Elia, T., Franchini, G. et al. (2019) Occupational Therapy in Fatigue Management in Multiple Sclerosis: An Umbrella Review. Multiple Sclerosis International 2019: 2027947	- Systematic review used as source of primary studies
San, A. U.; Yilmaz, B.; Kesikburun, S. (2019) The Effect of Repetitive Transcranial Magnetic Stimulation on Spasticity in Patients with	- No fatigue outcomes reported

Study	Code [Reason]
Multiple Sclerosis. Journal of Clinical Neurology 15(4): 461-467	
Sanchez-Lastra, M. A., Martinez-Aldao, D., Molina, A. J. et al. (2019) Pilates for people with multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 28: 199-212	- Systematic review used as source of primary studies
Sangelaji, B., Kordi, M., Banihashemi, F. et al. (2016) A combined exercise model for improving muscle strength, balance, walking distance, and motor agility in multiple sclerosis patients: A randomized clinical trial. Iranian Journal of Neurology 15(3): 111-20	- Insufficient reporting of fatigue outcomes - Treatment of fatigue was not one of the main aims of the study
Sangelaji, B., Smith, C. M., Paul, L. et al. (2016) The effectiveness of behaviour change interventions to increase physical activity participation in people with multiple sclerosis: a systematic review and meta-analysis. Clinical Rehabilitation 30(6): 559-76	- Systematic review used as source of primary studies
Santos, Iara, Soares Laurito, Gabrielle Stephanie, Soares Silva, Maria Nazaré et al. (2015) Classical massage in multiplesclerosis. Manual Therapy, Posturology & Rehabilitation Journal 13: 1-4	- Non-comparative study - No fatigue outcomes reported
Sarbaz, Yashar, Beni, Kamran Naderi, Hosseininejad, Azar et al. (2020) The effect of yoga practice on muscular strength improvement in patients with multiple sclerosis. International Journal of Therapy & Rehabilitation 27(9): 1-10	- No fatigue outcomes reported
Savsek, L., Stergar, T., Strojnik, V. et al. (2021) Impact of aerobic exercise on clinical and magnetic resonance imaging biomarkers in persons with multiple sclerosis: An exploratory randomized controlled trial. Journal of Rehabilitation Medicine 53(4): jrm00178	- Treatment of fatigue was not one of the main aims of the study
Scally, J. B., Baker, J. S., Rankin, J. et al. (2020) Evaluating functional electrical stimulation (FES) cycling on cardiovascular, musculoskeletal and functional outcomes in adults with multiple sclerosis and mobility impairment: A systematic review. Multiple Sclerosis and Related Disorders 37: 101485	- Order cancelled as difficulty ordering and deemed to be less relevant upon review of the abstract

Study	Code [Reason]
Seebacher, B., Kuisma, R., Glynn, A. et al. (2015) Rhythmic cued motor imagery and walking in people with multiple sclerosis: a randomised controlled feasibility study. Pilot & Feasibility Studies 1: 25	- Treatment of fatigue was not one of the main aims of the study
Seebacher, B., Kuisma, R., Glynn, A. et al. (2017) The effect of rhythmic-cued motor imagery on walking, fatigue and quality of life in people with multiple sclerosis: A randomised controlled trial. Multiple Sclerosis 23(2): 286-296	- Study does not contain an intervention relevant to this review protocol
Senders, A., Hanes, D., Bourdette, D. et al. (2019) Impact of mindfulness-based stress reduction for people with multiple sclerosis at 8 weeks and 12 months: A randomized clinical trial. Multiple Sclerosis 25(8): 1178-1188	- Treatment of fatigue was not one of the main aims of the study
Sesel, A. L., Sharpe, L., Beadnall, H. N. et al. (2019) The evaluation of an online mindfulness program for people with multiple sclerosis: study protocol. BMC Neurology 19(1): 129	- Protocol only
Sesel, A. L.; Sharpe, L.; Naismith, S. L. (2018) Efficacy of Psychosocial Interventions for People with Multiple Sclerosis: A Meta-Analysis of Specific Treatment Effects. Psychotherapy & Psychosomatics 87(2): 105-111	- Systematic review used as source of primary studies
Shanazari, Z.; Marandi, S. M.; Minasian, V. (2013) Effect of 12-week pilates and aquatic training on fatigue in women with multiple sclerosis. Journal of mazandaran university of medical sciences 23(98): 257-264	- Study not reported in English
Shohani, M., Kazemi, F., Rahmati, S. et al. (2020) The effect of yoga on the quality of life and fatigue in patients with multiple sclerosis: A systematic review and meta-analysis of randomized clinical trials. Complementary Therapies in Clinical Practice 39: 101087	- Systematic review used as source of primary studies
Siengsukon, C. F., Aldughmi, M., Kahya, M. et al. (2016) Randomized controlled trial of exercise interventions to improve sleep quality and daytime sleepiness in individuals with multiple sclerosis: A pilot study. Multiple Sclerosis Journal Experimental Translational & Clinical 2: 2055217316680639	- Treatment of fatigue was not one of the main aims of the study

