Neurol Sci (2017) 38:1901–1911
DOI 10.1007/s10072-017-3047-x

REVIEW ARTICLE

Effect of exercise therapy on quality of life of patients with multiple sclerosis in Iran: a systematic review and meta-analysis

Abolhassan Afkar[1,2] · **Asieh Ashouri**[2,3] · **Marjan Rahmani**[4] · **Abdolhosein Emami Sigaroudi**[1,3]

Received: 20 February 2017 / Accepted: 21 June 2017 / Published online: 7 July 2017

Abstract Multiple sclerosis (MS) is a chronic and progressive disease charachterized by disabilities which adversely affect individuals' quality of life (QOL). In the present study, the effect size of exercise therapy on patients' QOL in both physical and mental dimensions were investigated and the moderator effect of a number of selected theoretical and significant practical variables were assessed. Relevant studies, published before July 2015, were identified by searching PubMed, Scopus, Google scholar, and Persian medical databases including IranMedex, Irandoc, Magiran, Scientific Information Database (SID), and Medlib. Supplementary searches were also performed manually by reviewing the reference lists of the relevant articles. Next, using a randomized controlled trial (RCT) design, English and/or Persian-language articles conducted in Iran and evaluating the effect of exercise therapy on physical and/or mental aspects of QOL of MS patients were pooled. Afterwards, two competent reviewers in the field extracted the required data and rated the quality of the studies. Twenty-one journal articles were identified and reviewed, but only 13 of them contained the as much data as required to serve the purpose of the study. The mean effect size of exercise therapy on mental, physical, and overall QOL of the patients were 1.021 (95%CI 0.712–1.331, $P < .001$), 1.040 (95%CI 0.730–1.349, $P < .001$), and 0.846 (95%CI 0.508–1.184, $P < .001$), respectively. Based on the investigated Iranian studies, there is strong evidence confirming the effect of exercise therapy on QOL of patients with MS; there, however, exists a need for more studies to identify and establish effective exercise programs due to the heterogeneity of the studies conducted in this area.

Keywords Multiple sclerosis · Exercise · Quality of life · Systematic review · Iran

✉ Abdolhosein Emami Sigaroudi
emamisig@gmail.com; emamisig@gums.ac.ir

Abolhassan Afkar
hasanafkar@yahoo.com

Asieh Ashouri
ashouri@gums.ac.ir

Marjan Rahmani
mrj.rahmani@yahoo.com

1 Social Determinants of Health Research Center, Guilan University of Medical Sciences, Rasht, Iran

2 School of Health, Guilan University of Medical Sciences, Rasht, Iran

3 Cardiovascular Diseases Research Center, Department of Cardiology, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

4 MSc Student in Medical – Surgical Nursing, Shahid Beheshti School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

Introduction

Multiple sclerosis (MS) is a chronic and progressive disease, which is a demyelinating disorder attacking the central nervous system (CNC), in young adults [1–6]. MS is now found to be more prevalent in women than men (3:1). The onset of this disease is between 20 and 40 years of age [7–10]. The National MS Society in the USA announced that MS affects approximately 2.5 million people around the world, and nearly 200 new cases are diagnosed each week in the USA [11]. According to the Iran MS Society, there are more than 40,000 diagnosed MS cases in Iran, while only 9000 of them have been registered. The main cause of the disease is still unknown but it is known as an autoimmune disease or inflammatory disorder [12]. Most common symptoms of MS are as follows:

sensory problems, weakness, low muscle tone, vision problems, cognitive impairment, fatigue, organ temper, voiding dysfunction, forgetfulness, strabismus, and so forth. MS disease influences all aspects of individual and public life of patients [12]. Studies have shown that the quality of life (QOL) in MS patients is significantly lower than that of healthy persons and other people with chronic diseases like epilepsy, diabetes, rheumatoid arthritis, and irritable bowel syndrome [13–19]. Since MS is a chronic disease and there is not a certain cure for it, a decrease in intensity of clinical signs and, in turn, protection of QOL in the patients in the appropriate level are the main goals of clinical cares [13–18]. As pharmacotherapy has side effects and high costs, non-medicated ways such as exercise therapy can be considered suitable [13–18]. In the past, doing sport activities was not recommended for the MS patients because of increasing body temperature and causing fatigue, which intensify the disease [20–22]. Considering the potential of sport activities and rehabilitation in reducing different physical and mental problems in these patients, various studies on different sports like aerobics and endurance exercises, yoga, hydrotherapy, and so on with different protocols (frequency, intensity, duration, and type of activity) have been conducted in both Iran and the world [13, 17, 23–36]. The results of a few studies show that different exercises with different protocols can be effective or ineffective in some physical dimensions such as reducing muscle spams, fatigue, and pain; can be beneficial in increasing the power of the patients, flexibility of muscles, joints, and bone moves; and can be ineffective for some mental dimensions like improvement in mood and self-confidence or decreasing depression [23, 34, 37]. Recently, aggregation of the results extracted from review articles has changed the guidelines to present suggestions regarding training methods for these patients [31]. Up to now, few review articles have investigated the effects of exercise on total QOL in MS patients [28, 31]. A descriptive research with the aim of developing a guideline in this area found that, despite lack of evidence with high quality, there is sufficient evidence in order to develop physical activities in these patients [31]. The current research has not evaluated quantitatively the size of the effect and included all random and non-random trials [31]. To our knowledge, only in one review the size of the exercise effect on quality of life of patients has been reported, which has been reported little, but significant [28]. It should be noted that this study was comprised of both experimental and non-experimental trials, which is considered a limitation [28].

The primary purpose of our study was to estimate the effect size of exercise therapy on each of mental and physical dimensions of the QOL in MS patients in Iran only by using the results of randomized controlled trials (RCTs) as the best evidence. The second aim was to evaluate the effect of some selected theoretically or practically significant factors on this estimation (such as frequency, duration, type of exercise, type of questionnaire, articles' quality, and so on).

