Effects of Nonpharmaceutical Treatments on Symptom Management in Adults With Mild or Moderate Multiple Sclerosis: A Meta-analysis

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ABSTRACT

Objective: The aim of this study was to conduct a meta-analysis of clinical trials on the effect of nonpharmaceutical treatments on outcomes for multiple sclerosis (MS).

Methods: The CINAHL, Mantis, Medline, PEDro, PubMed, and Scopus databases were searched. Final papers meeting inclusion criteria were scored with the Physiotherapy Evidence Database for quality and included in a meta-analysis. Forty papers in the meta-analysis totaled 1673 participants. The interventions were grouped into 6 subcategories: physical activity, technology, rehabilitation, alternative, resistance training, and psychological.

Results: The combined effect of interventions produced a large overall effect size for the outcome fatigue; medium effect sizes for functionality, balance, and quality of life; and no effect on pain or spasticity. Physical activity had the greatest effect, improving fatigue, function, and balance. Rehabilitation and resistance training had a large effect on functionality. Comparatively, psychological approaches had only a small effect on improving quality of life. Sample sizes of included papers tended to be small with large variability in design. Therefore, results should be interpreted cautiously.

Conclusion: Our results suggest there may be effective nonpharmaceutical treatment options available that can improve the symptoms of fatigue, poor functionality, balance, and quality of life. We found that physical activity, alternative approaches, rehabilitation, and resistance training were effective for improving the management of a number of MS symptoms. (J Manipulative Physiol Ther 2019;42:514-531)

Key Indexing Terms: *Meta-analysis; Multiple Sclerosis; Complementary Therapies*

INTRODUCTION

The worldwide estimated number of people with multiple sclerosis (MS) increased from 2.1 million in 2008 to 2.3 million in 2013, which is partly reflective of improved reporting, but an increase in the prevalence and incidence of this disease has been reported in Europe, in the Mediterranean Basin, and it is speculated, globally.[1-3] Multiple sclerosis is an autoimmune demyelinating and progressively degenerative disease of the central nervous system (CNS).[4,5] The immune system attacks oligodendrocytes that myelinate central nervous system nerves. This results in a variety of symptoms that cause significant impairment in daily life. Symptoms may include weakness, spasticity, ataxia, tremor, and problems with coordination and balance. Fatigue, paresthesia, and pain are also typical.[6,7] Pharmaceutical treatments for relapsing-remitting MS, the most common form of the condition, can modify the course of the disease or control the disease process, but there is presently no cure.[1] People managing MS are increasingly turning to nonpharmaceutical treatment options,[8,9] thus this timely meta-analysis seeks to analyze the efficacy of such approaches.

Surveys suggest up to 70% of patients with MS have tried at least 1 form of alternative treatment for their symptoms,[10] and the longer they have had MS, the more they turn to complementary and alternative treatments.[11] Many also seek a holistic management of their disease and use multiple interventions simultaneously.[12] If this is the case, it becomes important to review the evidence for benefits that can be derived from these interventions to inform clinical decisions and future research.

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(Multiple Sclerosis) OR (MS)
AND

(Self-management intervention) OR (cognitive training) OR (diet) OR (fruit) OR (vegetables) OR (exercise) OR (Pilates) OR (physical activity) OR (targeted exercise) OR (non-targeted exercise) OR (antioxidants) OR (vitamin D) OR (mindfulness) OR (non-pharmaceutical) OR (tai chi) OR (vibration exercise) OR (bee sting therapy) OR (acupuncture) OR (electroacupuncture) OR (massage) OR (energy medicine) OR (reflexology) OR (education) OR (neural therapy) OR (naturopathic medicine) OR (progressive muscle relaxation) OR (biofeedback) OR (music therapy) OR (hypnosis) OR (Padma 28) OR (linoleic acid) OR (creatine) OR (carnitine) OR (linosine) OR (threonine) OR glucosamine OR (hyperbaric) OR (hippotherapy) OR (yoga)
OR (physiotherapy) OR (osteopathy) OR (chiropractic)
AND

(VAS) OR (NIPCM pain assessment scale) OR (2 & 6 minute walking test) OR (timed up and go test) OR (berg balance test) OR (MS walking scale) OR (modified fatigue impact scale) OR (QUALEFFO-41) OR (DASS-21) OR (chronic pain grade questionnaire) OR (McGill pain questionnaire) OR (multidimensional pain inventory) OR (pain disability questionnaire) OR (pain self-efficacy) OR (SF-36)
AND

(Control) OR (placebo) OR (comparator) OR (drug)
AND

(Random* controlled trial) OR (Clinical trial) OR (random allocation) OR (controlled trial) OR (control group)

DASS-21, Depression Anxiety Stress Scales; *MS,* multiple sclerosis; *NIPCM,* National Infection Prevention and Control Manual; *QUALEFFO-41,* Quality of Life Questionnaire; *SF-36,* 36-Item Short Form Health Survey; *VAS,* visual analog scale.

Fig 1. *Search Terms as Used in PubMed*

Nonpharmaceutical treatments are broadly defined as interventions outside of the MS licensed therapies, the traditional pharmaceutical interventions aimed to reduce inflammation and slow progression of the condition. Nonpharmaceutical treatments include complementary, alternative, and allied interventions in the broadest sense. We have taken this approach because defining what complementary and alternative medicine (CAM) encompasses has been shown to be confusing. The Cochrane Collaboration group has discussed the difficulty in defining what is, and is not, CAM.[13] Their paper concludes: "We … question whether it is possible to arrive upon a definitive set of therapies that are universally agreed upon as CAM."[13(p.12)] We believe our broad approach gives a comprehensive overview of the effects of a variety of nonpharmaceutical treatments (NPTs) to inform treatment approaches and possible areas of future research.

A number of studies have looked at the evidence for specific symptom amelioration.[14-17] Other studies have concentrated on the effects of just 1 form of complementary therapy.[18,19] A few systematic reviews have investigated randomized controlled trials of interventions that manage symptoms of MS.[13,20-22] But to the best of our knowledge, no research has undertaken a meta-analysis of the evidence for a broad range of NPTs in the management of many and various symptoms of MS.

The primary purpose of this study was to determine the effect of NPTs on outcomes for adults over 18 years with mild to moderate MS. The specific outcomes measured were fatigue, functionality, quality of life, balance, pain, paresthesia, and spasticity.

Methods

Data Sources and Searches

A systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[23] The online database search was carried out between February 1 and 5, 2017. The databases searched were CINAHL, Mantis, Medline, PEDro, PubMed, and Scopus. The search strategy used in PubMed is displayed in Figure 1.

Study Selection

The inclusion criteria required that participants were over 18 years, were diagnosed with MS, had no other diagnosed conditions, and had mild to moderate disability or a Kurtzke Expanded Disability Status Score of equal to or less than 6.5. The Expanded Disability Status Score is used to quantify and monitor disability in MS.[24] The intervention had to be nonpharmaceutical in nature, as previously defined. Studies had to measure, using a validated scale, 1 or more outcomes pertaining to pain, paresthesia, spasticity, fatigue, balance, quality of life, or functionality. Functional outcome measures related to an individual's ability to carry out activities of daily living; examples of these are the timed up-and-go test, the nine-hole peg test, and the 6-minute walk test. Randomized controlled and crossover trials (control or comparator) were included, and the articles were required to be published in English and available in full text. There was no restriction on publication date, and studies up to February 5, 2017 were included in our search.

Once references were extracted using the search terms; they were exported to a shared library using EndNote software. The authors independently completed the search, the removal of duplicates, the analysis of titles and abstracts, and the screening of the full papers according to the inclusion and exclusion criteria. Any differences were discussed to come to a consensus.

Data Extraction and Quality Assessment

The first author extracted the data onto an electronic data extraction sheet designed specifically for use in the meta-analysis software and piloted it using 3 randomly selected studies, refining it accordingly. The extracted data were verified by the second author. Data extracted included participant demographics and information on severity of MS, intervention, control or comparator information, outcome measures, and timeline of study. The mean and standard deviation of scores from each paper was extracted from the results sections of the included articles.

Several studies included more than 1 follow-up period; in these cases, the main follow-up period, as stated by the authors of the study, was used for the meta-analysis. Some studies reported more than 1 intervention group. To avoid giving undue weight to these studies and their samples, only the most relevant intervention and control group data were used in the current analyses. These decisions were based on the research questions of the studies, which reported the data and are herein elucidated. Fox et al[25] compared Pilates exercises with standard exercises and relaxation for people with MS. Of these 3 conditions, the Pilates group and relaxation group data were included in the current analyses as the best reflection of an intervention and control group, respectively. Al-Smadi et al[26] reported on 3 groups when examining the effects of transcutaneous electrical nerve stimulation: 4 Hz, 110 Hz, and placebo. Of the 3 conditions, 100 Hz and placebo group data were included in the current analyses for intervention and control groups, respectively. Razazian et al[27] examined 3 groups: yoga, aquatic exercise, and a non-exercise control group. Yoga (intervention) and non-exercise (control) group data were used in the current meta-analysis. Garrett et al[28] reported on 3 group interventions: physiotherapist led, yoga instructor led, and fitness instructor led compared to a control group, with minimal differences between the 3 instructors. The physiotherapist-led and control group data were included in the current meta-analysis.

