Relaxation and related therapies for people with multiple sclerosis (MS): A systematic review

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Introduction

Multiple sclerosis is a chronic, often disabling inflammatory disease of the brain and spinal cord. Loss of ability to perform daily activities is common, as is pain, fatigue, and communication and cognitive deficits.[1] Unsurprisingly, these symptoms and sequelae can have a significant negative impact on quality of life.[2, 3] Indeed, rates of anxiety, depression, and risk of suicide are higher in those with multiple sclerosis compared to the general population.[4]

Multiple sclerosis symptoms (cognitive and communication impairments in particular) can complicate delivery of psychological interventions to this population. In this context, experiential relaxation training - including autogenic training, progressive muscle relaxation[5, 6] and therapies with relaxation components (e.g., yoga, meditation, biofeedback) - may provide an accessible alternative to more talking based therapies (like Cognitive Behavioural Therapy). Relaxation training works by reducing autonomic nervous system arousal via modification of breathing patterns and awareness of the body. Notably, relaxation therapies present an efficient treatment option - yielding results even when delivered at low-intensity over a short timeframe (e.g., 4 weeks).[7] These therapies are also relatively easy for health professionals to deliver, and for patients to practice at home following training.[7, 8]

There is strong evidence that relaxation therapies are effective in reducing anxiety, pain, fatigue, sleep difficulties, and depression amongst the general population.[8-12] There is also emerging evidence that relaxation may be an effective intervention for alleviating the above conditions for people with multiple sclerosis.[13-15] However, to our knowledge, no systematic review has yet explored the effectiveness of relaxation therapies in this clinical group. This is the purpose of the current review.

Method

Following protocol registration with the International Prospective Register of Systematic Reviews (CRD42019108771), the PubMed, PsycINFO, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) electronic databases were searched for potentially eligible studies from database inception until 31 December 2021. Medical subject

headings (MeSH) and terms were developed and tailored to each database in consultation with a specialist librarian (see search strategy in Appendix). To capture unpublished literature and conference proceedings, and reduce the influence of publication bias, we additionally searched for studies on ProQuest Dissertations and Theses Global. The reference lists of included studies were also hand searched.

In addition to being published in the English language (or with English translation) and providing primary data, studies needed to meet the following inclusion criteria: 1) involve adult participants (≥18 years) who had been diagnosed with multiple sclerosis or disseminated sclerosis; 2) contain a relaxation intervention that targeted reductions in autonomic nervous system arousal (see Table 1 for list of therapies meeting this definition); 3) present quantitative data (e.g., groups means and standard deviations) regarding physical or psychological symptoms and/or functional outcomes were provided; 4) evaluate the efficacy of relaxation therapy using repeated measures, quasi-experimental, or controlled study designs (e.g., case series/case studies, randomised controlled trials). Studies which examined multi-modal therapies involving relaxation delivered in combination with non-relaxation interventions or strategies (e.g., Cognitive Behavioural Therapies) as well as those involving heterogeneous samples with a chronic illness or physical disability which did not provide data for persons with multiple sclerosis separately were excluded.

Table 1 about here

Identified records were exported into Covidence systematic review software for screening.[16] After the removal of duplicates, two researchers independently screened titles and abstracts, and full-texts against the eligibility criteria (see Figure 1). Disagreements in screening were resolved through discussion amongst screeners and consensus by the research team. A third, senior researcher, provided a determination on disagreements in screening. Authors of 38 records which were either unavailable, featured incomplete results/methods or potential duplication of data were contacted, with 17 responding to email requests. Several authors were able to advise of studies which featured partially overlapping samples, whereby a subset of participants participated in different randomised controlled trials at different times (i.e., separate studies or interventions involving some overlap in participants),[17, 18] or where studies overlapped completely.[19-23]

Figure 1 about here

*Figure 1***.** Flow diagram of review identification, screening and eligibility, and inclusion processes, adapted from PRISMA[24]

Data extraction was completed using Covidence software. As recommended by Higgins and Deeks,[25] we extracted data relating to key sample parameters (e.g., age, ethnicity and gender ratio of study participants, severity of disability), relaxation therapy characteristics (e.g., type, content, length), comparison groups (where applicable), and study design. We also extracted statistical information to calculate standardised mean differences for each individual physical, psychological or functional outcome. Both within and between-group differences in the short-term (i.e., group mean difference from baseline to immediately post-intervention) and longer-term (i.e., group mean difference from post-intervention to follow-up) were calculated. To enhance the generalisability of the results, only those outcomes that were examined by five or more studies were considered. Two researchers extracted the data for each study, which were then cross-checked for accuracy.

Two researchers independently assessed risk of bias using the Revised Cochrane Risk-of-Bias tool for randomized trials (RoB-2)[26] and Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I).[27] Some domains in the Revised Cochrane Risk-of-Bias were modified (e.g., measuring treatment expectancies/credibility ratings as a proxy for blinding of participants[28]). Ratings for each instrument were cross-checked; with discrepancies in judgements being resolved through discussion.

Statistical data, where available, were entered into Comprehensive Meta-Analysis (CMA) software and Hedges' *g* effect sizes calculated. To calculate *g*, a pre-post correlation is required. As many studies did not provide this information, a value of .70 was imputed; considered to be a conservative value for studies with a repeated measures design.[29] The direction of *g* was also standardized so that a positive value reflected improvement with relaxation therapy alone, or greater benefit compared to controls: the larger the *g* value, the greater the treatment effect.[30] Ninety-five percent confidence intervals determined the precision of each *g* with statistical significance examined via *p* values. Due to significant heterogeneity amongst study designs, relaxation interventions (including relaxation components, delivery and format) and comparison groups, pooling of effect sizes was not

deemed appropriate. Rather, a narrative synthesis was conducted to describe, organise, explore and interpret the study findings, focusing on the impact of relaxation therapies on multiple sclerosis symptoms and sequelae, which were subsequently categorized into six domains or constructs: depression, anxiety, stress, pain, fatigue, and quality of life. The synthesis considered methodological strengths and weaknesses as well as intervention characteristics and delivery.

Results

Twenty-eight studies met the review inclusion criteria, with all identified from the search databases and none sourced through hand searching of reference lists. Table 2 provides a summary of descriptive characteristics for the 23 randomised controlled trials. Descriptive characteristics for the five non-randomised quasi-experimental study designs (i.e., single group pre-post designs, non-randomised trials)[31-35] are provided in Supplementary Table 1. We report here on randomised controlled trials only.

Table 2 about here

The pooled sample of 1,246 randomised controlled trial participants were primarily women (range 47% to 100%) ranging in age from 18 to 80 years and recruited from multiple sclerosis clinics or associations. Among the relaxation therapy group, duration of multiple sclerosis varied (3 to 14.3 years). Disability severity was typically quantified using the Expanded Disability Status Scale (EDSS), with most participants classified as having mild to moderate disability (EDSS mean/median: 1 to 5.9). Three studies recruited persons with greater disability (EDSS average > 4.5[i]).[36-38] Where multiple sclerosis subtype was reported, relapsing-remitting forms were common (34.8% - 90%), followed by secondary progressive multiple sclerosis (8% - 34.8%) and primary progressive (2% - 21.7%). Studies did not frequently report participant co-morbidities or multiple sclerosis symptoms, such as cognitive impairments (which could affect engagement with, and outcomes of, the intervention). Consequently, there was limited information about the extent to which relaxation therapy was tailored or modified specifically for this cohort.

[i] EDSS scales range from 0-10; steps 1.0 to 4.5 refer to people with multiple sclerosis who can walk without any aids; while scores of 5 or more are indicative of severe disability as measured by impairment to walking.

Of 23 studies examined, one study compared two forms: relaxation and biofeedback to relaxation only,[39] whilst another compared multi-session relaxation versus a single session relaxation program.[14] The most common form of relaxation was progressive muscle relaxation examined by 18 studies (see Table 2). Interventions involving a combination of relaxation therapies were also prevalent (e.g., relaxation training combined with biofeedback, mindfulness meditation etc.). Relaxation was delivered as the primary (target) intervention in twelve studies, or as a comparison (control) treatment in eleven. Active comparison conditions included established psychological therapies: Acceptance and Commitment Therapy (ACT), Cognitive Behaviour Therapy (CBT), and Eye Movement Desensitisation and Reprocessing (EMDR) as well as multi-disciplinary interventions: cognitive training, physiotherapy-led exercise interventions (e.g., aerobics, hydrotherapy), interventions aimed at maximising energy conservation and occupational functioning, and complementary or alternative treatments (e.g., reflexology).