Study	Code [Reason]
Siengsukon, Catherine F.; Silveira Beck Jr, Eber; Drerup, Michelle (2021) Feasibility and Treatment Effect of a Web-Based Cognitive Behavioral Therapy for Insomnia Program in Individuals with Multiple Sclerosis: A Pilot Randomized Controlled Trial. International Journal of MS Care 23(3): 107-113	- Comparator in study does not match that specified in this review protocol
Simpson, R., Booth, J., Lawrence, M. et al. (2014) Mindfulness based interventions in multiple sclerosis--a systematic review. BMC Neurology 14: 15	- Systematic review used as source of primary studies
Simpson, R., Simpson, S., Ramparsad, N. et al. (2020) Effects of Mindfulness-based interventions on physical symptoms in people with multiple sclerosis - a systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 38: 101493	- Systematic review used as source of primary studies
Skjerbaek, A. G., Moller, A. B., Jensen, E. et al. (2013) Heat sensitive persons with multiple sclerosis are more tolerant to resistance exercise than to endurance exercise. Multiple Sclerosis 19(7): 932-40	- Treatment of fatigue was not one of the main aims of the study
Smith, D. C., Lanesskog, D., Cleeland, L. et al. (2012) Motivational interviewing may improve exercise experience for people with multiple sclerosis: a small randomized trial. Health & social work 37(2): 99-109	- Treatment of fatigue was not one of the main aims of the study
Solari, A., Giordano, A., Sastre-Garriga, J. et al. (2020) EAN guideline on palliative care of people with severe, progressive multiple sclerosis. European Journal of Neurology 27(8): 1510-1529	- Systematic review used as source of primary studies
Spina, E., Carotenuto, A., Aceto, M. G. et al. (2016) The effects of mechanical focal vibration on walking impairment in multiple sclerosis patients: A randomized, double-blinded vs placebo study. Restorative Neurology & Neuroscience 34(5): 869-76	- Treatment of fatigue was not one of the main aims of the study
Sterz, C., Heimes, S., Blessing, T. et al. (2013) Creative arts therapy improves quality of life in MS - Results of a randomized controlled trial during inpatient rehabilitation. Neurologie und rehabilitation 19(3): 176-182	- Study not reported in English

Study	Code [Reason]
Straudi, S., Fanciullacci, C., Martinuzzi, C. et al. (2016) The effects of robot-assisted gait training in progressive multiple sclerosis: A randomized controlled trial. Multiple Sclerosis 22(3): 373-84	- Treatment of fatigue was not one of the main aims of the study
Straudi, S., Manfredini, F., Lamberti, N. et al. (2020) Robot-assisted gait training is not superior to intensive overground walking in multiple sclerosis with severe disability (the RAGTIME study): A randomized controlled trial. Multiple Sclerosis 26(6): 716-724	- Treatment of fatigue was not one of the main aims of the study
Straudi, S., Manfredini, F., Lamberti, N. et al. (2017) The effectiveness of Robot-Assisted Gait Training versus conventional therapy on mobility in severely disabled progressIve MultiplE sclerosis patients (RAGTIME): study protocol for a randomized controlled trial. Trials [Electronic Resource] 18(1): 88	- Protocol only
Surakka, Jukka, Romberg, Anders, Ruutiainen, Juhani et al. (2004) Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial. Clinical rehabilitation 18(7): 737-746	- Fatigue reported but not as a patient-reported outcome scale
Tallner, A., Streber, R., Hentschke, C. et al. (2016) Internet-Supported Physical Exercise Training for Persons with Multiple Sclerosis-A Randomised, Controlled Study. International Journal of Molecular Sciences 17(10): 30	- Treatment of fatigue was not one of the main aims of the study
Tarakci, E., Tarakci, D., Hajebrahimi, F. et al. (2021) Supervised exercises versus telerehabilitation. Benefits for persons with multiple sclerosis. Acta Neurologica Scandinavica DOI: 10.1111/ane.13448	- Comparator in study does not match that specified in this review protocol
Taul-Madsen, L., Connolly, L., Dennett, R. et al. (2021) Is Aerobic or Resistance Training the Most Effective Exercise Modality for Improving Lower Extremity Physical Function and Perceived Fatigue in People With Multiple Sclerosis? A Systematic Review and Meta-analysis. Archives of Physical Medicine & Rehabilitation 102(10): 2032-2048	- Systematic review used as source of primary studies
Taylor, E. and Taylor-Piliae, R. E. (2017) The effects of Tai Chi on physical and psychosocial function among persons with multiple sclerosis:	- Systematic review used as source of primary studies