Methods

Search strategy, inclusion and exclusion criteria

Relevant studies were identified by a computer-aided search of PubMed, Scopus, Google scholar and Persian medical databases including IranMedex, Irandoc, Magiran, Scientific Information Database (SID), and Medlib. In addition, supplementary searches were performed manually by reviewing the reference lists of the relevant articles. The following comprehensive combination of keywords in English and Persian were used: "multiple sclerosis," "MS," "exercise," "training," "physical activity," "quality of life," "randomized trial," and "randomized controlled trial." The inclusion criteria for the articles were (1) being conducted in English or Persian in Iran, (2) focusing on only patients with MS, (3) having the randomized controlled trial (RCT) design, (4) having either an exercise intervention of at least 3 weeks or a comparison condition lacking exercise therapy (i.e., with usual care or activities), and (5) measuring at least one of the outcomes of physical or mental factors influencing QOL before and after exercise therapy. Studies were excluded if they (1) included exercise as one part of a multicomponent intervention but did not include the additional component in a comparison condition, (2) compared exercise only with an active treatment (e.g., massage therapy alone or another mode of exercise), (3) provided incomplete data or not available data. In this review, a wide range of exercise modalities such as aerobic, endurance training, resistance training, aquatics, and yoga or a mixtue of them with at least 3 weeks duration were all included under the umbrella term of exercise. A comprehensive search of electronic databases was conducted from January 2008 to July 2015.

Selection of studies and data extraction

All publications identified by the search strategy were downloaded into EndNote (version X7), and repeated cases were deleted. A reviewer screened publications for inclusion according to the pre-specified criteria. If it was clear from the title or abstract that a study did not meet the inclusion criteria, it was excluded. If it was unclear from the abstract whether a study met the selection criteria, the full paper was retrieved. Excluded studies were reviewed twice by a second reviewer. One reviewer extracted data from all included studies in a structured form. All extracted data were checked by the second reviewer. The following data were extracted from the included studies: first author, publication date, study design, number of participants, patient characteristics (e.g., age, sex, expanded disability status scale (EDSS)), type of experimental and control intervention, characteristics of the exercise intervention (e.g., exercise mode, number of sessions, time per session, frequency in weeks, relative intensity, and

adherence), time and scale of outcome assessment, and mean and standard deviation of the outcome measures in experimental and control intervention groups.

Quality assessment of studies

Independently, two reviewers rated the quality of each included study according to the Physiotherapy Evidence Database (PEDro) assessment tool, and any disagreement was resolved by discussion [38]. The scale evaluates the methodological aspects of RCTs such as having specified eligibility criteria, random allocation, concealment of allocation, comparability of groups at baseline, blinding of patients, investigators or outcome assessors, having completed follow-up for more than 85% of participants, analysis by intention to treat, between-group statistical comparisons, and complete outcome data (report of both point estimates and measures of variability at least for one outcome measure). The maximum possible score of the PEDro scale was 11, and higher scores indicated better methodological quality (Table 1).

Statistical analysis

Effect sizes were calculated by subtracting the mean change in the comparison condition from the mean change in the experimental condition, divided by the pooled standard deviation of baseline scores [49]. Effect sizes and 95% confidence interval (CI) were calculated for physical and mental QOL separately and are shown in the forest plots. The heterogeneity of the studies was checked visually by the Galbraith plots and assessed by the Cochrane chi-squared test and I2 statistics. Since the studies were heterogenous, a random-effect model was used to calculate the mean effect size. To adjust the mean effect size for the sample size of each study, Hedge's adjusted G was used [49]. To assess the hypotheses about the variation in the effect size by the moderators, variables such as sex, type of exercise, program length, and quality of study were assessed in the meta-regression model and subgroup analyses were conducted based on the significant moderators. According to the quality score, studies were divided into two groups: high quality and low quality, as the quality scores were ≥6 or not. To examine the risk of publication bias, the egger regression test was used. Moreover, a sensitivity analysis was performed to assess the contribution of each study to the overall effect. All statistical analyses were performed using STATA 11 (Stata Corp LC, Texas, USA).

Results

Figure 1 shows the flowchart depicting the search strategy. By using the electronic searching of the databases, 2367 publications (published from January 2008 to June 2015) were identified. After removing duplicated records, screening the articles related to the QOL in MS patients and hand-searching of the screened references, 21 articles were retrieved. Seven of 21 publications were excluded because the full texts were not available in two studies; the control group was missing in two studies [50, 51]; only some aspects of QOL were investigated in one study [34]; and one study was published in two reports and, then, aggregated [52], and there were not enough data on QOL measurement in one study [53].

Table 1 Quality score of papers according to the PEDro scale

First author name, year	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10	No. 11	Total score
Hassanpour-Dehkordi and Jivad [39]	1	1	1	1	0	0	0	1	1	1	1	8
Kargarfard et al. [18]	1	1	1	1	0	0	1	0	1	1	1	8
Sangelaji et al. [40]	1	1	0	1	0	0	1	1	1	1	1	8
Nornematolahi et al. [41]	1	0	0	0	0	0	0	1	1	1	1	5
Ahmadi et al. [24]	1	1	1	1	0	0	0	0	0	1	1	6
Fayazi et al. [42]	1	1	0	1	0	0	0	1	1	1	1	7
Attar sayah et al. [43]	1	1	0	1	0	0	0	0	0	1	1	5
Nasiriziba et al. [44]	1	1	0	1	0	0	0	0	0	1	1	5
Ghaffari et al. [45]	1	1	0	1	0	0	0	0	0	1	1	5
Shanazari et al. [46]	1	1	0	1	0	0	0	0	1	1	1	6
Eftekhari et al. [47]	1	1	0	1	0	0	0	1	1	1	1	7
Ghasemi et al. [48]	1	0	0	1	0	0	0	0	0	1	1	4