Collett et al[29] examined the effects of different intensity physical activity on a range of outcomes for MS patients. The study did not include a clear control condition, but reported 3 intervention groups: continuous, intermittent, and combined cycling. Although a randomized controlled trial design was used, this study was excluded from the current meta-analysis given the lack of a clear comparison group. Furthermore, no difference was found among the 3 groups and all improved. Had this study been included in the current meta-analysis, selection of a control condition would have been arbitrary and biased overall effect sizes.

Each paper was scored for risk of bias using the Physiotherapy Evidence Database (PEDro) method of assessment. Those papers scoring 5 of 10 or less were counted in our study, but not included in the final analysis. Data were extracted from the papers scoring 6 of 10 or above, and entered into a table for later analysis. Those studies with sufficient data were then included in the meta-analysis. This does not refer to the papers in which exclusion was based on PEDro scores. This refers to papers where there was missing data such as means and standard deviations listed in their results. The authors of these papers were contacted and asked to supply the missing data; of the 30 authors contacted, 7 replied, and these were included, but the remaining 23 papers were excluded from the meta-analysis. This research assumes that the pathologies have been correctly diagnosed.

Data Synthesis and Analysis

Analysis was performed using Comprehensive Meta-Analysis software,[30] and the effect size estimate Hedge's g was calculated, a variation of Cohen's d that accounts for small sample size biases.[31] Cohen has described effect sizes $\geq$ 0.2, 0.5, and 0.8 as *small*, *medium* and *large,* respectively.[32] As we anticipated considerable heterogeneity, all analyses were conducted using the more conservative random-effects model. Subgroup analyses were performed by testing differences in Hedge's g among outcome variables (fatigue, functionality, quality of life, balance, pain, and spasticity). Paresthesia was initially included in the current review, but because there were only 2 studies investigating this outcome, it was excluded from the analysis. The type of intervention (physical activity, rehabilitation, resistance training, technology-based, alternative approaches, or psychological) was also included in our analysis plan. If no means or standard deviations were reported in a study, other test statistics (eg t, f, or p) were converted into Hedge's g. When the correlations between pre- and postintervention measures were not available, we used the conservative estimate ($r = 0.7$), as recommended by Rosenthal[33] and used previously.[34] Given the diverse range of interventions reported, an intervention was assessed in the current meta-analysis if it was used in at least 3 included studies. We felt this cutoff was justified because 3 is the median number of studies included in Cochrane reviews and meta-analyses.[35]

In addition, the I^2 statistic and χ^2 statistic (Q) were calculated to measure potential heterogeneity. I^2 measures the proposition of variance that would remain if we removed sampling error, in other words, how much variance in scores reflects true variance rather than sampling error.[36] The Q statistic was also calculated to

assess whether the null hypothesis, that all studies included in the analysis share a common effect size, was supported.[36] To assess potential publication bias, funnel plots were created for each outcome analysis. Egger's regression test was also used as a measure of publication bias given its appropriateness for small sample sizes over Begg's rank correlation test.[37]

Results

Search Yield

The electronic database search yielded a total of 806 results, and a further 4 records were obtained through other sources (post hoc field review). Papers were then screened according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig 2). Papers meeting inclusion criteria were assessed according to the PEDro checklist; 69 papers scored <6 and were not included in any further analysis. Of the 63 papers with a score of 6 or above, 28 were missing the data necessary for inclusion into the meta-analysis, and authors were emailed, with 6 responders. One paper was also removed owing to incompatible study design (lack of a clear comparison group as described earlier),[29] leaving 40 papers included in the meta-analysis.

Characteristics of the Selected Studies

The final 40 papers included in the meta-analysis were all randomized controlled trials or cross-over studies, with a total of 1673 participants. The study characteristics of the included papers can be found in Table 1. Intervention periods ranged from single sessions to 1 year. The papers were separated into categories according to NPT type: physical activity (9), alternative (9), technology (9), psychological (5), rehabilitation (4), resistance (3). These intervention approaches were classified by the authors based on the description provided in each study. For example, the subgroup physical activity included the interventions step training, downhill treadmill, group exercise, strength and aerobic training, and home-based exercise. Psychological interventions were those treatments delivered by counselors/

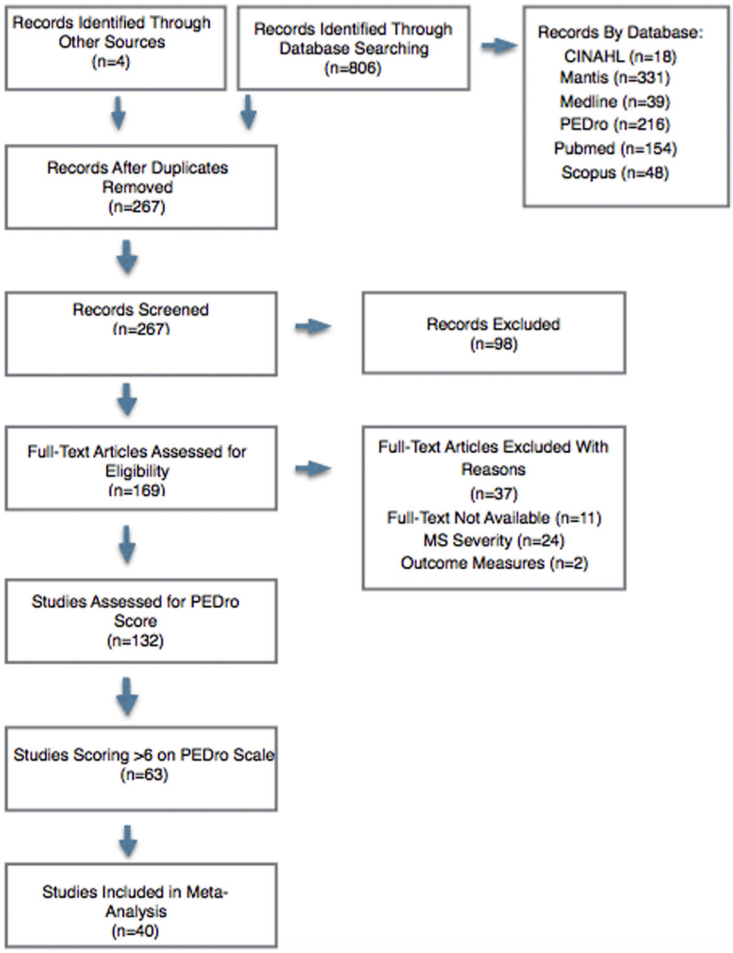

Fig 2. *Flow of paper selection.*

Table 1. *Study Characteristics*

Author (y)	PEDro Score	*N*	Mean Age (SD)	Sex (male/female)	Severity of MS[3]	Intervention Category	Tx	Control	Duration	Outcome Measures	Assessment Times
Broekmans (2011)[40]	6	36	Tx 1 44.9 (11.6) Tx 2 48.7 (8.6) Control 49.7 (11.3)	Tx 1 (6/5) Tx 2 (6/5) Control (11/3)	EDSS 2-6.5	Resistance	Resistance training with/without electrical stimulation	Normal living habits	2× 10-wk training period and 2-wk break	1 RM maximum, knee dynamometry, MAS, EDSS, TUG, timed 25-ft walk, 2MWT, FR, and the RMI	Baseline, 3 wk, 10 wk, and 20 wk
Coote (2015)[41]	6	25	Tx 51.8 (12.1) Control 51.8 (12.6)	Tx (4/6) Control (4/11)	Walk ≥10 m unaided	Resistance	Home resistance training (PRT) with electrical stimulation (NMES)	Home resistance training program	12 wk	Strength using handheld dynamometry, repeated sit to stand test, BBS, TUG test, 12-item MS walking scale, MS impact scale 29 version 2, and MFIS; the NMES group also completed a device usability questionnaire	Baseline and 12 wk
Dalgas (2010)[42]	6	31	Tx 47.7 (10.4) Control 49.1 (8.4)	Tx (10/5) Control (10/6)	EDSS 3-5.5	Resistance	PRT of lower extremities 2×/w for 12 wks; cross-over study	Daily activity level for the 12 wk, then PRT program for 12 wk; cross-over study	12 wk	FSS, MDI, PCS and MCS of SF-36	Baseline, 12 wk, and 24-wk follow-up
Braendvik (2016)[43]	6	26	Tx 46.6 (6.2) Control 49.1 (7.4)	Tx (4/7) Control (5/10)	EDSS <6	Physical activity	Group exercise 3×/wk; treadmill training without body weight support	Strength training at 80% max effort, 30 min per session	8 wk	FAP (gait), walking, work economy, trunk acceleration during walking	Prior to start, the week before training, and within a week after the last training session
DeBolt (2004)[44]	6	36	NR	Tx (4/15) Control (4/14)	EDSS 1-6.5	Physical activity	Home resistance training program	No intervention	10 wk	TUG, posterior-anterior sway, medial-lateral sway	Baseline and completion of intervention
Garrett (2013)[28]	6	12	NR	NR	0-2 score GNDS	Physical activity	Group exercise (PT-led)	Group exercise led by a yoga instructor Or group exercise led by an FI	10 wk	MSIS-29v2, MFIS, 6MWT	Baseline, 12 wk, and 24 wk
Hoang (2016)[45]	7	44	Tx 53.4 (10.7) Control 51.4 (12.8)	Tx (7/21) Control (5/17)	EDSS 2-6	Physical activity	Step training	Usual physical activity	12 wk	CSRT, SST time, postural sway, gait speed, cognitive tests, 9HPT, and MSFC	Baseline and completion of intervention