Relaxation training varied in length, duration and format. Training was delivered over 3 to 20 weeks[36, 40] with individual sessions ranging from 40 minutes[19] to 2 hours[38] in duration. Single session training, followed by home practice[14, 17, 18] was common. Twelve studies incorporated multiple training sessions followed by home practice occurring between 4 weeks to 6 months. A single study delivered progressive muscle relaxation remotely using a smartphone application.[41] Both group and individual formats featured, although seven studies did not specify their format, or appeared to involve a combination of individual and group practice. Interventions were delivered by psychologists,[15, 23, 38, 41-43] physiotherapists or occupational therapists,[17, 18, 36, 37, 44, 45] and nurses.[40, 46] Attrition rates were not clearly reported, nor were adverse effects of relaxation therapies: only six studies made reference to a lack of adverse events occurring within relaxation interventions.[17] No studies formally conducted cost-effective analyses.

Study Quality Assessment

Table 3 provides the risk of bias assessments based on the modified Revised Cochrane Risk-of-Bias tool for randomized trials.[26] Twenty-one of the 23 randomised controlled trials were judged as high risk of bias and two had some concerns. Most concerns arose from the measurement of study outcomes. While self-report data were appropriate and necessary for the majority of measures; most studies did not collect data regarding participant expectancies/credibility ratings across relaxation and control groups. This meant that it was

difficult to judge the degree to which treatment/comparison groups viewed their interventions as equivalent. Fourteen trials did not report information regarding allocation concealment during the randomisation process whilst only 10 registered their study protocol/trial or made their protocol available upon request. Two studies did not provide clear descriptions regarding their outcome measures.[14, 47]

Table 3 about here

All five non-randomised studies were rated as having a serious risk of bias using the Risk of Bias In Non-Randomized Studies of Interventions (see Supplementary Table 2).

Effectiveness of Relaxation and Related Therapies

Effect size data were provided by 20 trials. These are summarised below, grouped by symptom domain. See Tables S3-S6 in the online supplementary material for individual study data). Individual data for non RCTs are also reported in the online supplementary material (Tables S7-10).

Depression

Twelve trials examined depression or negative affect using eight different self-report measures. Within-group comparisons suggested that relaxation therapies contributed to statistically significant, small to very large and positive changes in symptom ratings in most studies. Between-group comparisons were mixed: relaxation was not as effective as physical exercise[18] or Cognitive Behaviour Therapy[23] in reducing depression, but was more efficacious than Acceptance and Commitment Therapy,[15] and routine care.[21, 47, 48]

Five studies provided data at 8 to 24-week follow-up, with two reporting significant effects. Reduced effects were noted with reflexology compared to minimal symptom change for relaxation training.[21] Large effects were also noted with eye movement desensitisation and reprocessing for targeted post-traumatic stress disorder symptoms compared to relaxation therapies, though no advantage was evident for depressive symptoms per se.[42]

Anxiety

Ten studies assessed state-anxiety, including cognitive (e.g., worry) and physical (e.g., tension) symptoms, using eight measures. Five studies reported significant medium to large within-group improvements for relaxation alone. Between-group differences also revealed greater effects for relaxation compared to medical care[21] but less efficacy in comparison to Cognitive Behaviour Therapy.[23]

Follow-up findings varied: participants assigned to relaxation therapies reported worsening symptoms after 8 weeks[21] but improvement at 12 weeks.[23] However, between-group differences were small or negligible across all time points.

Stress

Six studies examined stress symptoms, as measured by the Depression Anxiety Stress Scales or Perceived Stress Scales. Within-group comparisons revealed medium to very large and significant effects immediately following relaxation for five studies. Whilst between-group differences in stress ratings favoured well-established interventions (Acceptance and Commitment Therapy,[43] Cognitive Behaviour Therapy[23]), relaxation participants did report larger stress reductions compared to usual care.

In the longer-term, relaxation therapies produced small to medium gains up to 24 weeks post-intervention, although only Giovannetti et al[43] reported a significant between-group effect. In this study, relaxation was more efficacious than Acceptance and Commitment Therapy.[43]

Pain

Six studies measured pain intensity and pain-related disability using six established or modified pain measures (e.g., visual analogue scales, verbal rating scales). In three studies, relaxation significantly reduced pain ratings. In comparison to other active treatments, however, the evidence was mixed. Masoudi et al.[14] reported a very large and significant reduction in pain after 12 weeks of relaxation training compared to a single relaxation session, whilst Nazari et al.[20] reported greater improvement with reflexology.

Two studies provided 8-12 week follow-up data, reporting significant within and between group differences: individualised occupational therapy improved pain symptoms more so than relaxation therapy,[45] but reflexology did not.[20]

Fatigue

Eleven studies, using nine different self-report measures, evaluated immediate changes in symptoms of fatigue and interrelated constructs: vitality, exertion, and energy. Within-group comparisons revealed small to large improvements for relaxation alone. Between-group comparisons varied: in three studies, active comparisons were associated with greater gains than relaxation, however mean fatigue severity scores were also lower with relaxation compared to usual care[19] or no treatment.[49, 50]

In one study, participants who underwent multidisciplinary rehabilitation had better energy conservation strategies compared with those who underwent progressive muscle relaxation at 16-week-follow-up.[37] An additional five studies reported non-significant group effects for fatigue, regardless of the control condition.

Quality of Life (Mental)

Of the six randomised controlled trials that assessed mental health and emotional wellbeing more broadly, three identified medium to very large and positive changes with relaxation. However, between group comparisons indicated that progressive muscle relaxation was not as effective as an exercise program.[17]

Follow-up data were limited to three studies: the positive effects of relaxation therapy were sustained at 12 weeks, compared to Acceptance and Commitment Therapy,[43] but not in comparison to inpatient rehabilitation.[37]

Quality of Life (Physical)

Six studies examined physical functioning and health using the Short Form Health Survey and the Multiple Sclerosis Quality of Life Instrument. Giovannetti et al.[43] reported a significant and large within-group change with relaxation. However, Ozkul et al.[17] reported greater improvement in those allocated to exercise compared to those allocated to relaxation.

At follow up, rehabilitation inpatients were able to maintain gains in physical functioning more than those who received relaxation training;[37] however, there was a significant positive effect for relaxation training over Acceptance and Commitment Therapy for perceived physical health.[43]

Qualitative synthesis of studies where effect-sizes could not be calculated

Three independent studies reported pre- and post-outcomes following relaxation therapy although they did not provide sufficient information to compute a comparable effect-size.[36, 40, 44] Agland and colleagues[40] found that relaxation did not significantly reduce perceived stress or cortisol levels; but did improve quality of life in participants allocated to a progressive muscle relaxation and mindfulness meditation program compared to those allocated to a wait-list control group. The authors did, however, note substantial lack of adherence to home practice of the relaxation intervention (< 50% of the study cohort) as a major limitation.

Bulguroglu and colleagues[44] reported significant and positive difference to physical quality of life with relaxation, but no changes to mental quality of life or fatigue. However, participants in their comparison group, pilates, also reported improved quality of life in addition to lowered fatigue.

Castro-Sanchez and colleagues[36] compared relaxation to ai-chi hydrotherapy, reporting no significant changes in pain, depression, and fatigue over time. Moreover, hydrotherapy demonstrated immediate and statistically significant effects across measured outcomes.

Notably, the aforementioned studies[36, 40, 44] provided limited descriptions of their relaxation interventions. As such, it is difficult to know whether these results reflect reduced effectiveness for a particular kind of relaxation therapy.

Discussion

Many studies have reported relaxation therapies are effective interventions for people with multiple sclerosis. Significant pre-post changes were noted across multiple outcomes (e.g., depression, anxiety, stress, fatigue), particularly when relaxation was compared to an inactive control. The exception was quality of life and pain, where data were minimal. There was less evidence of effectiveness compared to comparison treatments, such as Cognitive Behaviour Therapy and Acceptance and Commitment Therapy.

We found relaxation therapies were not more effective in reducing anxiety than no-treatment usual care, which is surprising given the evidence for the efficacy of relaxation treatments for this outcome in the general population.[10] It is noteworthy, however, that comparison treatments which were more efficacious than relaxation therapies (e.g., hydrotherapy[36]) were often more intensive interventions than relaxation therapies, and largely not amenable to self-help modalities.

Importantly, no studies reported adverse events with respect to relaxation therapies for people with multiple sclerosis, and there was also no evidence for worsening of symptoms following relaxation therapies.

These results do need to be interpreted cautiously given that most of the randomised controlled trials reviewed were rated as 'high risk' of bias. High risk ratings were largely due a lack of participant expectancy/credibility ratings across treatment and comparison groups, which meant it was difficult to assess to what degree self-report data was influenced by knowledge of intervention allocation. Future randomised controlled trials studies should incorporate the required quality recommendations inherent in the Revised Cochrane Risk-of-Bias for randomized controlled trials. Specifically, researchers should incorporate participant expectancies/credibility ratings across treatment and comparison groups; ensure transparency of research plans and analyses intentions through publishing of protocols; and explicitly consider how confounding factors (e.g. expectancy) may influence the study results.