Study	Code [Reason]
A systematic review. Complementary Therapies in Medicine 31: 100-108	
Tecchio, F., Cancelli, A., Cottone, C. et al. (2015) Brain Plasticity Effects of Neuromodulation Against Multiple Sclerosis Fatigue. Frontiers in Neurology. 6: 141	- Study does not contain an intervention relevant to this review protocol
Tecchio, F., Cancelli, A., Cottone, C. et al. (2014) Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation. Journal of Neurology 261(8): 1552-8	- Study does not contain an intervention relevant to this review protocol
Thomas, S., Fazakarley, L., Thomas, P. W. et al. (2014) Testing the feasibility and acceptability of using the Nintendo Wii in the home to increase activity levels, vitality and well-being in people with multiple sclerosis (Mii-vitaliSe): protocol for a pilot randomised controlled study. BMJ Open 4(5): e005172	- Protocol only
Thomas, S., Fazakarley, L., Thomas, P. W. et al. (2017) Mii-vitaliSe: a pilot randomised controlled trial of a home gaming system (Nintendo Wii) to increase activity levels, vitality and well-being in people with multiple sclerosis. BMJ Open 7(9): e016966	- Treatment of fatigue was not one of the main aims of the study
Thomas, S., Kersten, P., Thomas, P. W. et al. (2015) Exploring strategies used following a group-based fatigue management programme for people with multiple sclerosis (FACETS) via the Fatigue Management Strategies Questionnaire (FMSQ). BMJ Open 5(10): e008274	- Secondary publication of an included study that does not provide any additional relevant information
Tramontano, M., Grasso, M. G., Soldi, S. et al. (2020) Cerebellar intermittent Theta-Burst stimulation combined with vestibular rehabilitation improves gait and balance in patients with multiple sclerosis: a preliminary double-blind randomized controlled trial. Cerebellum 19(6): 897-901	- Treatment of fatigue was not one of the main aims of the study
Tredinnick, A. R. and Probst, Y. C. (2020) Evaluating the effects of dietary interventions on disease progression and symptoms of adults with multiple sclerosis: An umbrella review. Advances in Nutrition 11(6): 1603-1615	- Systematic review used as source of primary studies

Study	Code [Reason]
Turner, A. P., Hartoonian, N., Sloan, A. P. et al. (2016) Improving fatigue and depression in individuals with multiple sclerosis using telephone-administered physical activity counseling. Journal of Consulting & Clinical Psychology 84(4): 297-309	- Comparator in study does not match that specified in this review protocol
Ulrichsen, K. M., Kaufmann, T., Dorum, E. S. et al. (2016) Clinical Utility of Mindfulness Training in the Treatment of Fatigue After Stroke, Traumatic Brain Injury and Multiple Sclerosis: A Systematic Literature Review and Meta-analysis. Frontiers in Psychology 7: 912	- Systematic review used as source of primary studies
Uszynski, M. K., Purtill, H., Donnelly, A. et al. (2016) Comparing the effects of whole-body vibration to standard exercise in ambulatory people with Multiple Sclerosis: a randomised controlled feasibility study. Clinical Rehabilitation 30(7): 657-68	- Treatment of fatigue was not one of the main aims of the study
van den Akker, L. E., Beckerman, H., Collette, E. H. et al. (2016) Effectiveness of cognitive behavioral therapy for the treatment of fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. Journal of Psychosomatic Research 90: 33-42	- Systematic review used as source of primary studies
van den Akker, L. E., Beckerman, H., Collette, E. H. et al. (2018) Cognitive behavioural therapy for MS-related fatigue explained: A longitudinal mediation analysis. Journal of Psychosomatic Research 106: 13-24	- Insufficient reporting of fatigue outcomes - Study design not relevant to this review protocol
Van Geel, F., Van Asch, P., Veldkamp, R. et al. (2020) Effects of a 10-week multimodal dance and art intervention program leading to a public performance in persons with multiple sclerosis - A controlled pilot-trial. Multiple Sclerosis and Related Disorders 44: 102256	- Non-randomised study
van Kessel, K.; Wouldes, T.; Moss-Morris, R. (2016) A New Zealand pilot randomized controlled trial of a web-based interactive self-management programme (MSInvigor8) with and without email support for the treatment of multiple sclerosis fatigue. Clin Rehabil 30(5): 454-62	- Comparator in study does not match that specified in this review protocol
Vazirinejad, R., Jafarzadeh, A., Yassini, S. M. et al. (2016) Effectiveness of psychological training	- No fatigue outcomes reported