Kargarfard (2012)[46]	7	21	Tx 33.7 (8.6) Control 31.6 (7.7)	NR	EDSS <3.5	Physical activity	Aquatic exercise	Maintain current treatment	8 wk	MFIS and MSQOL54	Baseline, 4 wk, and 8 wk
Learmonth (2017)[47]	6	51	Tx 48.7 (10.4) Control 48.2 (9.1)	Tx (1/28) Control (1/27)	EDSS <6	Physical activity	Home-based exercise	Wait-list control	4 mo	GLTEQ, MSWS, ABC, FSS, LLFDI, HADS, MPQ, MSIS, LMSQOL, ESES, EGPS, MOEES, EBBS, and SPS	Baseline and 4 mo
Romberg (2004)[48]	6	91	Tx 43.8 (6.3) Control 43.9 (7.1)	Tx (17/30) Control (17/31)	EDSS 1-5.5	Physical activity	Strength and aerobic training	Normal physical activity habits	6 mo (tx group 3 wk inpatient and 23 wk at home)	Walk speed measured by 7.62MWT and a 500MWT; knee extension and flexion on a dynamometer, upper extremity endurance, gross manual dexterity (box and block test), VO2 peak, static balance using the Equiscale	Baseline and 6 mo
Samaei (2016)[49]	7	31	Tx 33.9 (7.3) Control 32.1 (7.6)	NR	Walk without an aid	Physical activity	Downhill treadmill walking	Uphill treadmill walking	4 wk	MFIS, Modified RMI, GNDS, 2MWT, 25FWT, TUG, Biodex Balance System, and knee flexion and extension strength	Baseline, 4 wk, and 8 wk
Sandroff (2016)[50]	6	10	Tx 41.6 (11.5) Control 44.2 (6.6)	Tx (0/5) Control (0/5)	EDSS 1.5-4.0	Physical activity	Treadmill walking	Wait-list control	12 wk	SDMT, DKEFS, RT, IC-RT, 6MWT, VO2 peak, TTE	Baseline and 12 wk
Tarakci (2013)[51]	8	99	Tx 41.49 (9.37) Control 39.65 (11.18)	Tx (17/34) Control (18/30)	EDSS 2-6.5	Physical activity	Group exercise	Wait-list control	12 wk	BBS, 10-m walk test, 10-steps climbing test, MAS, FSS, MSIQoL	Baseline and 12 wk
Brichetto (2015)[52]	6	32	Tx 50.1 (13.5) Control 51.0 (8.9)	Tx (4/11) Control (5/12)	EDSS mean 3.7	Rehabilitation	PRG	TRG	4 wk	BBS, CS, CDP test, and MFIS	Baseline, 4 wk
Hebert (2011)[53]	8	38	Tx 46.8 (10.5) Control 1 42.6 (10.4) Control 2 50.2 (9.2)	Tx (3/9) Control 1 (2/11) Control 2 (2/11)	Walk 100 m with or without a single-sided device	Rehabilitation	Vestibular rehab	Exercise control or wait-list control	6 wk	MFIS, posturography, 6MWT, DHI, BDI-II	Baseline; wk 2 and 4 control); (6, 8, and 10 (intervention); 12 and 14 (follow-up)

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Table 1. (*continued*)

Author (y)	PEDro Score	*N*	Mean Age (SD)	Sex (male/female)	Severity of MS[3]	Intervention Category	Tx	Control	Duration	Outcome Measures	Assessment Times
Lord (1998)[54]	6	20	Tx 52.1 (11.0) Control 54.1 (8.1)	Not specified	6-13 on RMI	Rehabilitation	Facilitation PT	Task-oriented PT	15 tx over 5-7 wk	10-m timed walk, RMI, stride length, Rivermead Visual Gait Assessment, and BBS	Baseline and 1 wk after treatment
Rietberg (2014)[55]	6	44	Tx 45 (9.9) Control 47 (8.6)	Tx (9/14) Control (7/17)	Median EDSS 3	Rehabilitation	Outpatient rehab (MDR)	MS-nurse consult	12 wk	Checklist Individual Strength (CIS-20R), MFIS, FSS, FIM, DIP, MSIS, and IPA	Baseline (1 wk pretreatment and prior to beginning treatment), 12 wk, and 24 wk
Al-Smadi (2003)[26]	7	15	NR	NR	NR	Technology	TENS 1 (4 Hz, 200 T) or TENS2 (110 Hz, 200)	Placebo TENS	6 wk with 4-wk follow-up	VAS for LBP, right leg pain and left leg pain, Leeds Multiple Sclerosis Quality of Life questionnaire, Roland Morris Disability Questionnaire, SF36v1, MPQ.	Wk 1, 6, and 10
Chitsaz (2009)[56]	6	55	Tx 34.3 (6.9) Control 30.5 (8.7)	Tx (6/23) Control (9/21)	EDSS <6	Technology	Self-applied TENS	Nortriptyline	8 wk	Pain VAS	Baseline and 2, 4, and 8 wk
De Giglio (2015)[57]	8	33	Tx 44.64 (7.63) Control 42.99 (9.42)	Tx (4/14) Control (5/12)	EDSS 2-6	Technology	8 wk of training in Kawashima Brain Training	Wait-list control	8 wk	EDSS, ST, PASAT, SDMT, MFIS, MSQoL54	Baseline and 8 wk
Efterkhar-sadat (2015)[58]	6	30	Tx 33.4 (8.1) Control 37.0 (8.3)	Tx (5/10) Control (3/12)	Walking patients	Technology	PST using the Biodex Balance System SD; crossover study	No intervention; crossover study	12 wk	MMT for wrist, hip and knee, Ashworth Scale, Romberg, TUG, BBS, FRt, FRi, OSI	Baseline and 12 wk
Kalron (2016)[59]	7	30	Tx 47.3 (9.6) Control 43.9 (10.6)	Tx (5/10) Control (6/9)	EDSS <6	Technology	VR balance training using the CAREN system	Conventional balance exercise	6 wk	CoP, FRT, BBS, FSST, FES-I	Baseline and 6 wk

Prosperini (2013)[60]	6	34	Tx 35.3 (8.6) Control 37.41 (8.8)	Tx (5/13) Control (6/12)	EDSS 1.5-5	Technology	Nintendo WBB; crossover study	WBBS weeks 1-12; crossover study	12 wk	Force platform measures, FSST, 25FWT, MSIS29	Baseline, 12 wk, and 24 wk
Uszynski (2016)[61]	7	24	Tx 45.5 (median) Control 54	Tx (4/10) Control (0/13)	Diagnosed MS min gait impairments	Technology	Whole body vibration	Standard exercise	12 wk	Isokinetic muscle strength, vibration threshold, TUG, MBT, 6MWT, MSIS29, MFIS, and VAS	Baseline and 12 wk
Vaney (2012)[62]	6	48	Tx 58.23 (9.4) Control 54.22 (11.28)	RD	EDSS 3-6.5	Technology	RAGT	Walking	3 wk	Walking speed, activity level, well-being VAS, and EQ-5D European VAS, BBS, RMI, modified Ashworth Scale	Baseline, 3 wk, 8 wk, 9 mo
Wolfsegger (2014)[63]	6	17	Tx 43.0 (13.4) Control 39.3 (10.6)	Tx (1/8) Control (1/7)	EDSS <5	Technology	Whole body vibration	Sham whole body vibration	3 wk	Gait velocity, stride length, double support phase, single-step variability, TUG	Baseline and 3, 4, and 5 wk
Bombardier (2008)[64]	7	13	Tx 47.5 Control 45	Tx (17/53) Control (12/48)	EDSS <5.5	Psychological	Motivational interviewing-based telephone counseling	Wait-list control	12 wk	Health Promoting Lifestyle Profile II (HPLP II), MFIS, SF-36 (with an MCS and PCS), MOS, MSQoLI, MSFC, TMT-A, TMT-B, lower limb strength, aerobic capacity, self-selected walking speed	Baseline and 12 wk
Grossman (2010)[65]	8	15	Tx 45.93 (10.35) Control 48.68 (10.58)	Tx (17/59) Control (14/60)	EDSS <6	Psychological	Mindfulness (MBI)	UC	8 wk	PQOLC, HAQUAMS, CES-D, MFIS, and STAI	Baseline, 8 wk, and 6 mo
Suh (2015)[66]	6	68	Tx 50.1 (8.1) Control 48.0 (9.4)	Tx (4/30) Control (8/26)	Significant problems with daily activities	Psychological	SCT	Information regarding stress management	6 wk	GLTEQ, EXSE, MOEES, LL-FDI, EGPS, SSES, PDDS	Baseline and 6 wk