PEDro scale criteria specified as criteria #1: specified elegibility criteria, criteria #2: randomized allocation, criteria #3: concealed allocation, criteria #4: similarity between groups at baseline, criteria #5: blinding of subjects, criteria #6: blinding of therapists, criteria #7: blinding of assessors, criteria #8: outcome measures obtained from at least 85% of initially allocated subjects, criteria #9: all received treatment, or key outcome was analyzed by "intention to treat," criteria #10: between-group statistical comparisons, criteria #11: both point and variability measures provided

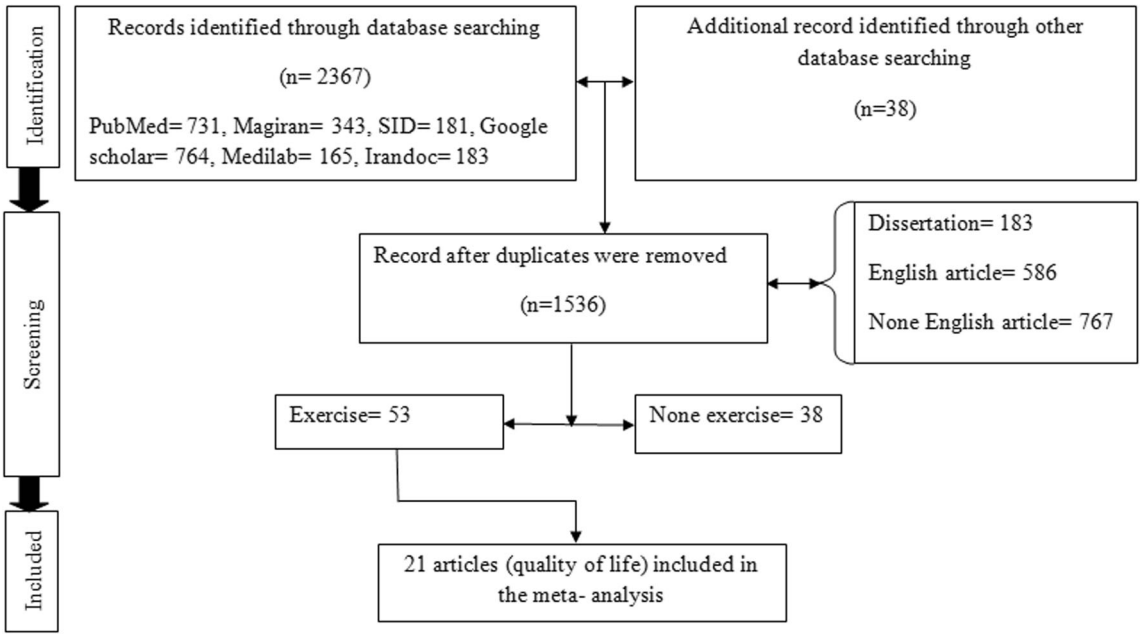


Fig. 1 Flowchart depicting the search strategy

Participants

Thirteen RCTs involving a total of 535 patients (279 patients in the intervention group and 256 patients in the control group) were included in this study. Individual study sizes ranged between 21 and 90 patients. Only in five studies, men entered into the studies. In total, 53 (10%) patients were male (30 patients in intervention group and 23 patients in control group). The mean (standard deviation) of patients' age was 33.75 years (2.79). Six studies were published in English and seven studies in Persian languages. The EDSS score was available in eight studies with a mean (sd) of 2.24 (0.49).

Outcome measures

Most of the studies (n = 7, 54%) measured the patients' QOL by the Multiple Sclerosis Quality of Life-54 questionnaire; three (23%) studies used Short-Form Health Survey-36 (SF-36) instrument; and three remaining studies were assessed QOL by using the SF-8 QOL, WHOQOL-BREF (World Health Organization Quality of Life-short version), and FAMS.Version2 (functional assessment of multiple sclerosis), respectively. Characteristics of the included studies [18, 24, 39–48, 54] are shown in Table 2. The PEDro scores of paper quality range from 4 to 8 points, whereas 54% of the papers have the score of 6 or more (Table 2).

Interventions

A wide variety of types of exercise were used in the studies but the aquatic exercise was the most common one (Table 3) [18, 41, 44, 46]. The mean (sd) length of the exercise was 9.57 weeks (2.50) and usually, the training sessions were done thrice per week (range 2–3 per week). The time of exercise ranged from 20 to 75 min per session (with 30–40 min per session in 57% of the interventions) and mean (sd) of 47 min (16). Proportion of drop-outs reported in the studies varied from none to almost 32%. None of the studies reported any adverse events for patients during the exercises.

Estimated effects of the interventions

Overall, 34 effect sizes were retrieved from the 13 studies because in some studies, there was more than one effect size per study. In one study [39], two different moods of exercise outcome were reported, and in three studies [18, 40, 45], the outcome was measured in different times following the exercise. Twelve effects were derived for overall QOL, and 11 effects were derived for mental and physical subscales of QOL (Fig. 2). In one study, the quality of work life was measured [41]. The effect size of each intervention has been shown in Fig. 2. As the effect sizes of mental, physical, and overall QOL were heterogeneous (Q = 19.95, df = 10, P = .030 with I2 = 49.9% for mental QOL, Q = 21.77, df = 10, P = .016 with I2 = 54.1% for physical QOL, and Q = 29.49, df = 11, P = .002 with I2 = 62.7% for overall QOL), the random effect models were used to calculate the mean effect size. The mean effect sizes of exercise therapy on mental, physical, and overall QOL were 1.021 (95%CI 0.712–1.331, P < .001), 1.040 (95%CI 0.730–1.349, P < .001), and 0.846 (95%CI 0.508–1.184, P < .001), respectively. The Galbraith plot identified that Kargarfard et al.'s [18] study is the most heterogeneous on the estimation of training effect on mental and physical QOL; however, exclusion of this study