Study	Code [Reason]
with gradual muscle relaxation technique on Fatigue in multiple sclerosis patients. Acta Medica Mediterranea 32(4): 987-990	
Venasse, M.; Edwards, T.; Pilutti, L. A. (2018) Exploring wellness interventions in progressive multiple sclerosis: An evidence-based review. Curr Treat Options Neurol 20(5): 13	- Review article but not a systematic review
Vermohlen, V., Schiller, P., Schickendantz, S. et al. (2018) Hippotherapy for patients with multiple sclerosis: A multicenter randomized controlled trial (MS-HIPPO). Multiple Sclerosis 24(10): 1375-1382	- Insufficient reporting of fatigue outcomes
Wahls, T., Scott, M. O., Alshare, Z. et al. (2018) Dietary approaches to treat MS-related fatigue: comparing the modified Paleolithic (Wahls Elimination) and low saturated fat (Swank) diets on perceived fatigue in persons with relapsing-remitting multiple sclerosis: study protocol for a randomized controlled trial. Trials 19(1): 309	- Protocol only
Walker, L. A. S.; Lindsay-Brown, A. P.; Berard, J. A. (2019) Cognitive Fatigability Interventions in Neurological Conditions: A Systematic Review. Neurology & Therapy 8(2): 251-271	- Systematic review used as source of primary studies
Wendebourg, M. J., Heesen, C., Finlayson, M. et al. (2017) Patient education for people with multiple sclerosis-associated fatigue: A systematic review. PLoS 12(3): e0173025	- Systematic review used as source of primary studies
Williams, K. L.; Low Choy, N. L.; Brauer, S. G. (2021) Center-Based Group and Home-Based Individual Exercise Programs Have Similar Impacts on Gait and Balance in People With Multiple Sclerosis: A Randomized Trial. PM and R 13(1): 9-18	- No fatigue outcomes reported
Willis, K. R., Barnes, L. J., Hewes, G. et al. (2017) The Effects of Aquatic Therapy on Fatigue and Quality of Life in Patients with Multiple Sclerosis: A Systematic Review. Journal of Aquatic Physical Therapy 25(2): 69-68	- Abstract only
Wollenweber, V., Drache, M., Schickendantz, S. et al. (2016) Study of the effectiveness of hippotherapy on the symptoms of multiple sclerosis - Outline of a randomised controlled	- Protocol only

Study	Code [Reason]
multicentre study (MS-HIPPO). Contemporary Clinical Trials Communications 3: 6-11	
Workman, C. D.; Kamholz, J.; Rudroff, T. (2020) Transcranial direct current stimulation (tDCS) for the treatment of a Multiple Sclerosis symptom cluster. Brain Stimul 13(1): 263-264	- Does not appear to have a washout period
Xiang, Y., Lu, L., Chen, X. et al. (2017) Does Tai Chi relieve fatigue? A systematic review and meta-analysis of randomized controlled trials. PLoS ONE 12(4): e0174872	- Systematic review used as source of primary studies
Yadav, V., Marracci, G., Kim, E. et al. (2016) Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Multiple Sclerosis and Related Disorders 9: 80-90	- Insufficient reporting of fatigue outcomes
Yeh, S. W., Lin, L. F., Tam, K. W. et al. (2020) Efficacy of robot-assisted gait training in multiple sclerosis: A systematic review and meta-analysis. Multiple Sclerosis and Related Disorders 41: 102034	- Systematic review used as source of primary studies
Young, H. J., Mehta, T. S., Herman, C. et al. (2019) The Effects of M2M and Adapted Yoga on Physical and Psychosocial Outcomes in People With Multiple Sclerosis. Archives of Physical Medicine & Rehabilitation 100(3): 391-400	- Treatment of fatigue was not one of the main aims of the study - Data for fatigue only reported as T-values which is not commonly used across other studies in this review
Yu, C. H. and Mathiowetz, V. (2014) Systematic review of occupational therapy-related interventions for people with multiple sclerosis: part 1. Activity and participation. American Journal of Occupational Therapy 68(1): 27-32	- Systematic review used as source of primary studies
Zhang, J., Yu, J., Tang, X. et al. (2017) Does whole-body vibration have benefits in patients with multiple sclerosis: A systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 10(7): 9996-10009	- Systematic review used as source of primary studies
Zielinska-Nowak, E., Wlodarczyk, L., Kostka, J. et al. (2020) New Strategies for Rehabilitation and Pharmacological Treatment of Fatigue Syndrome in Multiple Sclerosis. Journal of Clinical Medicine 9(11): 3592	- Review article but not a systematic review
Ziemssen, T.; Piatkowski, J.; Haase, R. (2011) Long-term effects of Bio-Electromagnetic-	- Non-randomised study