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Table 1. (*continued*)

Author (y)	PEDro Score	*N*	Mean Age (SD)	Sex (male/ female)	Severity of MS[3]	Intervention Category	Tx	Control	Duration	Outcome Measures	Assessment Times
Turner (2016)[67]	8	63	Tx 52.7 (11.6) Control 53.6 (13.1)	Tx (22/9) Control (19/14)	EDSS <6.5	Psychological	Telephone counseling	Self-directed physical activity education	6 mo	MFIS, depression module of the PHQ-9, GLTEQ	Baseline, 3 mo, and 6 mo
Van Kessel (2008)[68]	7	72	Tx 42.89 (9.29) Control 47.03 (9.45)	Tx (7/28) Control (10/27)	EDSS <6	Psychological	CBT	Relaxation training	8 wk	FSS, WSAS, HADS, PSS, SPQ, BIPQ	Baseline, 8 wk, 3 and 6 mo post-treatment.
Bitarafan (2016)[69]	10	93	Tx 30.4 (1.0) Control 23.3 (1.0)	Tx (12/35) Control (12/34)	EDSS <5	Alternative	RP for 12 mo	Placebo	1 y	MFIS, BDI II	Baseline and 12 mo
Fox (2016)[25]	8	94	Tx 1 53.97 (9.19) Tx 2 54.60 (11.54) Control 53.78 (9.72)	Tx (5/28) Tx2 (10/25) Control (11/21)	EDSS 4.0-6.5	Alternative	Pilates or standard exercises	Relaxation sessions	12 wk	10MTW, walking speed based on the 10MTW, functional reach, MSWS-12 v2, ABC, Numeric Rating Scale on difficulty carrying a drink while walking	Baseline, 12 wk, 16 wk
Gandolfi (2014)[70]	6	22	Tx 50.83 (8.42) Control 50.1 (6.29)	Tx (5/7) Control (1/9)	EDSS 1.5-6.5	Alternative	RAGT	SIBT	6 wk	BBS, ABC, SOBT, SA, FSS, cadence, step length, single and double support time, MSQoL54	Baseline, 6 wk, and 1-mo follow-up
Gandolfi (2015)[71]	7	80	Tx 47.21 (6.9) Control 49.56 (6.85)	Tx (11/28) Control (10/31)	EDSS 1.5-6.0	Alternative	SIBT	Conventional rehab	5 wk	BBS, ABC, MSQoL54, FSS, number of falls, and SOT	Baseline, 5 wk, and 1 mo follow-up
Piatkowski (2009)[72]	7	37	Tx 44 (8.3) Control 47.5 8.6)	Tx (2/17) Control (5/13)	Relapsing/ remitting ambulatory patients	Alternative	BEMER	Sham therapy	12 wk	MFIS, FSS, CES-D, ADS-L, MSFC, and EDSS	Baseline, 6 wk, and 12 wk
Razazian (2016)[27]	6	54	Tx 1 33.33 (7.4) Tx 2 35.39 (6.89) Control 33.11 (6.6)	Tx 1 (0/18) Tx 2 (0/18) Control (0/18)	EDSS <6	Alternative	Yoga or aqua exercise	Non-exercise group	8 wk	FSS, BDI, paresthesia VAS	Baseline and 8 wk

Siev-Ner (2003)[73]	8	53	Tx 46.2 (9.3) Control 49.2 (11.0)	Tx (10/17) Control (9/17)	MS with paresthesias and/or spasticity	Alternative	Reflexology once/wk for 45 min	Nonspecific calf massage	11 wk	Intensity of paresthesias by VAS, urinary symptoms by AUA6 scale, muscle strength by MRC scale and spasticity by Ashworth Scale	Baseline, 6 wk, 11 wk, and 23 wk
Widener (2009)[74]	7	36	Tx 55.7 (9.7) Control 53.2 (9.7)	Not specified	EDSS 2-5	Alternative	BBTW	No weights, or standard weight placement of 1.5% body weight	1 session with 2 phases	TUG, sharpened Romberg, 260° turns, 25FWT, posturography	Baseline and following intervention
Wiles (2001)[75]	7	40	NR	NR	EDSS 4-6.5	Alternative	Home physiotherapy twice/wk for 45 min for 8 wk	No treatment	8 wk	RMI, balance time, 6MWT, 9HPT	Baseline and following intervention

ABC, Activities-specific Balance Confidence Scale; *ADS-L,* general depression scale—long version; *AUA,* American Urological Association; *BBS,* Berg Balance Scale; *BBTW,* balance-based torso weighting; *BDI,* Beck Depression Inventory; *BEMER,* bio-electro magnetic energy regulation; *BIPQ,* Brief Illness Perceptions Questionnaire; *CBT,* cognitive behavioural therapy; *CDP,* computerized dynamic posturography; *CES-D,* Center for Epidemiologic Depression Scale; *CIS-20R,* Checklist Individual Strength; *CoP,* centre of pressure; *CS,* composite score; *CSRT,* choice stepping reaction time; *DHI,* Dizziness Handicap Inventory; *DIP,* Disability and Impact Profile; *DKEFS,* Delis-Kaplan Executive Function System; *EBBS,* Exercise Benefits and Barriers Scale; *EDSS,* Expanded Disability Status Scale; *EGPS,* Exercise Goal Setting and Planning Scale; *ESES,* Exercise self-efficacy scale; *FES-I,* Fals Efficacy Scale International; *FI,* fitness instructor; *FIM,* Functional Independence Measure; *500MWT,* 500-m walk test; *FR,* functional reach; *FRi,* Fall Risk index; *FRt,* Fall Risk test; *FRT,* Functional Reach Test; *FSS,* fatigue severity scale; *FSST,* Four Square Step Test; *GLTEQ,* Godin Leisure Time Questionnaire; *GNDS,* Guy's Neurological Disability Scale; *HADS,* Hospital Anxiety and Depression Scale; *HAQUAMS,* Hamburg Quality of Life Questionnaire in MS; *HPLP II,* Health Promoting Lifestyle Profile II; *IC-RT,* interference control reaction time; *IPA,* Impact on Participation and Autonomy; *LLFDI,* Late-Life Function and Disability Instrument; *LMSQOL,* Leeds MS Quality of Life Scale; *MAS,* Modified Ashworth Scale; *MBI,* mindfulness-based intervention; *MBT,* Mini-BESTest; *MCS,* mental component score; *MDI,* major depression inventory; *MDR,* Multidisciplinary Outpatient Rehabilitation; *MFIS,* modified fatigue impact scale; *MMT,* Manual Muscle Test; *MOEES,* Multidimensional Outcome Expectancies for Exercise Scale; *MOS,* Medical Outcomes Study; *MPQ,* Short form McGill Pain Questionnaire; *MRC,* Medical Research Council; *MS,* multiple sclerosis; *MSFC,* MS functional composite; *MSIQoL,* MS International Quality of Life; *MSIS,* MS Impact Scale; *MSIS-29v2,* MS Impact Scale 29 version 2; *MSQOL54,* MS Quality of Life-54; *MSWS12,* MS Walking Scale; *9HPT,* 9-hole peg test; *NMES,* neuromuscular electric stimulator; *NR,* not reported; *OSI,* Overall Stability Index; *PASAT,* Paced Auditory Serial Addition Test; *PCS,* physical component score; *PDDS,* Patient Determined Disease Steps; *PEDro,* Physiotherapy Evidence Database; *PHQ-9,* Patient Health Questionnaire; *PQOLC,* Profile of Health-Related Quality of Life in Chronic Disorders; *PRT,* progressive resistance training; *PRG,* personalized rehab group; *PSS,* Perceived Stress Scale; *PST,* postural stability training; *PT,* physical therapist/physical therapy; *RAGT,* robot-assisted gait training; *RD,* Random Distribution (sex not given); *RMI,* Rivermead Mobility Index; *RP,* retinyl palmitate; *RT,* reaction time; SA, Stabilometric Assessment; *SCT,* social cognitive theory; *SDMT,* Symbol Digit Modalities Test; *SF-36,* 36-Item Short-Form Health Survey; *SIBT,* sensory integration balance training; *6MWT,* 6-minute walk test; *7.62MWT,* 7.62-m walk test; *SOBT,* Sensory Organization Balance Test; *SOT,* Sensory Organisation Balance Test; *SPQ,* Sleep Problems Questionnaire; *SPS,* Social Provisions Scale; *SSES,* Social Support and Exercise Survey; *SST,* Stroop Stepping Test; *STAI,* Spielberger Trait Anxiety Inventory; *10MWT,* 10-metre Timed Walk Test; *TENS,* transcutaneous electrical nerve stimulation; *TMT-A,* Trail-Making Test part A; *TMT-B*, Trail Making Test part B; *TRG,* traditional rehab group; *TTE,* treadmill time to exhaustion; *TUG,* timed up and go; *25FWT,* timed 25-ft walk test; *2MWT,* 2-minute walk test; *Tx*, treatment; *UC,* usual care; *VAS,* visual analog scale; *VR,* virtual reality; *WBBS,* Wii balance board system; *WSAS,* Work and Social Adjustment Scale.