Table 2 Patients and outcome characteristics of included studies

First author name, year	Number of participants	Sex, no.	Mean age (SD), year	Mean EDSS (SD)	QOL measured outcome	Type of questionnaire	Quality score[a]
Hassanpour-Dehkordi and Jivad [39]	Aerobic 20, Yoga 21, CG 21	61F/1M	31.9		Overall	SF-36	8
Kargarfard et al. [18]	IG 10, CG 11	F	IG 33.7 (8.6), CG 31.6 (7.7)	IG 2.9 (.9), CG 3 (.7)	Mental and physical	MSQOL-54	7
Sangelaji et al. [40]	IG 39 CG 20	IG 24 F/15 M, CG 15F/7M	IG 33.05(7.68), CG 32.05 (6.35)	0–4	Mental and physical	MSQOL-54	8
Nornematolahi et al. [41]	IG 25, CG 20	F	20–50		Overall	FAMS.version2	5
Ahmadi et al. [24, 54][b]	Treadmill 10, Youga11, CG 10	F	Treadmill 36.8 (9.17), yoga 32.27 (8.68), CG 36.7 (9.32)	Treadmill 2.40 (1.24), yoga 2 (1.09), CG 2.25 (1.25)	Mental, physical, and overall	MSQOL-54	6
Fayazi et al. [42]	IG 8, CG 7	F	IG 34.5 (9.33), CG 33.14 (7.42)	IG 2 (1), CG 2.07 (.67)	Overall	SF-36	7
Attar sayah et al. [43]	IG 19, CG 18	IG 12 F/7M, CG 10F/8M	IG 34.53 (6.51), CG 36.78 (4.93)	IG 2.55 (1.15), CG 2.88 (.97)	Mental and overall	MSQOL-54	5
Nasiriziba et al. [44]	IG 44, CG 46	IG 38F/6M, CG 40F/6M	20–40		Physical	MSQOL-54	5
Ghaffari et al. [45]	IG 25, CG 25	F	28.9 (5.74)	1.54 (1.37)	Mental, physical, and overall	SF-8 QOL	5
Shanazari et al. [46]	IG 15, CG 15	F	20–40	<4.5	Overall	WHOQOL-BREF	6
Eftekhari et al. [47]	IG 12, CG 12	F	20–45	IG 2.1 (.4), CG 2.6 (.7)	Overall	SF-36	7
Ghasemi et al. [48]	IG 10, CG 10	F	IG 40.6 (7.35), CG 36.5 (10.02)	IG 2.35 (1.08), CG 1.37 (2.30)	Mental and physical	MSQOL-54	4

IG indicates intervention group, *CG* control group; *SD* standard deviation, *EDSS* Expanded Disability Status Scale, *QOL* quality of life, *F* female, *M* male, *SF* short form, *MSQOL* multiple sclerosis quality of life, *FAMS* functional assessment of multiple sclerosis, *WHOQOL* world health organization quality of life

[a] Quality score was derived based on PEDro scale

[b] Information of two manuscripts originated from a trial was aggregated

Table 3 Exercise characteristics of included studies

First author name, year	Intervention types and comparison groups	Duration, no. of sessions and frequency in a week	Time per session	Intensity[a]
Hassanpour-Dehkordi and Jivad [39]	Aerobic exercise, yoga exercise	12-week, 3 times in week	40 min	
Kargarfard et al. [18]	Aquatic exercise, 4 and 8 week assessment	4-week, 12 session, 3	60 min	50–75% HR
Sangelaji et al. [40]	Combination exercise, 10 week and one year assessment	10-week, 30 session, 3	40 min	40–70% HR
Nornematolahi et al. [41]	Aquatic aerobic training	8-week, 24 session, 3	30–40 min	50–60% HR
Ahmadi et al. [24, 54]	Treadmill training, yoga exercise	8-week, 24 session, 3	Treadmill training 30 min, yoga exercise 60–70 min	40–75% age-predicted maximal HR
Fayazi et al. [42]	Treadmill training	8-week, 24 session, 3	20–40 min	60–80% HR
Attar sayah et al. [43]	Combination exercise	8-week, 24 session, 3	50–70 min	< 70% 1RM
Nasiriziba et al. [44]	Stretching exercise	12-week, 36 session, 3	30 min	
Ghaffari et al. [45]	Aquatic exercise, 4, 8 and 12 week assessment	12-week, 24 session, 2	60 min	
Shanazari et al. [46]	Aquatic exercise	12-week, 36 session, 3	60 min	
Eftekhari et al. [47]	Resistance training	12-week, 36 session, 3	30 min	max 90%
Ghasemi et al. [48]	Combination exercise	8-week, 24 session, 3	75 min	