Study	Code [Reason]
Energy Regulation therapy on fatigue in patients with multiple sclerosis. Alternative therapies in health and medicine 17(6): 22-28	
Zou, L., Wang, H., Xiao, Z. et al. (2017) Tai chi for health benefits in patients with multiple sclerosis: A systematic review. PLoS ONE [Electronic Resource] 12(2): e0170212	- Systematic review used as source of primary studies
Zrzavy, T., Pfitzner, A., Flachenecker, P. et al. (2021) Effects of normobaric hypoxic endurance training on fatigue in patients with multiple sclerosis: a randomized prospective pilot study. Journal of Neurology DOI: 10.1007/s00415-021-10596-5	- Insufficient reporting of fatigue outcomes
Zucchella, C., Mantovani, E., De Icco, R. et al. (2020) Non-invasive Brain and Spinal Stimulation for Pain and Related Symptoms in Multiple Sclerosis: A Systematic Review. Frontiers in Neuroscience 14: 547069	- Systematic review used as source of primary studies

I.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 87: Studies excluded from the health economic review

Reference	Reason for exclusion
None	

Appendix K – Research recommendations – full details

K.1 Research recommendation

For adults with MS, including people receiving palliative care, what is the clinical and cost effectiveness of non-pharmacological interventions for fatigue?

K.1.1 Why this is important

Fatigue is a major problem for people with MS. Studies indicate that between 80-90% of all people with MS experience fatigue and up to 40% describe it as the most disabling symptom of the condition. Much is written regarding the effects on daily life including its impact on employment, where fatigue is one of the key factors leading to early retirement.

MS fatigue is often described as primary fatigue (directly related to the condition due to causes such as nerve fibre fatigue, heat sensitive fatigue or lassitude) or secondary fatigue, where other factors may worsen the fatigue experienced, such as infection, low mood or environmental challenges. Further research is needed to explore the clinical and cost effectiveness of non-pharmacological intervention to manage fatigue.

When planning the research it is important to recognise that there are fatigue scales that focus on severity, on frequency and on impact; some scales are uni-dimensional others are multi-dimensional. One (the Chalder Fatigue Questionnaire) asks respondents to make responses relative to "usual" which might be challenging for people with MS given its fluctuating nature. Some fatigue questionnaires include items that might confound fatigue with physical functioning – for example asking about weakness. The recent MRC guidance for complex interventions suggests it can sometimes be appropriate to have more than one primary outcome – with a multi-dimensional symptom such as fatigue perhaps this is warranted. It is also important to consider work-related measures given the impact fatigue has on people stopping work early or reducing hours. Ecological momentary assessment might also be helpful for measuring fatigue although there is the possibility it could lead to symptom focusing.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	If non-pharmacological Interventions are shown to offer clinically important benefits to the management of fatigue for people with MS, at a reasonable cost threshold, then it may be an important modality to improve current practice and enhance clinical outcomes in this patient group. If specific interventions are identified to be effective, this can support people with MS to choose effective interventions while an increased understanding of optimal strategies can help standardise care and improve patient outcomes.
Relevance to NICE guidance	This research can reduce the existing uncertainty regarding the clinical and cost-effectiveness of non-pharmacological interventions for fatigue and support decision making in the development of future recommendations.
Relevance to the NHS	A clear recommendation for the non-pharmacological interventions for fatigue will offer clinicians clearer guidance on best care for