Table 2. *PEDro Score Distribution*

Section	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10	10/10	Total Papers	Total <6	Total ≥6
Total	0	1	7	23	38	27	21	11	0	2	130	69	61

PEDro, Physiotherapy Evidence Database.

psychologists/psychiatrists. It would include any education delivered by one of the above, as most of these did, with interventions such as telephone counseling and cognitive behavioral therapy. Rehabilitation included any interventions specifically referred to as rehabilitation based, such as personalized rehabilitation group and vestibular rehabilitation. Comparatively, *technology* referred to any intervention that incorporated technology, such as Nintendo Wii, virtual reality, or transcutaneous electrical nerve stimulation, and *alternative* referred to alternative or complementary approaches such as reflexology, Pilates, or diet (Figure 1).

Risk of Bias Assessment

Full-text articles that met criteria were screened for risk of bias according to the PEDro checklist (Table 2). To explore the risk of publication bias across all studies, funnel plots were constructed and asymmetry formally tested using Egger's regression test[37] (Fig 3). The outcome measures pain and spasticity had insufficient data points to conduct a publication bias analysis. The funnel plot for balance appeared to be reasonably symmetrical, and the intercept for Egger's test was -1.28 (95% CI: -3.05 to 0.50, $t = 1.54$, $df = 14$, $P = .15$), suggesting a low risk of publication bias. Comparatively, fatigue, function, and quality-of-life outcomes demonstrated a positive intercept, suggesting smaller studies tended to report larger than average effects.[36] For these 3 outcomes, the funnel plots appeared skewed and Egger's test produced significant 1-tailed P value for all intercepts ($P < .05$). Thus the studies that reported on fatigue, function, and quality of life may be subject to publication bias.

Meta-analysis

The interventions were grouped into the 6 subcategories for the purposes of meta-analysis with interpretation for outcomes reported in 3 or more studies.[38] Hedge's g with 95% CIs, significance testing, and forest plots for the 6 primary outcomes are individually presented in Figures 4 through 7. Each forest plot reports the overall effect of NPTs on each outcome and the individual effect of each subcategory of intervention.

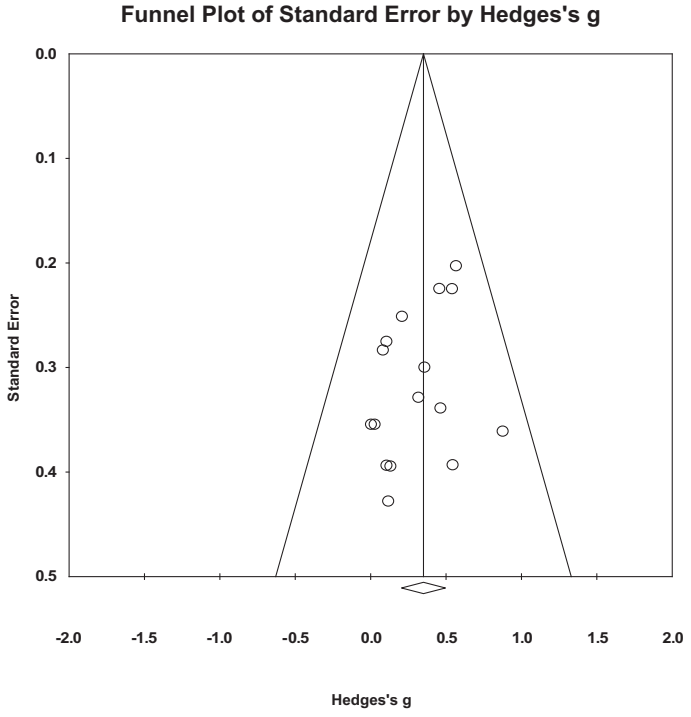


Fig 3. *Funnel plot of potential publication bias for the studies reporting balance as an outcome.*

Group by Treatment	Study name	Outcome	Hedges's g	Variance	Lower limit	Upper limit	Z-Value	*P*-Value
Alternative	Gandolfi (2015)	Fatigue	0.28	0.05	-0.16	0.71	1.25	.212
Alternative	Piatkowski (2009)	Combined	0.38	0.11	-0.26	1.01	1.16	.245
Alternative	Bitarafan (2016)	Fatigue	1.17	0.05	0.73	1.60	5.24	.000
Alternative	Razazian (2016)	Fatigue	2.03	0.16	1.24	2.82	5.02	.000
Alternative			0.92	0.13	0.23	1.62	2.61	.009
Physical activity	Learmonth (2017)	Fatigue	0.12	0.08	-0.42	0.66	0.42	.671
Physical activity	Garrett (2013)	Fatigue	0.17	0.05	-0.26	0.60	0.77	.440
Physical activity	Tarakci (2013)	Fatigue	1.35	0.05	0.91	1.78	6.09	.000
Physical activity	Kargarfard (2012)	Fatigue	3.05	0.40	1.81	4.28	4.84	.000
Physical activity			1.03	0.22	0.10	1.95	2.18	.030
Psychological	Garcia (2012)	Combined	0.15	0.17	-0.65	0.95	0.37	.710
Psychological	Bombardier (2008)	Fatigue	0.22	0.03	-0.12	0.57	1.27	.204
Psychological	van Kessel (2008)	Fatigue	0.88	0.06	0.40	1.35	3.58	.000
Psychological	Turner (2016)	Fatigue	3.31	0.15	2.56	4.07	8.58	.000
Psychological			1.12	0.36	-0.06	2.30	1.87	.062
Rehab	Rietberg (2014)	Combined	0.15	0.09	-0.43	0.73	0.50	.617
Rehab	Brichetto (2015)	Fatigue	0.43	0.12	-0.25	1.11	1.23	.217
Rehab	Hebert (2011)	Fatigue	1.04	0.17	0.23	1.85	2.51	.012
Rehab			0.48	0.06	-0.01	0.96	1.91	.056
Resistance	Dalgas (2010)	Combined	0.46	0.13	-0.24	1.15	1.28	.200
Resistance	Coote (2015)	Fatigue	0.50	0.16	-0.28	1.29	1.26	.208
Resistance			0.48	0.07	-0.04	1.00	1.79	.073
Technology	Vaney (2012)	Combined	0.19	0.08	-0.37	0.75	0.67	.500
Technology	Uszynski (2016)	Fatigue	0.31	0.16	-0.47	1.09	0.78	.436
Technology	De Giglio (2015)	Fatigue	2.06	0.18	1.23	2.89	4.86	.000
Technology			0.83	0.32	-0.28	1.94	1.46	.144
Overall			0.66	0.02	0.38	0.94	4.60	.000

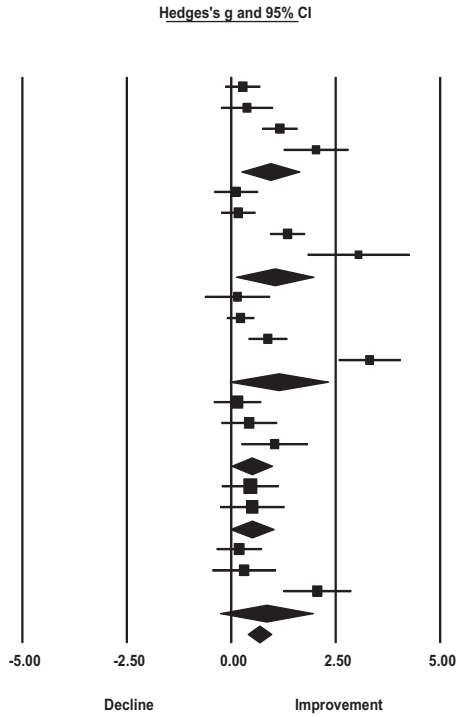
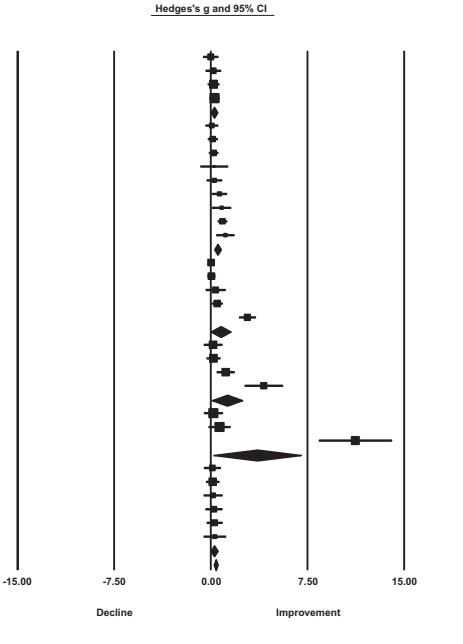