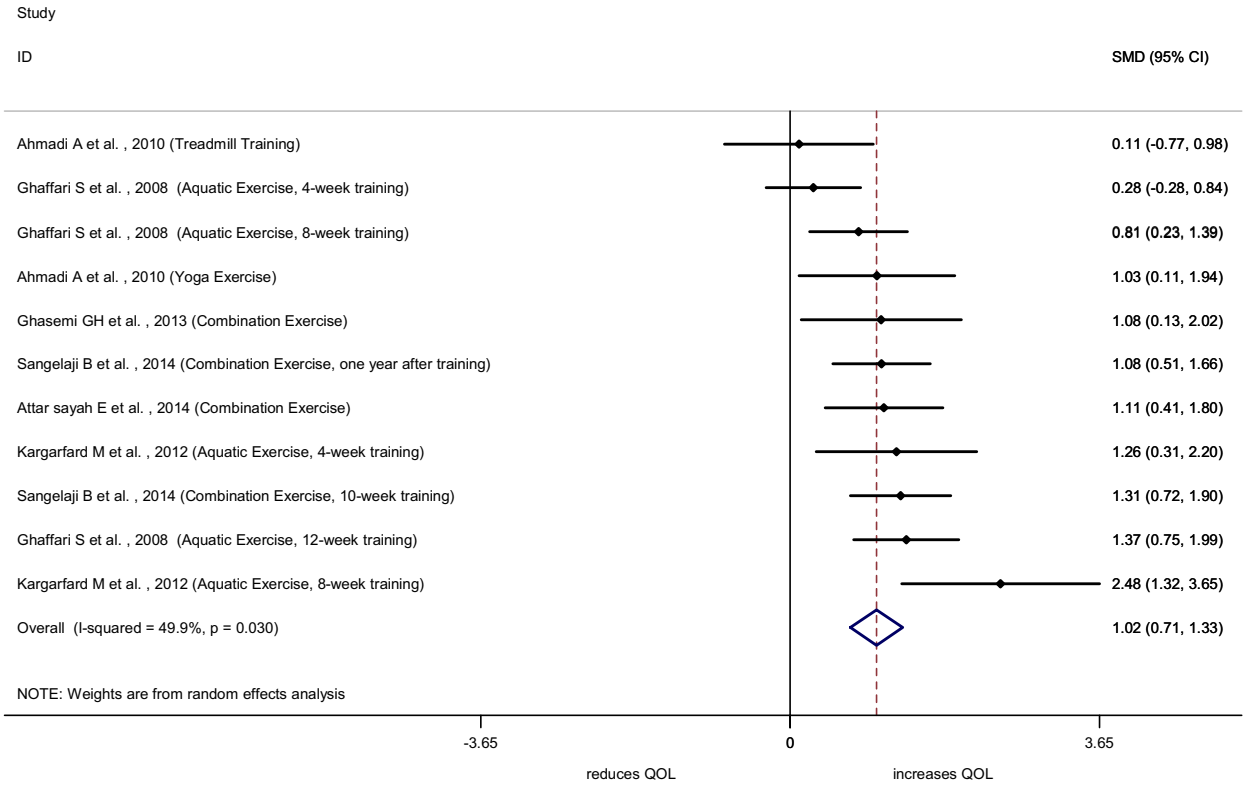
HR heart rate

[a] Level of maximal heart rate reserved in the study

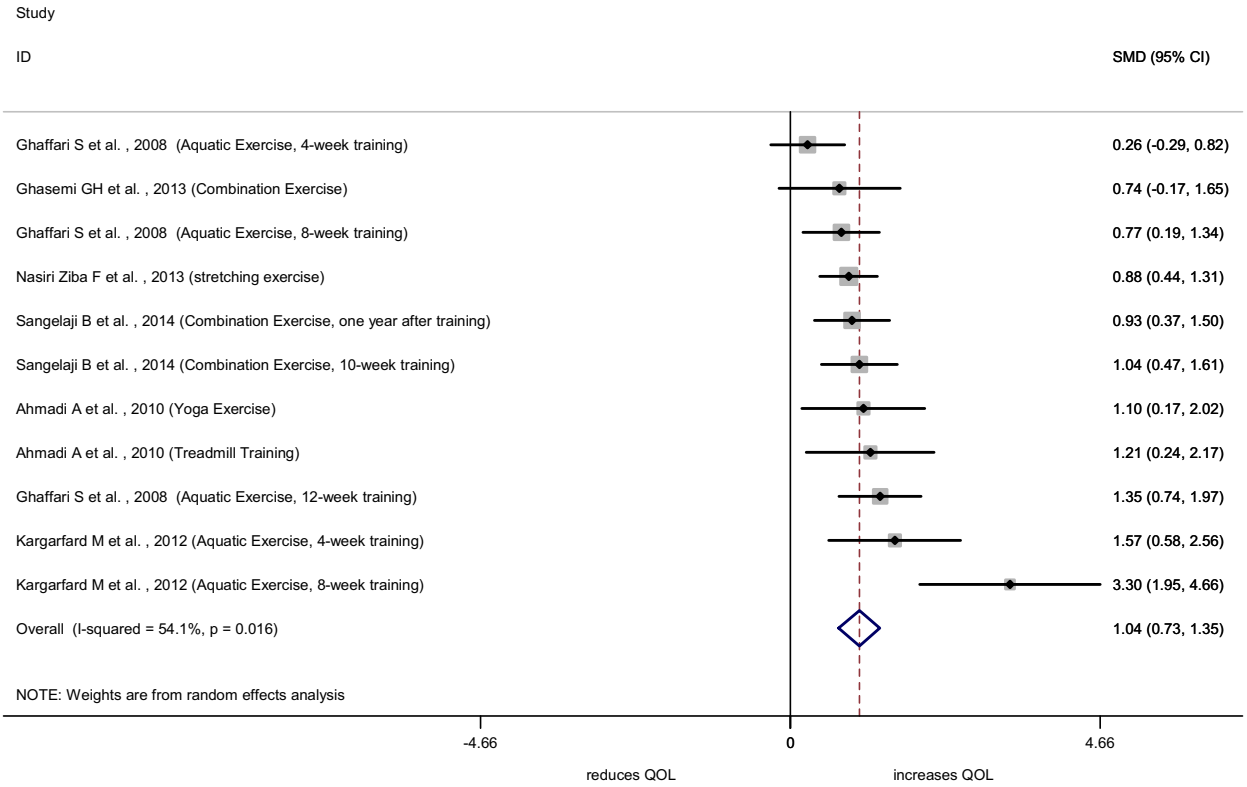
did not significantly alter the results; and with the study excluded, the effect sizes of exercise therapy on mental and physical QOL were 0.941 (95%CI 0.672–1.210) and 0.914 (95%CI 0.699–1.128), respectively. Furthermore, three effects of (Hassanpour-dehkordi et al. [39] and Eftekhari et al. [47]) studies were the most heterogeneous on the estimation of training effect on overall QOL and with exclusion of these studies, the mean effects estimation (0.596 with 95%CI 0.310–0.882) decreased. To describe the heterogeneity, variation of the effects was tested according to some selected variables as moderators. However, none of the moderators were related to the mental and physical QOL effect size (details of the results are not shown here but $P > .1$ was set for all regression coefficients); the mean effect size of overall QOL was influenced by the length of the exercise ($P = .049$) and questionnaire type ($P = .023$). Therefore, the effect size of exercise on overall QOL on an 8-week exercise was lower than a 12-week-exercise (effect size 0.393 (95%CI 0.054–0.732, $P = .023$) vs. 1.122 (95%CI 0.668–1.575, $P < .001$)). Also, the effect sizes of exercise on overall QOL assessed by SF-36 or SF-8 QOL was higher than others (effect size of 1.173 (95%CI 0.726–1.619, $P < .001$) for SF-36 or SF-8 QOL questionnaire vs. .379 (95%CI 0.058–0.700, $P = .021$) for other assessment tools, respectively); albeit, there was a significant relation between questionnaire type and the length of the exercise ($r = .657$, $P = .020$).The egger regression test revealed no publication bias for exercise effects on mental and overall QOL ($P = .313$ and $P = .500$, respectively), but the test detected a small evidence of publication bias for trials assessing exercise effects on physical QOL ($P = .047$).