This review has some limitations. The heterogeneity across outcome measures, study designs, and samples prevented a meta-analysis of quantitative data. Researchers might consider future studies that build on existing studies or using a core set of outcome measures for people with multiple sclerosis to allow comparison across trials. For logistical reasons, only English language papers were included. Moreover, due to lack of reporting information in the included studies, it is unclear whether the conclusions of this review reflect a diverse or representative sample of people with multiple sclerosis. Future studies should endeavour to include detailed descriptions of samples, as well as efforts to recruit participants of varying illness severity to ensure that results can be generalised outside of white middle-class participants with milder forms of disability. The cost-effectiveness of relaxation therapies for people with multiple sclerosis also warrants consideration in future studies, as it may be

relaxation therapies are more cost-effective than more resource-heavy psychological interventions.

Clinical messages

- Many controlled studies have found relaxation and related therapies can improve psychological, physical and functional outcomes in people with multiple sclerosis.
- Despite the positive findings, most of the included studies had a high risk of bias which means the beneficial effects of relaxation and related therapies for people with multiple sclerosis is uncertain.
- In light of potential benefits and absence of adverse events, clinical use of relaxation and related therapies is supported.

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Supplemental material

Supplemental material for this paper is available online.

Author contributions

IK led the project. IK and RDN conceived the project. All authors (IK, RDN, BVZ, DD, RR, SL, DQ, AT, DK and JR) designed the project. BVZ collected and synthesized the data. IK and DD consulted on inclusion and/or evaluation disagreements. DD calculated the effect sizes. IK, RDN and BVZ drafted the initial version of the manuscript with all authors contributing to and approving the final version.

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Appendix

PubMed Search Strategy:

"Relaxation Therapy"[mh]
OR Relaxation[tw]
OR Meditation*[tw]
OR Yoga*[tw]
OR "Muscle Relaxation"[mh]
OR "Autogenic Training"[mh]
OR Autogen*[tw]
OR "Mindfulness"[mh]
OR Mindfulness*[tw]
OR "Breathing Exercises"[mh]
OR Breathing*[tw]
OR Muscle Training*[tw]
OR Muscular Training*[tw]
OR Respiratory Muscle Training*[tw]

AND

"Multiple Sclerosis"[mh]
OR Multiple Sclerosis[tw]
OR Disseminated Sclerosis[tw]

PsycINFO:

DE "Relaxation Therapy"
OR DE "Progressive Relaxation Therapy"
OR TX Relaxation
OR DE "Meditation"
OR TX Meditation*
OR DE "Yoga"
OR TX Yoga*
OR DE "Muscle Relaxation"
OR TX Autogen*
OR DE "Mindfulness"
OR TX Mindfulness*
OR TX Breathing*
OR TX "Muscle Training*"
OR TX "Muscular Training"
OR TX "Respiratory Muscle Training*"

AND

DE "Multiple Sclerosis"
OR TX "Multiple Sclerosis"
OR TX "Disseminated Sclerosis"

Embase

Relaxation training/
OR Relaxation.mp.
OR Meditation*.mp.
OR Yoga/
OR Yoga*.mp.
OR Autogenic training/
OR Autogen*.mp.
OR Mindfulness/
OR Mindfulness*.mp.
OR breathing exercise/
OR breathing*.mp.
OR muscle training*.mp.
OR muscular training*.mp.
OR respiratory muscle training*.mp.

AND

Multiple sclerosis/
OR multiple sclerosis.mp.
OR disseminated sclerosis.mp.

CINAHL

TX Relaxation
OR MH "Relaxation Techniques"
OR MH Meditation
OR TX Meditation*
OR MH Yoga
OR TX Yoga*
OR MH "Muscle Relaxation"
OR TX Autogen*
OR MH Mindfulness
OR TX Mindfulness*
OR MH "Breathing Exercises"
OR TX Breathing*
OR TX "Muscle Training*"
OR TX "Muscular Training*"
OR TX "Respiratory Muscle Training*"

AND

MH "Multiple Sclerosis"
OR TX "Multiple Sclerosis"
OR TX "Disseminated Sclerosis"

ProQuest Dissertations and Theses Global:

noft("relaxation therapy" OR "progressive relaxation therapy" OR "relaxation" OR meditation OR yoga OR "muscle relaxation" OR autogen OR mindfulness OR breathing OR "muscle training" OR "muscular training" OR "respiratory muscle training") AND noft("multiple sclerosis" OR "disseminated sclerosis")

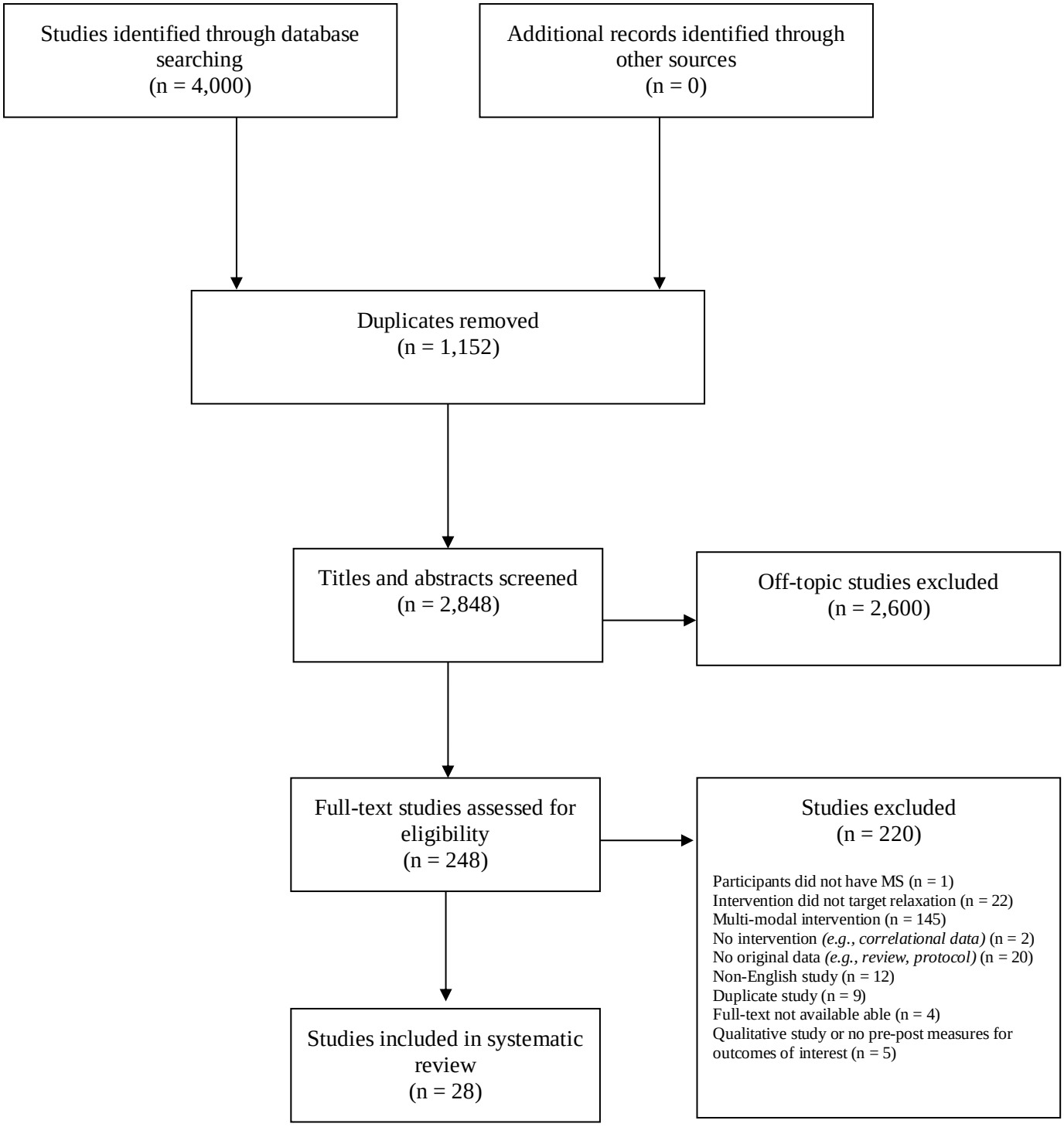

Figure 1. Flow diagram of review identification, screening and eligibility, and inclusion processes, adapted from PRISMA[24]