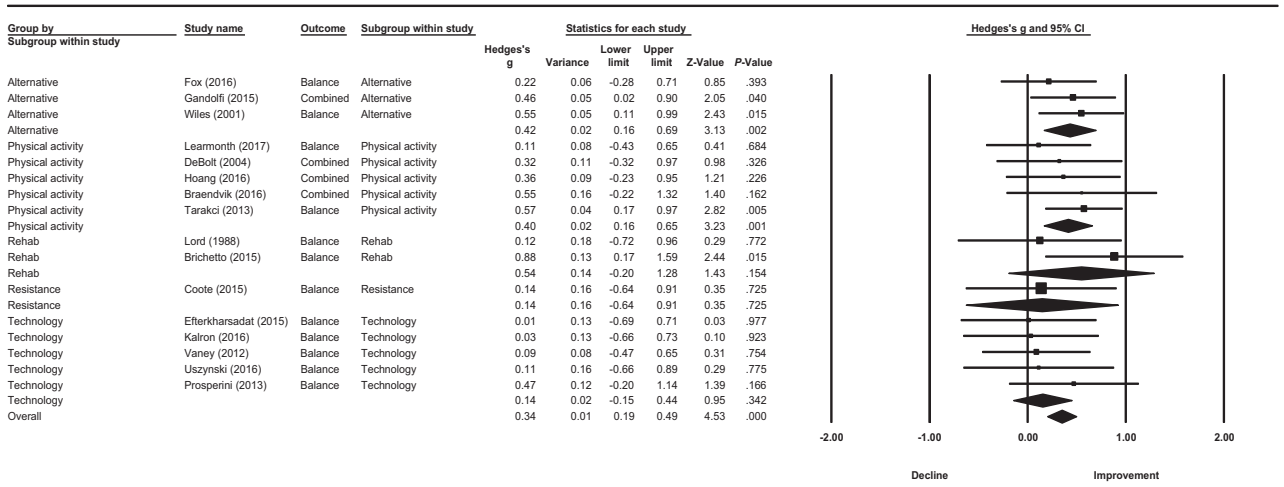
Fig 4. *Effect sizes with heterogeneity statistics for the effects of different nonpharmaceutical approaches on the outcome fatigue.*

Group by Subgroup within study	Study name	Outcome	Subgroup within study	Hedges's g	Variance	Lower limit	Upper limit	Z-Value	*P*-Value
Alternative	Piatkowski (2009)	Functional	Alternative	0.00	0.10	-0.63	0.63	0.00	1.000
Alternative	Widener (2009)	Combined	Alternative	0.20	0.11	-0.44	0.84	0.61	.540
Alternative	Fox (2016)	Combined	Alternative	0.22	0.06	-0.28	0.71	0.87	.387
Alternative	Wiles (2001)	Combined	Alternative	0.30	0.05	-0.14	0.74	1.34	.181
Alternative				0.21	0.02	-0.06	0.47	1.53	.127
Physical activity	Learmonth (2017)	Combined	Physical activity	0.08	0.08	-0.46	0.62	0.30	.767
Physical activity	Garrett (2013)	Combined	Physical activity	0.16	0.05	-0.27	0.59	0.73	.467
Physical activity	Romberg (2004)	Combined	Physical activity	0.23	0.04	-0.18	0.63	1.08	.280
Physical activity	Sandroff (2016)	Functional	Physical activity	0.27	0.33	-0.86	1.39	0.47	.642
Physical activity	DeBolt (2004)	Functional	Physical activity	0.28	0.11	-0.36	0.92	0.85	.393
Physical activity	Hoang (2016)	Combined	Physical activity	0.68	0.10	0.05	1.30	2.12	.034
Physical activity	Braendvik (2016)	Functional	Physical activity	0.84	0.16	0.05	1.63	2.09	.037
Physical activity	Tarakci (2013)	Combined	Physical activity	0.90	0.04	0.49	1.31	4.28	.000
Physical activity	Samei (2016)	Combined	Physical activity	1.14	0.14	0.39	1.88	2.99	.003
Physical activity				0.48	0.02	0.22	0.74	3.65	.000
Psychological	O'Hara (2002)	Functional	Psychological	0.03	0.02	-0.27	0.33	0.19	.851
Psychological	Bombardier (2008)	Functional	Psychological	0.06	0.03	-0.29	0.40	0.32	.753
Psychological	Garcia (2012)	Combined	Psychological	0.37	0.17	-0.43	1.18	0.91	.361
Psychological	Suh (2015)	Functional	Psychological	0.50	0.06	0.02	0.97	2.04	.041
Psychological	Turner (2016)	Functional	Psychological	2.85	0.13	2.15	3.54	8.01	.000
Psychological				0.72	0.16	-0.05	1.50	1.83	.068
Rehab	Hebert (2011)	Functional	Rehab	0.18	0.15	-0.58	0.94	0.47	.640
Rehab	Rietberg (2014)	Functional	Rehab	0.21	0.09	-0.37	0.80	0.72	.472
Rehab	Brichetto (2015)	Functional	Rehab	1.16	0.14	0.42	1.89	3.10	.002
Rehab	Lord (1988)	Functional	Rehab	4.11	0.61	2.59	5.64	5.28	.000
Rehab				1.22	0.36	0.05	2.40	2.04	.041
Resistance	Coote (2015)	Combined	Resistance	0.21	0.16	-0.57	0.98	0.52	.604
Resistance	Broekmans (2011)	Combined	Resistance	0.68	0.21	-0.21	1.57	1.50	.134
Resistance	Dalgas (2010)	Functional FS	Resistance	11.22	2.15	8.35	14.10	7.65	.000
Resistance				3.55	3.00	0.16	6.94	2.05	.040
Technology	Efterkharsadat (2015)	Functional	Technology	0.13	0.13	-0.57	0.82	0.35	.725
Technology	Vaney (2012)	Combined	Technology	0.15	0.08	-0.41	0.71	0.52	.600
Technology	Uszynski (2016)	Functional	Technology	0.18	0.16	-0.59	0.96	0.46	.643
Technology	Kalron (2016)	Combined	Technology	0.25	0.13	-0.45	0.95	0.70	.484
Technology	Prosperini (2013)	Combined	Technology	0.30	0.11	-0.37	0.96	0.87	.382
Technology	Wolfsegger (2014)	Functional	Technology	0.31	0.22	-0.60	1.22	0.67	.503
Technology				0.21	0.02	-0.07	0.49	1.44	.149
Overall				0.34	0.01	0.19	0.49	4.47	.000



Meta Analysis

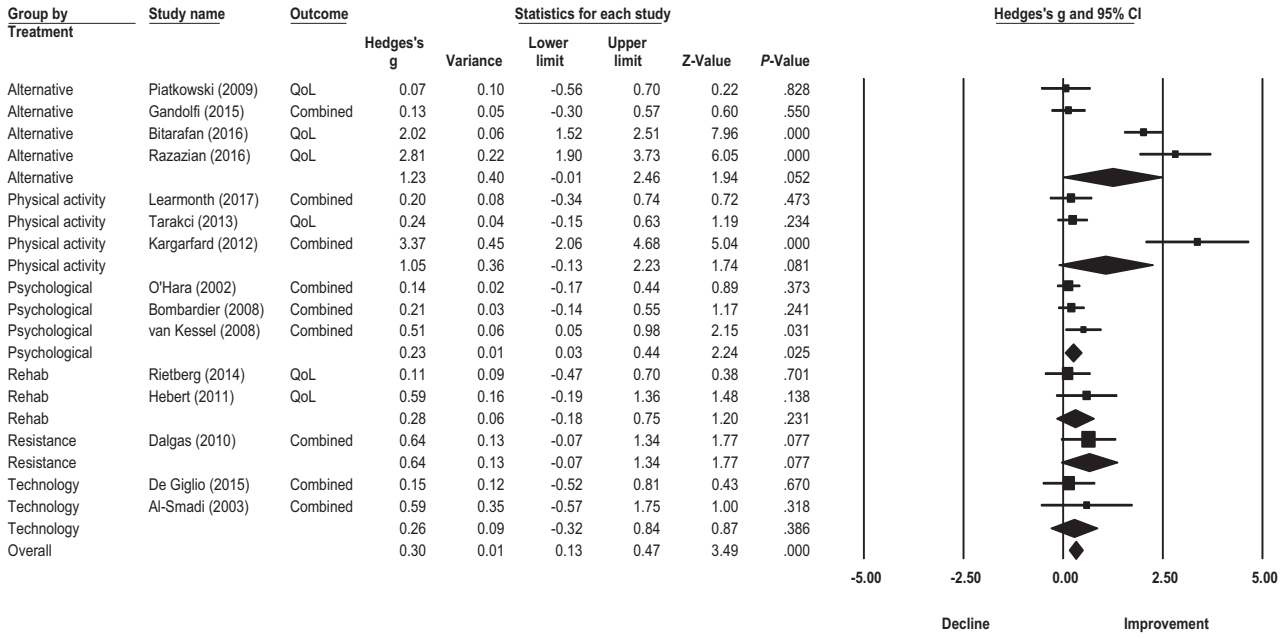
Fig 5. *Effect sizes with heterogeneity statistics for the effects of different nonpharmaceutical approaches on the outcome function.*