Discussion

Exercise therapy can be introduced as a practical and safe method for patients with chronic diseases like MS with a mild to moderate disability. Several review articles have assessed the effect of doing exercises on different physical and mental problems of MS patients such as spasticity, mobility, balance, walking, fitness, fatigue, depression, and health-related quality of life [14, 25, 26, 28, 29, 35, 55–64]. Based on these studies, some guidelines and recommendations have been published [31, 65–67]. However, these guidelines do not accord with each other and suffer from a few drawbacks in methodology (like not being evidence-based, lack of evaluating the quality of the reviewed evidence or not setting a robust, standardized guideline development process). Also, these guidelines just review fitness outcomes descriptively and not quantitatively. Generally, it cannot be concluded that doing exercises can undoubtedly enhance health-related QOL in individuals with MS [30, 31]. The main objective of the present study was quantitative evaluation of the effect of doing exercises on overall QoL as well as physical and mental dimensions in MS patients based on the conducted studies in Iran. Unlike previous studies, in our investigation, we considered only randomized clinical trials (RCTs). Approximately half of the studies included in this study were RCTs with good quality (6 or more) [67]. The results of Iranian RCTs showed that 90% of the patients were women and different kinds of exercise interventions including aerobic; yoga; and aquatic, stretching, endurance, and combinatorial exercises have been used. In general, the length of the exercise was about 10 weeks and training sessions were 3 times per week.

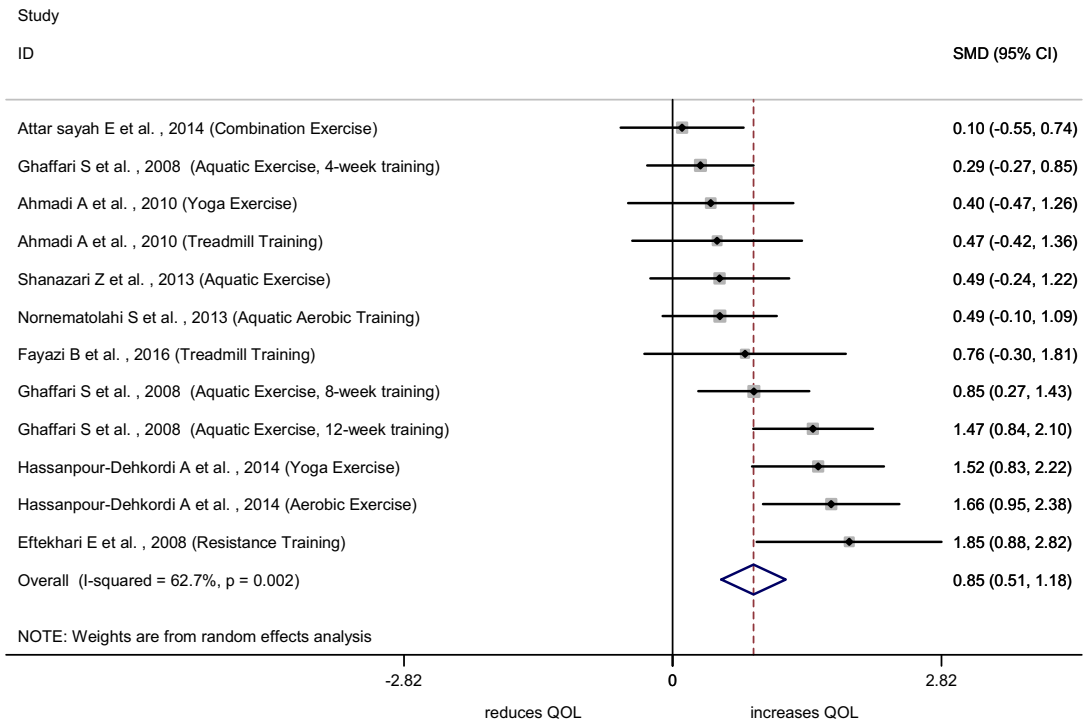


(A)



(B)

Fig. 2 **a**, **b**, **c** Individual and overall effect sizes (with 95% confidence interval) for mental, physical, and overall quality of life, respectively (mental, physical and overall QOL were heterogeneous so Q = 19.95, df = 10, $P = .030$ with I2 = 49.9% for mental QOL, Q = 21.77, df = 10, $P = .016$ with I2 = 54.1% for physical QOL, and Q = 29.49, df = 11, $P = .002$ with I2 = 62.7% for overall QOL were calculated)



(C)

Fig. 2 continued.