Table 1.
Types of Relaxation and Related Therapies Interventions

Progressive Muscle Relaxation (i.e., systematic tensing and releasing of muscles with aim of reducing tension, and increasing relaxation and awareness of the relationship between bodily tension and stress)
Autogenic Training (i.e., relaxation technique utilising repeated visualisations and systematic exercises (focusing on heaviness, warmth, calm, heart and respiration) to reduce sympathetic nervous system activity)
Meditative Breathing (i.e., guided meditation; including mindfulness and transcendental meditation, and yogic breathing such as yoga nidra; these methods typically draw attention to the breath and present moment through guided slow breathing)
Biofeedback (i.e., method that provides real-time physiological feedback that can assist participants in heart rate and respiration to encourage relaxation)
Relaxation Training (i.e., generic term used for relaxation interventions; often involving slowed breathing to induce feelings of relaxation; and used as active control/comparison in trials)

Table 2
Summary of descriptive characteristics for randomised controlled trials

Lead author (date)	Country	Sample characteristics			Relaxation characteristics					Control /comparator
		n	Mean or median age (years)	Time since diagnosis (years)	Type	Duration & frequency	Modality	Therapist	Format	
Agland (2018)	Australia	100	Relaxation: 44 Control: 43	Relaxation: 9.8 Control: 9.90	PMR+	Weekly sessions for 3 weeks + daily home practise 20 minutes for 6 months	In-person + remote	MS Clinical Nurse Specialist	Individual	Waitlist
Artemiadis (2012)	Greece	73	Relaxation: 37.55 Control: 41.97	Relaxation: 7.15 Control: 7.31	PMR & Breathing	Home practice twice a day for 8 weeks (maximum 112 sessions)	In-person + remote	Healthcare workers	Group	Attention control
Bulguroglu (2017)	Turkey	59	Relaxation: 40 Comparison 1: 45 Comparison 2: 37	Relaxation: 3 Mat pilates: 4.5 Reformer pilates: 5	Relaxation & Breathing	Twice per week x 8 weeks	Remote (web, telehealth, CD rom) + home practice	Physiotherapists	Individual	1. Mat Pilates 2. Reformer Pilates
Carletto (2016)	Italy	50	Relaxation: 40.66 Comparison: 39.52	Both groups: 7	PMR+	10 x 60 min sessions over 12 weeks	In-person	Psychotherapists	Individual	EMDR
Castro-Sanchez (2012)	Spain	73	Relaxation: 50 Comparison: 46	Relaxation: 11.9 Ai-Chi: 10.7	PMR & Breathing	Twice weekly for 20 weeks	In-person	Physiotherapist	Individual	Ai-chi hydrotherapy
Giovannetti (2020)	Italy	39	Relaxation: 46.53 Comparison: 44.80	Relaxation: 10.7 Comparison: 13.7	Autogenic Training	7 x 1-hour weekly group sessions; followed by a booster session after 5 weeks	In-person + remote	Psychologist	Group	READY-MS
Hersche (2019)	Switzerland	47	Relaxation: 51.8 Comparison: 51.2	Relaxation: 14.3 Comparison: 13.5	PMR	6 x 1-hour sessions twice a week over 3 weeks	In-person	Physical Therapist	Group	Energy management education
Javdan (2021)	Iran	76	Total sample: 36	Total sample: 8.2	PMR	4 education sessions, PMR done once daily for 8 weeks	In-person + remote	Not specified	Group	No treatment
Kos (2016)	Belgium	31	Relaxation: 44 Comparison: 37	Not specified	PMR	3 individual sessions at 60-90 mins each for 3 weeks.	Occupational therapy	Physical therapist & Occupational therapist	In-person	Not specified

Lead author (date)	Country	Sample characteristics			Relaxation characteristics					Control /comparator
		n	Mean or median age (years)	Time since diagnosis (years)	Type	Duration & frequency	Modality	Therapist	Format	
Mackay (2015)	Australia	40	Relaxation: 46.35 Comparison: 45.45	Relaxation: 9.0& Comparison: 8.29	PMR+	3 x 1 hour sessions over 3 weeks	In-person	Not specified	Not specified	Biofeedback & PMR+
Mackereth (2009)	United Kingdom	53	Relaxation: 48.12 Comparison: 52.52	Not specified	PMR	6 weekly sessions (40 min each)	In-person	Nurse	Not specified	Reflexology
Manglani (2020)	United States	61	Relaxation: 46.5 Comparison: 44.8 Control: 46	Relaxation: 10.1 Comparison: 12.3 Control: 11.3	Mindfulness Meditation	2 hour weekly sessions for 4 weeks +. 40 mins daily practice	In-person + remote	2 doctoral students supervised by a psychologist	Group	Adaptive cognitive training Waitlist control
Masoudi (2013)	Iran	70	Relaxation: 18% 20-30 yr 17% 31-40 yr Comparison: 20% 20-30 yr 15% 31-40 yr	Not specified	PMR	Five days of training + 3 months of daily PMR practice	Single session relaxation	In-person + remote	Not specified	Not specified
Minen (2020)	United States	62	Relaxation: 38.2 Comparison: 41.2	Relaxation: first symptoms 26.8 yr Comparison: first symptoms: 27.9 yr	PMR	Daily headache diary + 15-minute PMR session + 5-minute PMR per day over 6 months.	Attention control	Remote (web, telehealth, CD rom practice)	PMR delivered via app. Original recordings of PMR were delivered by a psychologist.	Individual
Nascimento Novais (2016)	Brazil	40	Relaxation: 20% 21-30 yr 30% 31-40 yr 40% 41-50 yr 10% 51-60 yr Control: 5% <20 yr 35% 21-30 yr 25% 31-40 yr 15% 41-50 yr 20% 51-60 yr	Relaxation: 40% 1-5 yr 40% 6-10 yr 15% 11-15 yr 5% > 20 yr Control: 60% 1-5 yr 15% 6-10 yr 15% 11-15 yr 5% 16-20 yr 5% > 20 yr	PMR	Not specified	In-person + remote	Not specified	Individual + group	Attention control

Lead author (date)	Country	Sample characteristics			Relaxation characteristics					Control /comparator
		n	Mean or median age (years)	Time since diagnosis (years)	Type	Duration & frequency	Modality	Therapist	Format	
Nazari (2015, 2016, 2017)	Iran	75	Relaxation: 33.90 Comparison: 34.40 Control: 34.40	Not specified	PMR & visualisation	Twice a week for 40 minutes for 4 weeks	In-person	Not specified	Group	Reflexology
Nordin (2012)	Sweden	21	Relaxation: 48.5 Comparison: 43	Relaxation: 9 Comparison: 5	Relaxation training	5 sessions over 15 weeks + 3 month booster session	In-person + remote	Psychologists	Group	ACT
Ozkul (2020a)	Turkey	54	Relaxation: 34 Comparison 1: 29 Comparison 2: 34	Relaxation: 4 Comparisons: 4	PMR	Single face:face session + 15-20 minutes home practice twice daily for 8 weeks	In-person + remote	Physiotherapist	Individual	1. Immersive Virtual Reality 2. Balance training
Ozkul (2020b)	Turkey	34	Relaxation: 36.76 Comparison: 35.88	Relaxation: 5.71 Comparison: 7.18	PMR	Single PMR session + home practice 15-20 minutes 3 times a week for 8 weeks.	In-person + remote	Physiotherapist	Not specified	Aerobic training + pilates
Safi (2015)	Iran	30	Second decade: 30% Third decade: 37% Fourth decade: 23% Fifth decade: 10%	< 2 yrs: 27% 2 to 5 yrs: 17% 5 to 10 yrs: 50% > 10 yrs: 6%	PMR	12 sessions (each 60 minutes). Twice weekly for six weeks.	In-person	Not specified	Not specified	Treatment as usual
Sutherland (2005)	Australia	26	Relaxation: 43.55 Control: 40.82	Relaxation: 9.36 Control: 6.45	Autogenic Training	1 supervised session per week for 10 weeks + daily home practice	In-person	Not specified	Group	No treatment
van Kessel (2008)	New Zealand	72	Relaxation: 47.03 Comparison: 42.89	Relaxation: 6.65 Comparison: 5.54	PMR+	8 weekly sessions for 50 mins each	In-person + remote	Psychologist	Individual	CBT
Vazirinejad (2016)	Iran	60	Relaxation: 32.6 Control: 31.8	Relaxation: 6.23 Control: 5.77	PMR	12 sessions – twice a week for 6 weeks.	Not specified	Not specified	Not specified	No treatment

Abbreviations: n - number of participants per study; RCT - randomised controlled trial, PMR – progressive muscle relaxation, EMDR - Eye Movement Desensitization and Reprocessing, ACT - Acceptance and Commitment Therapy, CBT Cognitive Behaviour Therapy, READY-MS - REsilience and Activities for every DaY for people with multiple sclerosis (READY for MS), PMR+ - PMR and ≥ 2 other relaxation techniques.