	people with MS. Increased knowledge of non-pharmacological interventions would improve and standardise care. If people are able to manage their fatigue this will reduce the impact on the NHS for example less reliance on pharmacological interventions and a decrease in the need for clinical support.
National priorities	The national service framework for long term conditions supports the early management of symptoms. QR5 People with long-term neurological conditions living at home are to have ongoing access to a comprehensive range of rehabilitation, advice and support to meet their continuing and changing needs, increase their independence and autonomy and help them to live as they wish.
Current evidence base	Despite there being a large number of new studies since the previous update, based on limitations such as small sample sizes, uncertainty in the direction and/or size of the effect for most outcomes and low-very low quality for most reported outcomes, the committee could not strengthen most existing recommendations, but used the additional evidence identified within this update as further support for existing recommendations on which interventions may be beneficial in MS-related fatigue.
Equality considerations	Trials are unlikely to impact on equality issues.

K.1.3 Modified PICO table

Population	<u>Inclusion:</u> Adults (≥18 years) with MS, including people receiving palliative care, who are experiencing fatigue. <u>Exclusion:</u> Children and young people (≤18 years).
Intervention	Any non-pharmacological intervention for fatigue, for example: • Multidisciplinary rehabilitation/programmes including progressive resistance training • Energy conservation programs • Mindfulness based training • Exercise including aerobic exercise training • Resistance training – (distinguish it from balance and vestibular rehab)

	• Vestibular rehabilitation • Getting To Grips • Gym prescription • Self-management programmes • Fatigue management programmes • FACETS (Fatigue: Applying Cognitive behavioural and Energy effectiveness Techniques to lifeStyle) • FatiMa (Fatigue management in MS–patient education programme) • Diet (ketogenic, intermittent fasting and George Jelinek* which is plant based, wholefood diet, excluding dairy and minimising saturated fat intake) • Yoga, • Tai chi • Pilates • Relaxation • Cognitive behavioural therapy • Hyperbaric oxygen Combinations may be included if relevant to clinical practice (to be checked with GC if unsure) *This may also be known as 'Overcoming MS' lifestyle programme which includes
Comparator	Interventions will be compared to each other placebo/sham, usual care or no treatment.
Outcome	All outcomes are considered equally important for decision making and therefore have all been rated as critical. • Patient-reported outcome measures to assess MS fatigue, including MFIS Fatigue Severity Scale (FSS), National Fatigue Index (NFI), MS-specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS), and Visual Analogue Scale (VAS) • Health-related Quality of Life, for example EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale. • Impact on carers. • Functional scales that quantify level of disability, such as the Expanded Disability Status Scale (EDSS), the Multiple Sclerosis

	Functional Composite (MSFC), the Cambridge Multiple Sclerosis Basic Score (CAMBS), or the Functional Assessment of Multiple Sclerosis (FAMS). • Cognitive functions, such as memory and concentration • Psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments. • Adverse effects of treatment for example: o Incidence of adverse events o Adverse events leading to withdrawal • Outcomes measuring how acceptable to intervention was. These may be measured in terms of how acceptable it was to patients, completion rates, response to follow up, adherence, engagement or disengagement. Follow up: • 3-6 months (minimum of 3 months) • >6 months – 1 year
Study design	RCT
Timeframe	Medium term
Additional information	Studies must be adequately powered for the main outcomes

References

1. Cakit BD, Nacir B, Genc H, Saracoglu M, Karagoz A, Erdem HR et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. American Journal of Physical Medicine and Rehabilitation. 2010; 89(6):446-457
2. Carter A, Daley A, Humphreys L, Snowdon N, Woodroofe N, Petty J et al. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial. Multiple Sclerosis. 2014; 20(8):1112-1122
3. Moss-Morris R, McCrone P, Yardley L, van Kessel K, Wills G, Dennison L. A pilot randomised controlled trial of an internet-based cognitive behavioural therapy self-management programme (MS Invigor8) for multiple sclerosis fatigue. Behaviour Research and Therapy. 2012; 50(6):415-421
4. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview
5. National Institute for Health and Care Excellence. Multiple sclerosis: management of multiple sclerosis in primary and secondary care. NICE guideline 186. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/guidance/cg186/evidence/full-guideline-pdf-193254305#page=187&zoom=100,129,212
6. Thomas S, Thomas PW, Kersten P, Jones R, Green C, Nock A et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2013; 84(10):1092-1099
7. Tosh J, Dixon S, Carter A, Daley A, Petty J, Roalfe A et al. Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial. Multiple Sclerosis. 2014; 20(8):1123-1130
8. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue. Psychosomatic Medicine. 2008; 70(2):205-213