Moreover, in half of these studies, the MS specific tool was used for recording QOL. We found a dramatic improvement in all aspects of QOL. In other words, the mean effect sizes indicated that doing exercise makes a basic improvement in effect (about one SD) in all mental, physical, and overall QOL of patients with MS. In the review article by Cruickshank et al., the effect of the endurance exercise on the QOL in MS patients has been reported [64]. In this study, the aggregated size of the effects was not calculated. However, a significant improvement in QOL was claimed in two of three studies entered in this review article. Similar results were reported in the review article by Kjølhede et al. [55]. The effect size was calculated only in one review study, which was significant but small in magnitude [28]. The reason for this difference in the results of this study and our study can be attributed to the methodological differences of the two studies. In our study, we used only interventional studies which are stronger in terms of evidence for deduction but in the study by Motl et al. [28], effects of both interventional and observational studies were aggregated. Also, in our study, in more than half of the studies, the measurements were evaluated with a MS-specific tool, MSQOL-54, while in Motl et al.'s [28] study, the measures of QOL were quite diverse ranging from generic measures of QOL (e.g., Medical Outcomes Study Short Form-36) through measures of fatigue as a component of QOL (e.g., Fatigue Severity Scale). It is notable that a study showed that the path of exercise effectiveness on QOL is indirect due to influence of exercises on fatigue, pain, social support, and self-efficacy in individuals with MS [68]. Similar to Motl et al.'s [68] study, results of our study showed that the effect of overall QOL differed based on the type of the questionnaire. Our study illustrated that using general tools like SF8 or SF36 for measurement of QOL shows a higher effect of exercise, whereas in Motl et al., effect sizes estimated based on MS-specific tools were higher and significant. These results stated that lack of accuracy and specificity of general tools as well as lack of record and cover of all special dimensions of QOL in individuals with special diseases like MS may affect the results in both direction of over or underestimation. In addition, our data showed that a longer period of exercise (3 vs. 2 months) influences the overall QOL more. This result is consistent with that of other studies, as the time of 3-month programs is among the logical underpinnings of the exercise initiation. Also, it is worth mentioning that Motl et al. [28] explained that exercise interventions, shorter than 3 months, have a higher effect size than interventions with a period of 3 months or more. This can be described by difficulty in sustaining exercise adherence rates in the long term. However, we could not investigate this pattern because of insufficient data. In addition to the type of measuring tools and the duration of exercise program, Motl et al. [28] concluded that the kind of exercise (aerobic against non-aerobics or combination exercises), and time of each session (more than 90 min) are related to a higher effect on QOL. The authors stated that the effect of the aerobic exercise on QOL is significant, but the effect of different non-aerobic exercises (like yoga, endurance and so on) is not significant. Nonetheless, Cruickshank et al. [64] explained that the endurance exercises are effective in QOL. In our study, we did not find any relationship between

the type, duration, and time of exercise per session and QOL. It may be attributed to the heterogeneity of exercise programs performed in Iranian studies and also insufficient data. Thus, considering that some of exercises are only effective in fitness parameters and do not increase the QOL and most of the present studies are descriptive, more studies are required to compare the effect of different exercises on QOL in MS individuals. In addition to the limitations of performed initial studies such as self-reporting of QOL, lack of concealment, and blinded outcome assessment, the data on clinical courses of individuals with MS (such as relapsing-remitting against progressive or different stages of disease remission) had not been reported in the included studies. Also, despite trying to collect all published studies, we observed a weak effect of publication bias in the estimation of exercise effect on physical QOL. Furthermore, it should be noted that in the present study, only eight EDSS studies were reported and the mean EDSS score was ≤4, indicating that most patients in the studies had a low disability status. Also, since the effect of exercise on men population may be different in terms of physiological features and most of the present studies have included women, more studies on men are needed. In conclusion, as no complications for the participants in exercise programs have been reported (even though this issue was not clearly mentioned by some studies), it can be stated that doing exercises is definitely helpful for improving the QOL in MS patients. And, since the rate of doing exercises in these individuals is low [27], performing interventions to enhance the exercise behavior of MS patients can be helpful. Furthermore, to develop a guideline for physical activity of these patients and to determine the properties of the most suitable and effective exercise programs such as exercise type, frequency, length, and intensity, more studies are needed.

Conclusions

The overall effect of exercise therapy interventions on QOL among individuals with MS was studied by using the meta-analysis procedures. The mean effect size of overall QOL was higher for 12 vs. 8 weeks length of the exercise and was lower for the MS-specific questionnaires. Based on the Iranian studies, there is a strong evidence of exercise therapy effect on QOL in patients with MS, but due to the heterogeneity of the studies, more studies are needed to establish the effective exercise program.