Group by Subgroup within study	Study name	Outcome	Subgroup within study	Hedges's g	Variance	Lower limit	Upper limit	Z-Value	P-Value
Alternative	Fox (2016)	Balance	Alternative	0.22	0.06	-0.28	0.71	0.85	.393
Alternative	Gandolfi (2015)	Combined	Alternative	0.46	0.05	0.02	0.90	2.05	.040
Alternative	Wiles (2001)	Balance	Alternative	0.55	0.05	0.11	0.99	2.43	.015
Alternative				0.42	0.02	0.16	0.69	3.13	.002
Physical activity	Learmonth (2017)	Balance	Physical activity	0.11	0.08	-0.43	0.65	0.41	.684
Physical activity	DeBolt (2004)	Combined	Physical activity	0.32	0.11	-0.32	0.97	0.98	.326
Physical activity	Hoang (2016)	Combined	Physical activity	0.36	0.09	-0.23	0.95	1.21	.226
Physical activity	Braendvik (2016)	Combined	Physical activity	0.55	0.16	-0.22	1.32	1.40	.162
Physical activity	Tarakci (2013)	Balance	Physical activity	0.57	0.04	0.17	0.97	2.82	.005
Physical activity				0.40	0.02	0.16	0.65	3.23	.001
Rehab	Lord (1988)	Balance	Rehab	0.12	0.18	-0.72	0.96	0.29	.772
Rehab	Brichetto (2015)	Balance	Rehab	0.88	0.13	0.17	1.59	2.44	.015
Rehab				0.54	0.14	-0.20	1.28	1.43	.154
Resistance	Coote (2015)	Balance	Resistance	0.14	0.16	-0.64	0.91	0.35	.725
Resistance				0.14	0.16	-0.64	0.91	0.35	.725
Technology	Efterkharsadat (2015)	Balance	Technology	0.01	0.13	-0.69	0.71	0.03	.977
Technology	Kalron (2016)	Balance	Technology	0.03	0.13	-0.66	0.73	0.10	.923
Technology	Vaney (2012)	Balance	Technology	0.09	0.08	-0.47	0.65	0.31	.754
Technology	Uszynski (2016)	Balance	Technology	0.11	0.16	-0.66	0.89	0.29	.775
Technology	Prosperini (2013)	Balance	Technology	0.47	0.12	-0.20	1.14	1.39	.166
Technology				0.14	0.02	-0.15	0.44	0.95	.342
Overall				0.34	0.01	0.19	0.49	4.53	.000

Meta Analysis

Fig 6. *Effect sizes with heterogeneity statistics for the effects of different nonpharmaceutical approaches on the outcome balance.*



Group by Treatment	Study name	Outcome	Hedges's g	Variance	Lower limit	Upper limit	Z-Value	P-Value
Alternative	Piatkowski (2009)	QoL	0.07	0.10	-0.56	0.70	0.22	.828
Alternative	Gandolfi (2015)	Combined	0.13	0.05	-0.30	0.57	0.60	.550
Alternative	Bitarafan (2016)	QoL	2.02	0.06	1.52	2.51	7.96	.000
Alternative	Razazian (2016)	QoL	2.81	0.22	1.90	3.73	6.05	.000
Alternative			1.23	0.40	-0.01	2.46	1.94	.052
Physical activity	Learmonth (2017)	Combined	0.20	0.08	-0.34	0.74	0.72	.473
Physical activity	Tarakci (2013)	QoL	0.24	0.04	-0.15	0.63	1.19	.234
Physical activity	Kargarfard (2012)	Combined	3.37	0.45	2.06	4.68	5.04	.000
Physical activity			1.05	0.36	-0.13	2.23	1.74	.081
Psychological	O'Hara (2002)	Combined	0.14	0.02	-0.17	0.44	0.89	.373
Psychological	Bombardier (2008)	Combined	0.21	0.03	-0.14	0.55	1.17	.241
Psychological	van Kessel (2008)	Combined	0.51	0.06	0.05	0.98	2.15	.031
Psychological			0.23	0.01	0.03	0.44	2.24	.025
Rehab	Rietberg (2014)	QoL	0.11	0.09	-0.47	0.70	0.38	.701
Rehab	Hebert (2011)	QoL	0.59	0.16	-0.19	1.36	1.48	.138
Rehab			0.28	0.06	-0.18	0.75	1.20	.231
Resistance	Dalgas (2010)	Combined	0.64	0.13	-0.07	1.34	1.77	.077
Resistance			0.64	0.13	-0.07	1.34	1.77	.077
Technology	De Giglio (2015)	Combined	0.15	0.12	-0.52	0.81	0.43	.670
Technology	Al-Smadi (2003)	Combined	0.59	0.35	-0.57	1.75	1.00	.318
Technology			0.26	0.09	-0.32	0.84	0.87	.386
Overall			0.30	0.01	0.13	0.47	3.49	.000

Fig 7. *Effect sizes with heterogeneity statistics for the effects of different nonpharmaceutical approaches on the outcome quality of life.*

Subgroup Analyses

Effects on Fatigue. Fatigue was the most common outcome measure across all studies, with 21 papers having some form of measure of fatigue. The most common measures used were the Fatigue Impact Scale, Modified Fatigue Impact Scale, or the Fatigue Severity Scale. Quality-of-life and functional outcomes were nearly as common, with 32 papers including each of these outcomes. Other outcomes were less common, with balance being included in 19 papers, spasticity in 7, and pain in only 5 papers.

Overall, from pre to post, NPTs combined produced a *large* effect for fatigue symptoms (k = 20, $g = 0.66$; 95% CI: 0.94-4.60, $P < .001$). The Z value for testing the null hypothesis (that there is no effect on fatigue) was 4.60 ($P < .001$), thus we can reject the null hypothesis and conclude that NPTs lead to a significant improvement in self-reported fatigue symptoms. The Q statistic was 85.16

($df = 19$, $P < .001$), therefore the true effect size varies from study to study. I^2 was 85.16, thus approximately 85% of the variance in the observed effects represents variance in the true effects.

We also examined the specific effect of each intervention approach independently (Fig 4). In relation to fatigue, physical activity (k = 4, $g = 1.03$; 95% CI: 0.10-1.95, $P < .030$) and alternative interventions both had a *large* effect (k = 4, $g = 0.92$; 95% CI: 0.23-1.62, $P = .009$). The remaining intervention approaches had a nonsignificant effect on fatigue outcomes, including psychological interventions (k = 4, $g = 1.12$; 95% CI: -0.06 to 2.30, $P = .062$), rehabilitation interventions (k = 3, $g = 0.48$; 95% CI: -0.01 to 0.96, $P = .056$), and technology-based interventions (k = 3, $g = 0.66$; 95% CI: -0.28 to 1.94, $P = .144$).

Effects on Function. Overall, NPTs combined produced a *medium* effect size for improvement (k = 31, $g = 0.34$; 95% CI: 0.19-0.49, $P < .001$). The heterogeneity of these studies was high ($Z = 4.47$, $P < .001$; $Q = 159.10$; $df = 30$, $P < .001$; $I^2 = 81.14$). When examining intervention approaches individually (Fig 5), 3 approaches reported *large* effects on function including physical activity (k = 9, $g = 0.48$; 95% CI: 0.22-0.74, $P < .001$), rehabilitation (k = 4, $g = 1.22$; 95% CI: 0.05-2.40, $P = .041$), and resistance training (k = 3, $g = 3.55$; 95% CI: 0.16-6.94, $P = 0.040$). The remaining 3 approaches did not have a significant effect on function scores including alternative interventions (k = 4, $g = 0.21$; 95% CI: -0.06 to 0.47, $P = .127$), psychological interventions (k = 5, $g = 0.72$; 95% CI: -0.05 to 1.50, $P = .068$), and technology-based interventions (k = 6, $g = 0.21$; 95% CI: -0.07 to 0.49, $P = .149$).