Table 3.
Risk of bias for randomised controlled trials (ROB-2 – modified for psychotherapy studies)

Study ID	Randomisation	Effect of Assignment to Intervention	Missing Outcome Data	Measurement of the Outcome	Selection of Reported Result	Overall Risk
Agland_2018	Some concerns	Some concerns	High risk	High risk (self-report outcomes) Low risk (physiological measures)	Some concerns	High risk
Artemiadis_2012	High risk	Low risk	High risk	High risk	Some concerns	High risk
Bulguroglu_2017	Some concerns	High risk	High risk	High risk (self-report outcomes) Low risk (observed outcomes)	Some concerns	High risk
Carletto_2016	Low risk	High risk	High risk	High risk	Low risk	High risk
Castro-Sánchez_2012	Low risk	Some concerns	Low risk	High risk (self-report outcomes) Low risk (observed outcomes)	Some concerns	High risk
Giovannetti_2020	Low risk	Some concerns	Low risk	High risk (self-report outcomes) Low risk (observed outcomes)	Low risk	High risk
Hersche_2019	Low risk	Low risk	High risk	High risk	Low risk	High risk
Javdan_2021	Some concerns	Some concerns	Low risk	High risk	Some concerns	High risk
Kos_2016	Low risk	Some concerns	Low risk	High risk (self-report outcomes) Low risk (observed outcomes)	Some concerns	High risk
Mackay_2015	Some concerns	Some concerns	Low risk	High risk (sef-report outcomes) Low risk (physiological measures)	Some concerns	High risk
Mackereth_2009	Low risk	Some concerns	High risk	High risk (sef-report outcomes) Low risk (physiological measures)	Some concerns	High risk
Manglani_2020	Some concerns	Some concerns	Low risk	High risk (self-report outcomes) Low risk (observed outcomes)	Low risk	High risk

Masoudi_2013	Some concerns	Some concerns	Low risk	High risk	Some concerns	High risk
Minen_2020	Some concerns	Some concerns	Some concerns	High risk	Some concerns	High risk
Nascimento Novais_2016	Some concerns	Some concerns	High risk	High risk (self-report outcomes) Low risk (physiological measures)	Some concerns	High risk
Nazari 2015; 2016; 2017	Some concerns	Some concerns	Low risk	High risk	Some concerns	High risk
Nordin_2012	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Ozkul_2020a	Low risk	Some concerns	Low risk	High risk (self-report outcomes) Low risk (observed outcomes)	High risk	High risk
Ozkul_2020b	Low risk	Some concerns	Low risk	High risk (self-report outcomes) Low risk (observed outcomes)	Low risk	High risk
Safi_2015	Some concerns	Some concerns	Low risk	High risk	Some concerns	High risk
Sutherland_2005	High risk	Some concerns	Low risk	High risk	Some concerns	High risk
vanKessel_2008	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Vazirinejad_2016	Some concerns	High risk	High risk	High risk	Some concerns	High risk

SUPPLEMENTARY MATERIAL

Table S1. Study Characteristics for non RCTs

Lead author (date)	Design	Country	Sample characteristics			Relaxation characteristics					Control /comparator
			n	Mean or median age (years)	Time since diagnosis (years)	Type	Duration & frequency	Modality	Therapist	Format	
Davapoglu (2012)	Non-randomised	Turkey	32	38.15	43.8% < 2 yr 18.8% 3-5 yr 15.5% 6-8 yr 21.9% > 8 yr	PMR or Relaxation training	1 hour session + home practice for 6 weeks. Booster session at 2 weeks	In-person + remote	Not specified	Individual	Nil
Ghafari (2009)	Non-randomised	Iran	66	Relaxation: 31.93 Control: 31.12	Relaxation: 54.5% 1-6 yr 36.4% 7-13 yr 9.1% 14-20 yr Control: 75.8% 1-6 yr 24.2% 7-13 yr	PMR or Relaxation Training	3 days for training + daily home practice for 8 weeks (total 60 sessions)	In-person + remote	Not specified	Not specified	No treatment
Jensen (2009)	Non-randomised	United States	22	51.7	Not specified	PMR or Relaxation Training	10 sessions in person + daily home practice	In-person + remote	Not specified	Not specified	Self-hypnosis training
Pritchard (2010)	Non-randomised	United States	12	Not specified	Not specified	Yogic breathing	90 mins weekly for 6 weeks + daily home practice	In-person + remote	Not specified	Group	Nil
Saifan (2021)	Non-randomised	Jordan	105	33.11	14 (13.3) < 1 yr 41 (39) 1-2 yr 36 (34.3) 2-3 yr 14 (13.3) > 3 yr	Benson Relaxation Training	2 initial learning sessions + 2x daily (10min) for 8 weeks	In-person + remote	Interventionist	Not specified	TAU

Abbreviations: n - number of participants per study; PMR – progressive muscle relaxation, TAU – treatment as usual.

Table S2. Risk of bias for non-randomised trials as rated by ROBINS-I

Study ID	Bias due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias due to Deviations from Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Results	Overall Risk of Bias
Dayapoglu (2012)	Serious risk	Low risk	Low risk	No information	No information	Serious risk	Moderate risk	Serious risk
Ghafari (2009)	Serious risk	Low risk	Low risk	No information	No information	Serious risk	Moderate risk	Serious risk
Jensen (2009)	Serious risk	Moderate risk	Low risk	No information	Low risk	Low risk	Moderate risk	Serious risk
Pritchard (2010)	Serious risk	Low risk	Low risk	No information	No information	Serious risk	Moderate risk	Serious risk
Saifan (2021)	Serious risk	Low risk	Low risk	No information	No information	Low risk	Moderate risk	Serious risk

Table S3. Within group differences: pre to post-intervention – RCT only

Construct	Measure	*Relaxation*				*Active Control*				*Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		N	*g*	95% CI		
Depression	BDI	10	0.93*	0.39	1.48	11	1.08*	0.53	1.63					Nordin (2012)
		20	0.29	-0.05	0.62	20	0.11	-0.22	0.44	21	0.28	-0.04	0.61	Manglani (2020)
		17	-0.37*	-0.74	-0.01	17	0.24	-0.12	0.60					Ozkul (2020b)
		15	0.78*	0.35	1.21	15	-0.01	-0.38	0.36					Safi (2015)
		31	0.57*	0.29	0.86					30	0.11	-0.16	0.38	Artemiadis (2012)
	CMDI	22	0.86*	0.49	1.23	20	0.47*	0.12	0.81					Carletto (2016)
	GHQ-28 Depression	25	0.34*	0.04	0.64	25	0.41*	0.10	0.72					Mackereth (2009)
	DASS Depression	20	0.45*	0.11	0.79	20	0.37*	0.03	0.70					Mackay (2015)
		25	0.71*	0.38	1.04	25	1.03*	0.66	1.40	25	0.13	-0.17	0.42	Soheili (2017)
	CES-D	11	0.27	-0.16	0.70					11	0.02	-0.41	0.44	Sutherland (2005)
	POMS-SF Affect	11	0.09	-0.33	0.52					11	0.00	-0.42	0.42	Sutherland (2005)
	HADS Depression	10	0.99*	0.44	1.55	11	0.05	-0.37	0.47					Nordin (2012)
		19	0.05	-0.28	0.39	18	0.45*	0.09	0.81					Giovannetti (2020)
		37	0.24	-0.01	0.48	35	0.77*	0.48	1.05					Van Kessel (2008)
		22	0.98*	0.60	1.37	20	0.76*	0.39	1.13					Carletto (2016)
Anxiety	PSWQ	20	-0.30	-0.64	0.03	20	0.23	-0.10	0.56	21	0.15	-0.17	0.47	Manglani (2020)
	STAI	25	0.93*	0.57	1.28	25	0.72*	0.38	1.05					Mackereth (2009)
		31	0.64*	0.34	0.93					30	0.27*	0.00	0.55	Artemiadis (2012)
	GHQ-28 Tension	25	0.67*	0.35	1.00	25	1.46*	1.03	1.89					Mackereth (2009)
	DASS Anxiety	20	0.63*	0.27	0.99	20	0.34*	0.01	0.69					Mackay (2015)
		25	0.77*	0.43	1.10	25	0.87*	0.52	1.21	25	0.28	-0.02	0.58	Soheili (2017)
	HADS Anxiety	10	0.26	-0.19	0.71	11	0.21	-0.22	0.64					Nordin (2012)
		19	029	-0.05	0.63	20	0.27	-0.07	0.60					Giovannetti (2020)
		37	0.19	-0.06	0.44	35	0.60*	0.33	0.88					Van Kessel (2008)
		22	0.94*	0.56	1.32	20	0.91*	0.52	1.30					Carletto (2016)
	POMS-SF Tension	11	0.22	-0.21	0.65					11	0.08	-0.35	0.50	Sutherland (2005)
Stress	DASS Stress	20	0.66*	0.30	1.02	20	0.49*	0.15	0.84					Mackay (2015)
		25	0.82*	0.48	1.17	25	0.81*	0.47	1.15	25	0.04	-0.25	0.34	Soheili (2017)
	PSS	19	0.06	-0.28	0.39	18	0.65*	0.27	1.03					Giovannetti (2020)
		37	0.16	-0.09	0.40	35	0.78*	0.49	1.06					Van Kessel (2008)
		31	0.59*	0.29	0.88					30	0.12	-0.16	0.39	Artemiadis (2012)
		20	1.47*	0.99	1.95					20	0.05	-0.28	0.37	Nascimento Novais (2016)

Table S3. Continued

Construct	Measure	*Relaxation*				*Active Control*				*Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		N	*g*	95% CI		
Pain	SF-36 Pain	25	0.03	-0.29	0.29	25	0.35*	0.04	0.65					Mackereth (2009)
		11	0.36	-0.08	0.80	14	0.42*	0.02	0.82					Kos (2016)
	Subjective pain	35	2.32*	1.83	2.81	35	-0.17	-0.42	0.09					Masoudi (2013)
	NPS	25	0.36*	0.06	0.67	25	1.21*	0.82	1.61	25	0.15	-0.15	0.44	Nazari (2016)
	MSQOL-54 Pain	11	0.51*	0.06	0.97					11	0.03	-0.40	0.45	Sutherland (2005)
	MIDAS	23	0.10	-0.21	0.41	21	0.42*	0.09	0.76					Minen (2020)
	PES	14	0.00	-0.38	0.38	18	0.43*	0.08	0.79					Minen (2020)
Fatigue	SF-36 Vitality	17	0.82*	0.41	1.24	18	1.17*	0.72	1.63					Hersche (2019)
		25	0.11	-0.19	0.40	25	0.32*	0.02	0.62					Mackereth (2009)
		11	0.39	-0.05	0.83	14	0.28	-0.11	0.67					Kos (2016)
	MSQOL-54 Energy	11	1.13*	0.57	1.69					11	-0.27	-0.69	0.17	Sutherland (2005)
	MFIS	17	0.80*	0.39	1.21	18	1.06*	0.62	1.49					Hersche (2019)
		11	0.38	-0.06	0.82	14	0.86*	0.40	1.31					Kos (2016)
	CIS Fatigue	11	0.20	-0.23	0.62	14	0.87*	0.41	1.32					Kos (2016)
	FSS	13	-0.25	-0.65	0.15	13	0.83*	0.36	1.29					Ozkul (2020a)
						13	0.87*	0.40	1.34					Ozkul (2020a)
		20	0.70*	0.33	1.06	20	0.29	-0.05	0.62					Mackay (2015)
		22	0.48*	0.15	0.81	20	0.14	-0.19	0.47					Carletto (2016)
		25	0.92*	0.57	1.28	25	1.29*	0.88	1.69	25	0.11	-0.19	0.40	Nazari (2015)
		30	1.11*	0.76	1.45					30	0.14	-0.14	-0.41	Vazirinejad (2016)
	FIS	17	-0.27	-0.62	0.09	17	0.60*	0.21	0.98					Ozkul (2020b)
	POMS-SF Fatigue	11	0.44	-0.10	0.88					11	0.07	-0.35	0.50	Sutherland (2005)
	POMS-SF Vitality	11	0.41	-0.03	0.86					11	-0.06	-0.49	0.36	Sutherland (2005)
	WSA Fatigue	37	0.26*	0.02	0.51	35	0.46*	0.20	0.73					Van Kessel (2008)
	CFQ	37	1.74*	1.35	2.13	35	2.97*	2.37	3.56					Van Kessel (2008)
Quality of Life (Mental)	SF-36 Emotional wellbeing	17	0.64*	0.25	1.03	18	0.59*	0.22	0.97					Hersche (2019)
	SF-36 Mental health	25	0.34*	0.04	0.64	25	0.56*	0.24	0.88					Mackereth (2009)
		11	-0.03	-0.45	0.39	14	0.18	-0.20	0.57					Kos (2016)
	MSQOL-54 Mental health	17	-0.27	-0.63	0.09	17	0.61*	0.23	0.99					Ozkul (2020b)
		19	1.30*	0.84	1.77	18	1.56*	1.04	2.08					Giovannetti (2020)
	MSQOL-54 Emotional wellbeing	11	0.18	-0.25	0.61					11	0.00	-0.42	0.42	Sutherland (2005)

Table S3. Continued

Construct	Measure	*Relaxation*				*Active Control*				*Inactive Control*				Lead author (date)
		N	*g*	95% CI		*N*	*g*	95% CI		*N*	*g*	95% CI		
Quality of Life (Physical)	SF-36 Physical function	17	0.21	-0.14	0.57	18	0.53*	0.16	0.90					Hersche (2019)
		25	0.07	-0.22	0.37	25	0.10	-0.19	0.40					Mackereth (2009)
		11	0.29	-0.14	0.72	14	0.18	-0.21	0.56					Kos (2016)
	MSQOL-54 Physical health	17	-0.34	-0.70	0.02	17	0.69*	0.29	1.08					Ozkul (2020b)
		11	-0.07	-0.49	0.35					11	-0.02	-0.44	0.41	Sutherland (2005)
	MSQOL-54 Physical component	19	0.69*	0.31	1.06	18	0.49*	0.13	0.86					Giovannetti (2020)

Table S4. Between group differences: pre to post-intervention – RCT only

Construct	Measure	*Relaxation vs. Active Control*				*Relaxation vs. Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		
Depression	BDI	21	0.12	-0.71	0.94					Nordin (2012)
		40	0.24	-0.37	0.85	41	0.10	-0.50	0.70	Manglani (2020)
		34	-0.82*	-1.50	-0.13					Ozkul (2020b)
		30	1.03*	0.29	1.77					Safi (2015)
						61	0.84*	0.32	1.35	Artemiadis (2012)
	CMDI	42	0.42	-0.18	1.03					Carletto (2016)
	GHQ-28 Depression	50	0.04	-0.51	0.59					Mackereth (2009)
	DASS Depression	40	0.16	-0.45	0.77					Mackay (2015)
		50	-0.47	-1.02	0.08	50	0.77*	0.21	1.34	Soheili (2017)
	CES-D					22	0.19	-0.62	0.99	Sutherland (2005)
	POMS-SF Affect					22	0.09	-0.71	0.90	Sutherland (2005)
	HADS Depression	21	1.02*	0.14	1.90					Nordin (2012)
		37	-0.51	-1.16	0.13					Giovannetti (2020)
		72	-0.58*	-1.05	-0.12					Van Kessel (2008)
		42	0.44	-0.16	1.04					Carletto (2016)
Anxiety	PSWQ	40	0.19	-0.42	0.79	41	0.19	-0.41	0.79	Manglani (2020)
	STAI	50	-0.28	-0.83	0.27					Mackereth (2009)
						61	0.47	-0.03	0.98	Artemiadis (2012)
	GHQ-28 Tension	50	-0.06	-0.61	0.49					Mackereth (2009)
	DASS Anxiety	40	0.20	-0.41	0.81					Mackay (2015)
		50	-0.26	-0.81	0.29	50	0.60*	0.04	1.15	Soheili (2017)
	HADS Anxiety	21	0.00	-0.82	0.82					Nordin (2012)
		39	0.02	-0.60	0.63					Giovannetti (2020)
		72	-0.70*	-1.17	-0.23					Van Kessel (2008)
		42	0.01	-0.58	0.60					Carletto (2016)
	POMS-SF Tension					22	0.09	-0.72	0.89	Sutherland (2005)
Stress	DASS Stress	40	0.11	-0.49	0.72					Mackay (2015)
		50	0.04	-0.50	0.59	50	1.17*	0.58	1.76	Soheili(2017)
	PSS	37	-0.81*	-1.46	-0.15					Giovannetti (2020)
		72	-0.90*	-1.38	-0.42					Van Kessel (2008)
						61	0.61*	0.10	1.12	Artemiadis (2012)
						40	1.85*	1.12	2.58	Nascimento Novais (2016)

Table S4. Continued.