Effects on Balance. Overall, NPTs combined produced a *medium* effect size for improving balance (k = 14, $g = 0.34$; 95% CI: 0.19-0.49, $P < .001$). I^2 was < 0.0001, thus the risk of sampling error for studies examining the outcome balance is high ($Z = 4.53$, $P < .001$; $Q = 9.29$; $df = 15$, $P = .86$). When examining intervention approaches individually, 3 approaches were used by 3 or more studies (Fig 6). Physical activity interventions had a *medium* effect on improving balance (k = 5, $g = 0.40$; 95% CI: 0.16-0.65, $P = .001$), as did alternative interventions (k = 3, $g = 0.42$; 95% CI: 0.16-0.69, $P = .002$), whereas interventions that used technology had a nonsignificant effect (k = 5, $g = 0.14$; 95% CI: -0.15 to 0.44, $P = .34$). The remaining 4 intervention approaches were assessed in 2 or fewer studies, and thus only considered in the combined analysis.

Effects on Quality of Life. Overall, NPTs combined produced a *medium* effect on quality of life (k = 15, $g = 0.30$; 95% CI: 0.13-0.47, $P < .001$). The heterogeneity of these studies was high ($Z = 3.49$, $P < .001$; $Q = 5.01$; $df = 5$, $P = .414$; $I^2 = 85.58$). Three intervention approaches were tested in at least 3 independent studies (Fig 7). Alternative approaches had a *large* effect on quality-of-life outcomes (k = 4, $g = 1.23$; 95% CI: -0.01 to 2.46, $P = .052$), and psychological approaches had a *small* effect (k = 3, $g = 0.23$; 95% CI: 0.03-0.44, $P = .025$). Comparatively, physical activity had a nonsignificant effect on quality-of-life outcomes (k = 3, $g = 1.05$; 95% CI: -0.13 to 2.23, $P = .081$). The remaining 3 intervention approaches were assessed in 2 or fewer studies, and thus only considered in the combined analysis.

Effects on Pain. Overall, NPTs had no significant effect on pain outcomes (k = 4, $g = 0.29$; 95% CI: -0.01 to 0.59, $P = .060$). The risk of sampling error for studies examining the outcome pain was high. This high risk of heterogeneity is likely to be due to the very limited number of studies that examined pain as an outcome ($Z = 1.88$, $p = 0.060$; $Q = 0.84$; $df = 3$, $P = .84$; $I^2 = 0.00$). Four studies examined the outcome pain, 1 used a physical activity approach, and the remaining 3 used a technology-based approach. Of the 3 studies that used a technology-based approach, a nonsignificant effect was found for pain (k = 3, $g = 0.29$; 95% CI: -0.01 to 0.59, $P = .060$).

Effects on Spasticity. Similar to the outcome pain, NPTs overall had no significant effect on spasticity (k = 3, $g = 0.36$; 95% CI: -0.04 to 0.75, $P = .075$). The risk of sampling error for studies examining the outcome pain was high ($Z = 1.78$, $P = .075$; $Q = 1.24$; $df = 2$, $P = .54$; $I^2 = 0.00$). This high risk of heterogeneity is also likely to be due to the very limited number of studies that examined spasticity as an outcome. The 3 studies measuring spasticity each examined a different intervention approach (alternative, psychological, and technology-based), thus no further analyses were conducted.

Discussion

This review identified 40 peer-reviewed publications that met inclusion criteria. By investigating a broad range of NPTs, this study allows for an overview of the options available to MS patients and the strengths and weaknesses in the management of particular symptoms of the disease. Overall, the combined effect of NPTs was most beneficial for the outcome fatigue, providing a large overall effect size with medium effect sizes for functionality, balance, and quality of life. Comparatively, the combined effect was not significant in pain or spasticity symptoms. This suggests that there may be evidence-based efficacious NPT options available for specific needs in MS populations, particularly improving symptoms of fatigue, poor functionality, balance, and quality of life. We were unable to investigate through which mechanism these approaches had an effect on specific symptoms. We are also unclear why certain approaches benefited specific symptoms but not others. Future research could consider why specific approaches have a targeted effect on certain symptoms.

A review of the specific NPT approaches identified trends in the most effective forms for different areas of function. Physical activity seemed to have the greatest

effect, improving fatigue, function, and balance. Alternative approaches had a large effect on improving fatigue symptoms and quality of life, but no effect on function. Both rehabilitation and resistance-based treatment had a large effect on improving functionality. Comparatively, psychological approaches had no effect on improving fatigue or functionality, and a small effect on improving quality of life. Furthermore, technology-based approaches also had no effect on fatigue or functionality, but a small effect on improving balance.

The effectiveness of NPTs for a range of different outcomes, despite significant heterogeneity in the type of approach, suggests that there are options available to MS patients. As mentioned, however, no interventions showed a significant effect on pain or spasticity symptoms. There were only 3 studies investigating spasticity as an outcome, and each used a different intervention, contributing to a high score for heterogeneity. The same is true of pain, which was investigated in only 4 studies. These trends suggest a strong need for future research and innovative clinical interventions to be developed which target these symptoms.

The benefit of physical activity in MS is well evidenced in the literature. A 2004 Cochrane systematic review found exercise therapy beneficial for MS.[18] The review showed strong evidence for improving muscle power, exercise tolerance, and mobility; moderate evidence for improving mood; and no evidence for fatigue compared to no exercise therapy. Our results, of studies mostly conducted after 2004, did show that physical activity was greatly beneficial for improving fatigue, function, and balance. A 2017 systematic review of reviews[14] and a 2017 paper found exercise yielded beneficial effects on fatigue, a frequent symptom in MS. The latter paper also found that it improved muscle strength, balance, gait, and aerobic capacity.[16]

A 2017 systematic review of reviews investigated rehabilitation interventions,[22] including physical activity, psychological, occupational, whole-body vibration, dietary, and other interventions in MS. Similar to our study, they found physical therapies reduced fatigue. They also found physical therapies improved mobility, strength, and aerobic capacity. They rated the evidence for these outcomes to be of high quality. They found low-quality evidence for exercise improving balance. Another 2016 review of exercise training and cognitive rehabilitation found multidisciplinary interventions had a symbiotic effect in improving walking and cognition in multiple sclerosis.[39] Finally, Thomas et al conducted a 2006 systematic review of the benefits of psychological interventions for MS[19] and concluded that cognitive behavioral therapy helped participants to cope and improved depression. Our study indicated that psychological approaches had a small effect on improving quality of life.

Not all studies are in agreement. A review of complementary and alternative treatments of MS conducted from 2001 to 2016 investigated "cannabis, diet, exercise, psychological approaches and other" interventions.[21] Their chosen interventions differ from our own, making comparisons difficult, and the heterogeneity they encountered prohibited a meta-analysis of their results. The authors of the study did, however, find that exercise, greatly represented in their review, improved health outcomes for MS patients, which is similar to our findings.

Limitations

There are a number of limitations with the current meta-analysis. Many publications tended to report on small sample sizes and often lacked a control comparison group. These papers included a comparator rather than a control group. As a result, the results are compared to another treatment, and therefore may lead to differing margins of improvement between groups. There was also often large variability in the type of treatment, mode of delivery, and duration within treatment approaches. For example, the technology-based approaches, although intrinsically electronic-based, showed large variability in the type of technology, application, and goals. Furthermore, details about exact doses of treatments were often not explicitly reported, obscuring the effects of these treatments.

This meta-analysis was restricted to analyzing peer-reviewed publications to ensure results were based on more rigorous methodologies. We cannot be certain how great the risk of publication bias is, and how many studies have not been published due to nonsignificant findings. In particular, the studies that reported on fatigue, function, and quality-of-life outcomes produced funnel plots that appeared skewed, and Egger's test produced a significant 1-tailed P value for all intercepts ($P < .05$), indicating these studies are likely to be subject to publication bias.

Conclusion

This meta-analysis strengthens the emerging evidence--base for the efficacy of NPTs to improve symptom management for adults with mild to moderate MS. The results suggest there may be effective NPT options available that can improve the symptoms of fatigue, poor functionality, balance, and quality of life. We found that physical activity, alternative approaches, rehabilitation, and resistance training were effective for improving the management of a number of MS symptoms. The evidence supporting NPTs reported here offers important options that could be pursued alongside other existing treatments, for a high-risk population managing a challenging chronic health condition.

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Contributorship Information

Concept development (provided idea for the research): K.L.B., S.W.
Design (planned the methods to generate the results): K.L.B., S.W.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): S.W.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): K.L.B., S.W.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): K.L.B.
Literature search (performed the literature search): K.L.B., S.W.
Writing (responsible for writing a substantive part of the manuscript): S.W., K.L.B.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): S.W., K.L.B.

Practical Applications

- This study gives a comprehensive overview of the effects of a variety of NPTs on MS to inform treatment approaches and possible areas of future research.
- The study findings show NPTs, especially physical activity, have a large effect on fatigue and a medium effect on functionality, balance, and quality of life.
- These results suggest NPTs could offer options beyond drug treatments.

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