Construct	Measure	*Relaxation vs. Active Control*				*Relaxation vs. Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		
Pain	SF-36 Pain	50	-0.45	-1.00	0.11					Mackereth (2006)
		25	-0.13	-0.90	0.63					Kos (2016)
	Subjective pain	70	3.69*	2.92	4.46					Masoudi (2013)
	NPS	50	-1.24*	-1.83	-0.64	50	0.28	-0.27	0.83	Nazari (2016)
	MSQOL-54 Pain					22	0.56	-0.26	1.38	Sutherland (2005)
	MIDAS	44	-0.39	-0.97	0.20					Minen (2020)
	PES	32	-0.63	-1.33	0.07					Minen (2020)
Fatigue	SF-36 Vitality	35	-0.29	-0.85	0.24					Hersche (2019)
		50	-0.31	-0.85	0.24					Mackereth (2009)
		25	0.18	-0.59	0.95					Kos (2016)
	MSQOL-54 Energy					22	1.65*	0.71	2.59	Sutherland (2005)
	MFIS	35	-0.28	-0.93	0.37					Hersche (2019)
		25	-0.41	-1.18	0.36					Kos (2016)
	CIS Fatigue	25	-0.62	-1.40	0.17					Kos (2016)
	FSS					76	1.33*	0.86	1.82	Javdan (2021)
		26	-1.42*	-2.26	-0.58					Ozkul (2020a)
		26	-1.42*	-2.25	-0.58					Ozkul (2020a)
		40	0.37	-0.24	0.99					Mackay (2015)
		42	0.46	-0.15	1.06					Carletto (2016)
		50	-0.74*	-1.31	-0.18	50	0.97*	0.39	1.55	Nazari (2015)
						60	1.43*	0.86	1.99	Vazirinejad (2016)
	FIS	34	-1.06*	-1.76	-0.35					Ozkul (2020a)
	POMS-SF Fatigue					22	0.37	-0.45	1.18	Sutherland (2005)
	POMS-SF Vigour					22	0.73	-0.11	1.59	Sutherland (2005)
	WSA Fatigue	72	0.27	-0.19	0.73					Van Kessel (2008)
	CFQ	72	-1.18*	-1.68	-0.69					Van Kessel (2008)
Quality of Life (Mental)	SF-36 Emotional wellbeing	35	0.05	-0.60	0.69					Hersche (2019)
	SF-36 Mental health	50	-0.29	-0.84	0.26					Mackereth (2009)
		25	-0.27	-1.04	0.49					Kos (2016)
	MSQOL-54 Mental health	34	-1.15*	-1.86	-0.44					Ozkul (2020b)
		37	-0.41	-1.04	0.23					Giovannetti (2020)
	MSQOL-54 Emotional wellbeing					22	0.23	-0.58	1.03	Sutherland (2005)

Table S4. Continued

Construct	Measure	*Relaxation vs. Active Control*				*Relaxation vs. Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		
Quality of Life (Physical)	SF-36 Physical function	35	-0.46	-1.11	0.20					Hersche (2019)
		50	-0.05	-0.59	0.50					Mackereth (2009)
		25	0.16	-0.60	0.93					Kos (2016)
	MSQOL-54 Physical health	34	-1.31*	-2.04	-0.58					Ozkul (2020b)
						22	-0.07	-0.87	0.74	Sutherland (2005)
		37	0.23	-0.40	0.87					Giovannetti (2020)

Table S5. Within group differences: post-intervention to follow-up – RCT only

Construct	Measure	Time	*Relaxation*				*Active Control*				*Inactive Control*				Lead author (date)
			N	*g*	95% CI		N	*g*	95% CI		N	*g*	95% CI		
Depression	DASS-21 Depression	8 weeks	25	-0.18	-0.48	0.11	25	-0.40*	-0.70	-0.09	25	0.01	-0.28	0.31	Soheili (2017)
	BDI	12 weeks	10	0.32	-0.14	0.77	11	-0.22	-0.65	0.21					Nordin (2012)
	HADS Depression	5 weeks	19	0.21	-0.13	0.54	18	0.03	-0.32	0.37					Giovannetti (2020)
		12 weeks	19	0.24	-0.10	0.58	18	0.05	-0.29	0.39					Giovannetti (2020)
		12 weeks	10	-0.28	-0.72	0.17	11	-0.11	-0.54	0.31					Nordin (2012)
		12 weeks	37	-0.02	-0.27	0.22	35	0.12	-0.13	0.37					Van Kessel (2008)
		24 weeks	37	0.00	-0.24	0.24	35	0.00	-0.25	0.25					Van Kessel (2008)
		24 weeks	22	-0.33*	-0.65	0.00	20	0.04	-0.29	0.36					Carletto (2016)
	CMDI	24 weeks	22	-0.29	-0.61	0.03	20	0.33*	0.00	0.67					Carletto (2016)
Anxiety	DASS-21 Anxiety	8 weeks	25	-0.43*	-0.74	-0.13	25	-0.23	-0.53	0.07	25	0.01	-0.29	0.31	Soheili (2017)
	HADS Anxiety	5 weeks	19	0.07	-0.27	0.40	18	-0.03	-0.37	0.32					Giovannetti (2020)
		12 weeks	19	0.17	-0.17	0.50	18	0..23	-0.12	0.58					Giovannetti (2020)
		12 weeks	10	0.25	-0.19	0.70	11	0.15	-0.28	0.57					Nordin (2012)
		12 weeks	37	0.31*	0.06	0.56	35	0.17	-0.08	0.42					Van Kessel (2008)
		24 weeks	22	-0.02	-0.33	0.29	20	0.22	-0.11	0.55					Carletto (2016)
Stress	DASS-21 Stress	8 weeks	25	-0.15	-0.45	0.14	25	-0.25	-0.55	-0.05	25	0.06	-0.23	-.36	Soheili(2017)
	PSS	5 weeks	19	0.44*	0.09	0.79	18	0.00	-0.34	0.34					Giovannetti (2020)
		12 weeks	19	0.57*	0.20	0.93	18	0.01	-0.33	0.36					Giovannetti (2020)
		12 weeks	37	0.29*	0.05	0.55	35	0.18	-0.07	0.44					Van Kessel (2008)
		24 weeks	37	0.27*	0.02	0.52	35	0.10	0.15	0.35					Van Kessel (2008)
Pain	SF-36 Pain	12 weeks	11	-0.30	-0.73	0.13	14	0.51*	0.10	0.92					Kos (2016)
	NPS	8 weeks	25	-0.04	-0.34	0.25	25	-0.70*	-1.01	-0.36	25	0.15	-0.14	0.45	Nazari (2016)
Fatigue	SF-36 Vitality	12 weeks	11	-0.23	-0.66	0.35	14	0.09	-0.30	0.47					Kos (2016)
		16 weeks	17	-0.41*	-0.78	-0.05	18	0.79*	0.40	1.19					Hersche (2019)
	MFIS	12 weeks	11	-0.17	-0.59	0.26	14	0.13	-0.25	0.52					Kos (2016)
		16 weeks	17	-0.17	-1.01	0.67	18	-0.17	-0.52	0.17					Hersche (2019)
	CIS Fatigue	12 weeks	11	0.12	-0.31	0.54	14	-0.01	-0.39	0.38					Kos (2016)
	FSS	8 weeks	25	-0.30*	-0.60	0.00	25	-0.26	-0.56	0.04	25	0.04	-0.25	0.34	Nazari (2015)
		12 weeks	30	-0.22	-0.49	0.05					30	-0.02	-0.29	0.25	Vazirinejad (2016)
		24 weeks	22	-0.19	-0.50	0.13	20	0.17	-0.16	0.50					Carletto (2016)
	WSA Fatigue	12 weeks	37	0.05	-0.53	0.63	35	0.29*	0.03	0.54					Van Kessel (2008)
		24 weeks	37	-0.04	-0.29	0.20	35	0.11	-0.14	0.37					Van Kessel (2008)
	CFQ	12 weeks	37	0.09	-0.16	0.34	35	-0.22	-0.47	0.04					Van Kessel (2008)
		24 weeks	37	-0.17	-0.42	0.08	35	0.45	-0.18	1.08					Van Kessel (2008)

Table S5. Continued

Construct	Measure	Time	*Relaxation*				*Active Control*				*Inactive Control*			Lead author
			N	*g*	95% CI		N	*g*	95% CI		N	*g*	95% CI	
Quality of Life (Mental)	SF-36 Emotional wellbeing	12 weeks	11	0.33	-0.11	0.76	14	-0.30	-0.69	0.10				Kos (2016)
	SF-36 Mental health	16 weeks	17	-0.34	-0.70	0.02	18	0.36*	0.01	0.72				Hersche (2019)
	MSQOL-54 Mental health	12 weeks	19	1.21*	0.76	1.65	18	0.42*	0.07	0.78				Giovannetti (2020)
Quality of Life (Physical)	SF-36 Physical function	12 weeks	11	-0.01	-0.43	0.42	14	-0.02	-0.40	0.36				Kos (2016)
		16 weeks	17	-0.33	-0.70	0.02	18	0.40*	0.05	0.76				Hersche (2019)
	MSQOL-54 Physical health	12 weeks	19	1.09*	0.66	1.52	18	-0.07	-0.41	0.27				Giovannetti (2020)

Table S6. Between group differences: post-intervention to follow-up – RCT only

Construct	Measure	Time	*Relaxation vs. Active Control*				*Relaxation vs. Inactive Control*				Lead author (date)
			N	*g*	95% CI		N	*g*	95% CI		
Depression	DASS-21 Depression	8 weeks	50	0.28	-0.26	0.83	50	-0.26	-0.81	0.29	Soheili (2017)
	BDI	12 weeks	21	0.73	-0.12	1.58					Nordin (2012)
	HADS Depression	5 weeks	37	0.24	-0.39	0.87					Giovannetti (2020)
		12 weeks	37	0.26	-0.37	0.89					Giovannetti (2020)
		12 weeks	21	-0.22	-1.04	0.61					Nordin (2012)
		12 weeks	72	-0.18	-0.64	0.29					Van Kessel (2008)
		24 weeks	72	0.00	-0.46	0.46					Van Kessel (2008)
		24 weeks	42	-0.50	-1.11	0.10					Carletto (2016)
	CMDI	24 weeks	42	-0.82*	-1.44	-0.20					Carletto (2016)
Anxiety	DASS-21 Anxiety	8 weeks	50	-0.09	-0.64	0.46	50	-0.51	-1.06	0.05	Soheili (2017)
	HADS Anxiety	5 weeks	37	0.12	-0.51	0.76					Giovannetti (2020)
		12 weeks	37	-0.10	-0.73	0.53					Giovannetti (2020)
		12 weeks	21	0.16	-0.66	0.99					Nordin (2012)
		12 weeks	72	0.16	-0.30	0.61					Van Kessel (2008)
		24 weeks	42	-0.28	-0.88	0.32					Carletto (2016)
Stress	DASS-21 Stress	8 weeks	50	0.10	-0.44	0.65	50	-0.29	-0.84	0.26	Soheili (2017)
	PSS	5 weeks	37	0.57	-0.08	1.21					Giovannetti (2020)
		12 weeks	37	0.72*	0.07	1.38					Giovannetti (2020)
		12 weeks	72	0.11	-0.35	0.57					Van Kessel (2008)
		24 weeks	72	0.17	-0.29	0.62					Van Kessel (2008)
Pain	SF-36 Pain	12 weeks	25	-1.09*	-1.91	-0.27					Kos (2016)
	NPS	8 weeks	50	0.90*	0.33	1.47	50	0.25	-0.29	0.80	Nazari (2016)
Fatigue	SF-36 Vitality	12 weeks	25	-0.42	-1.19	0.35					Kos (2016)
		16 weeks	35	-1.56*	-2.29	-0.81					Hersche (2019)
	MFIS	12 weeks	25	-0.41	-1.18	0.36					Kos (2016)
		16 weeks	35	0.03	-0.61	0.68					Hersche (2019)
	CIS Fatigue	12 weeks	25	0.21	-0.56	0.97					Kos (2016)
	FSS	8 weeks	50	-0.03	-0.57	0.52	50	-0.42	-0.97	0.13	Nazari (2015)
		12 weeks					60	-0.30	-0.80	0.20	Vazirinejad (2016)
		24 weeks	42	-0.47	-1.07	0.14					Carletto (2016)
	WSA Fatigue	12 weeks	72	0.40	-0.06	0.86					Van Kessel (2008)
		24 weeks	72	-0.09	-0.54	0.37					Van Kessel (2008)
	CFQ	12 weeks	72	-0.13	-0.59	0.33					Van Kessel (2008)
		24 weeks	72	0.36	-0.11	0.82					Van Kessel (2008)

Table S6. Continued

Construct	Measure	Time	*Relaxation vs. Active Control*			*Relaxation vs. Inactive Control*			Lead author (date)
			N	*g*	95% CI	N	*g*	95% CI	
Quality of Life (Mental)	SF-36 Emotional wellbeing	12 weeks	25	-0.85*	-1.64 -0.05				Kos (2016)
	SF-36 Mental health	16 weeks	35	-0.92*	-1.61 -0.24				Hersche (2019)
	MSQOL-54 Mental health	12 weeks	37	1.01*	0.34 1.68				Giovannetti (2020)
Quality of Life (Physical)	SF-36 Physical function	12 weeks	25	-0.02	-0.78 0.75				Kos (2016)
		16 weeks	35	-0.98*	-1.67 -0.29				Hersche (2019)
	MSQOL-54 Physical health	12 weeks	37	1.51*	0.79 2.23				Giovannetti (2020)

Table S7. Within group differences: pre to post-intervention – non RCTs

Construct	Measure	*Relaxation*				*Active Control*				*Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		N	*g*	95% CI		
Depression	DASS-21 Depression	60	2.12*	1.76	2.47	45	0.03	0.19	0.25					Saifan (2021)
Anxiety	DASS-21 Anxiety	60	1.69*	1.39	1.99	45	0.04	-0.18	0.26					Saifan (2021)
Stress	DASS-21 Stress	60	0.68*	0.46	0.89	45	0.10	-0.13	0.32					Saifan (2021)
		9	1.00*	0.42	1.58									Pritchard (2010)
Pain	Pain intensity	7	-0.03	-0.53	0.47	15	0.81*	0.37	1.24					Jensen (2009)
	Pain interference	7	-0.06	-0.56	0.44	15	0.64*	0.22	1.05					Jensen (2009)
Fatigue	FSS	32	1.58*	1.18	1.98									Dayapaglou (2012)
Quality of Life (Mental)	SF-8 Mental health	33	1.29*	0.94	1.65	33				33	0.22	-0.04	0.48	Ghafari (2009)
Quality of Life (Physical)	SF-8 Physical health	33	1.21*	0.87	1.55					33	0.20	-0.06	0.46	Ghafari (2009)

Table S8. Between group differences: pre to post-intervention – non RCTs

Construct	Measure	*Relaxation vs. Active Control*				*Relaxation vs. Inactive Control*				Lead author (date)
		N	*g*	95% CI		N	*g*	95% CI		
Depression	DASS-21 Depression	105	3.02*	2.46	3.58					Saifan (2021)
Anxiety	DASS-21 Anxiety	105	2.44*	1.93	2.94					Saifan (2021)
Stress	DASS-21 Stress	105	0.94*	0.53	1.34					Saifan (2021)
Pain	Pain intensity	22	-1.10*	-2.03	-0.18					Jensen (2009)
	Pain interference	22	-0.84	-1.74	0.06					Jensen (2009)
Quality of Life (Mental)	SF-8 Mental health					66	1.80*	1.23	2.37	Ghafari (2009)
Quality of Life (Physical)	SF-8 Physical health					66	1.69*	1.14	2.25	Ghafari (2009)

Table S9. Within group differences: post-intervention to follow-up – non RCTs

Construct	Measure	Time	*Relaxation*			*Active Control*			*Inactive Control*			Lead author (date)
			N	*g*	95% CI	N	*g*	95% CI	N	*g*	95% CI	
Pain	Pain intensity	12 weeks	7	0.37	-0.15 0.89	15	-0.15	-0.53 0.22				Jensen (2009)
	Pain interference	12 weeks	7	0.09	-0.41 0.59	15	-0.26	-0.63 0.12				Jensen (2009)

Table S10. Between group differences: post-intervention to follow-up – non RCTs

Construct	Measure	Time	*Relaxation vs. Active Control*				*Relaxation vs. Inactive Control*				Lead author (date)
			N	*g*	95% CI		N	*g*	95% CI		
Pain	Pain intensity	12 weeks	22	0.71	-0.18	1.60					Jensen (2009)
	Pain interference	12 weeks	22	0.46	-0.42	1.33					Jensen (2009)

N = number of participants providing this data; *g* = standardised mean difference (Hedges' *g*), CI = 95% confidence interval (lower and upper limits), * $p \leq 0.05$

Positive values indicate improvement or greater change in relaxation group.

Measure abbreviations: BDI - Beck Depression Inventory, CMDI - Chicago Multiscale Depression Inventory, GHQ – General Health Questionnaire, DASS - Depression Anxiety Stress Scales, CES-D – Centre Epidemiological Studies Depression Scale, POMS – Profile of Mood States, HADS - Hospital Anxiety and Depression Scale, PSW – Penn State Worry Questionnaire, STAI – State Trait Anxiety Inventory, PSS - Perceived Stress Scale, SF-36 Medical Outcomes Short Form Health Survey, NPS – Numerical Pain Scale, MSQOL - Multiple Sclerosis Quality of Life Instrument, MIDAS – The Migraine Disability Assessment Test, PES - Medical Outcomes Study Pain Effects Scale, MFIS – Modified Fatigue Impact Scale, CIS - Checklist Individual Strength, FSS – Fatigue Severity Scale, FIS – Fatigue Impact Scale, WSA – Work and Social Adjustment Scale, CFQ – Chalder Fatigue Questionnaire.