Acknowledgements Thanks are due to Guilan University of Medical Sciences, Rasht, Iran, and to everyone who has made a contribution to the completion of this research project.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Zamani SN, Fazilatpoor M (2014) The effect of cognitive–behavioral stress management training on anxiety, depression and cognitive disorder of individuals with multiple sclerosis. J Clin Psycol 5(4):43–53
2. Tofighi AA, Saki Y, Razmjoo K (2013) Effect of 12-week progressive resistance training on balance, fatigue and disability in women with MS. Jundishapur Sci Med J 12(2):159–167
3. Azimzadeh E, Hosseini MA, Nourozi K et al (2015) Effect of Tai Chi Chuan on balance in women with multiple sclerosis. Complement Ther Clin Pract 21(1):57–60
4. Salehpoor G, Rezaei S, Hosseininezhad M (2014) Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: a bicenter study from north of Iran. Iran J Nurs Midwifery Res 19(6):593–599
5. Ferrè L, Nuara A, Pavan G et al (2016) Efficacy and safety of nabiximols (Sativex®) on multiple sclerosis spasticity in a real-life Italian monocentric study. Neurol Sci 37(2):235–242
6. Totaro R, Di Carmine C, Splendiani A et al (2016) Occurrence and long-term outcome of tumefactive demyelinating lesions in multiple sclerosis. Neurol Sci 37(7):1113–1117
7. Karpatkin HI (2005) Multiple sclerosis and exercise: a review of the evidence. Int J MS Care 7(2):36–41
8. Taraghi Z, Ilali E, Abedini M et al (2007) Quality of life among multiple sclerosis patients. Iran J Nurs 20(50):51–59
9. Dalgas U, Ingemann-Hansen T, Stenager E (2009) Physical exercise and MS recommendations. Int MS J 16(1):5–11
10. Vollmer T, Huynh L, Kelley C et al (2016) Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: a systematic literature review. Neurol Sci 37(2): 165–179
11. National Multiple Sclerosis Society. About MS: what we know about MS. http://www.nationalmssociety.org/about-multiplesclerosis/what-we-know-about-ms/index.aspx. Accessed October.
12. Tullman MJ (2013) Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. Am J Manag Care 19(2 Suppl):S15–S20
13. Ahmadi A, Arastoo AA, Nikbakht M et al (2013) Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in MS patients. Iran Red Crescent Med J 15(6):449–454
14. Asano M, Finlayson ML (2014) Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Mult Scler Int 2014:1–12
15. Atri AE, Saeedi M, Sarvari F et al (2012) The effect of aquatic exercise program on fatigue in women with multiple sclerosis. J Mazandaran Univ Med Sci (JMUMS) 22(94):54–61
16. Barbar A, Bahadoran R, Ghasemzadeh Y (2014) The effect of aquatic exercise on balance of adults with multiple sclerosis. Europ J Exp Biol 4(1):38–43
17. Dehghani A, Mohammadkhan Kermanshahi S, Memarian R (2012) Effect of applying peer group designed education plan on depression of multiple sclerosis patients. Modern Care J 9(4):301–309
18. Kargarfard M, Etemadifar M, Baker P et al (2012) Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. Arch Phys Med Rehabil 93(10): 1701–1708
19. Etemadifar M, Sayahi F, Alroughani R et al (2016) Effects of prolonged fasting on fatigue and quality of life in patients with multiple sclerosis. Neurol Sci 37(6):929–933
20. Solari A, Filippini G, Gasco P et al (1999) Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. Neurology 52(1):57–57

21. White A, Wilson T, Davis S et al (2000) Effect of precooling on physical performance in multiple sclerosis. Mult Scler 6(3):176–180
22. Bol Y, Smolders J, Duits A et al (2012) Fatigue and heat sensitivity in patients with multiple sclerosis. Acta Neurol Scand 126(6):384–389
23. Ahadi F, Rajabpour M, Ghadamgahi A et al (2013) Effect of 8-week aerobic exercise and yoga training on depression, anxiety, and quality of life among multiple sclerosis patients. Iran Rehabil J 11(17):75–80
24. Ahmadi A, Arastoo AA, Nikbakht M (2010) The effects of a treadmill training programme on balance, speed and endurance walking, fatigue and quality of life in people with multiple sclerosis. Intern Sport Med J 11(4):389–397
25. Snook EM, Motl RW (2009) Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. Neurorehabil Neural Repair 23(2):108–116
26. Ensari I, Motl RW, Pilutti LA (2014) Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. J Psychosom Res 76(6):465–471
27. Gillison FB, Skevington SM, Sato A et al (2009) The effects of exercise interventions on quality of life in clinical and healthy populations; a meta-analysis. Soc Sci Med 68(9):1700–1710
28. Motl RW, Gosney JL (2007) Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult Scler 14(1):129–135
29. Motl RW, Pilutti LA (2012) The benefits of exercise training in multiple sclerosis. Nat Rev Neurol 8(9):487–497
30. Giesser BS (2015) Exercise in the management of persons with multiple sclerosis. Ther Adv Neurol Disord 8(3):123–130
31. Latimer-Cheung AE, Pilutti LA, Hicks AL et al (2013) Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. Arch Phys Med Rehabil 94(9):1800–1828
32. Moradi M, Kordi M, Sahraian M et al (2012) The effect of eight-week resistance training on muscular strength and balance in men with multiple sclerosis. Sport Biosci (Harakat) 11(5):5–22
33. Moradi M, Sahraian MA, Aghsaie A et al (2015) Effects of eight-week resistance training program in men with multiple sclerosis. Asian J Sports Med 6(2):1–7
34. Najafi-Dolatabad S, Noureyan K, Najafi-Dolatabad A et al (2012) The effect of yoga techniques on quality of life among women with multiple sclerosis. J Hormozgan Univ Med Sci 16(2):143–150
35. Rietberg MB, Brooks D, Uitdehaag BM et al (2004) Exercise therapy for multiple sclerosis. Cochrane Database Syst Rev 3(3):1–33
36. Tarakci E, Yeldan I, Huseyinsinoglu BE et al (2013) Group exercise training for balance, functional status, spasticity, fatigue and quality of life in multiple sclerosis: a randomized controlled trial. Clin Rehabil 27(9):813–822
37. Romberg A, Virtanen A, Ruutiainen J (2005) Long–term exercise improves functional impairment but not quality of life in multiple sclerosis. J Neurol 252(7):839–845
38. Maher CG, Sherrington C, Herbert RD et al (2003) Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther 83(8):713–721
39. Hassanpour-Dehkordi A, Jivad N (2014) Comparison of regular aerobic and yoga on the quality of life in patients with multiple sclerosis. Med J Islam Repub Iran 28(1):946–952
40. Sangelaji B, Nabavi SM, Estebsari F et al (2014) Effect of combination exercise therapy on walking distance, postural balance, fatigue and quality of life in multiple sclerosis patients: a clinical trial study. Iran Red Crescent Med J 16(6):e17173–e17180
41. Nornematolahi S, Soltani M, Hejazi SM et al (2013) The effect of aquatic aerobic training on quality of work life in multiple sclerosis (MS) patients. Europ J Exp Biol 3(4):7–12
42. Fayazi B, Parnow A, Ahsan B (2016) Effect aerobic exercises on fatigue and quality of life in women with multiple sclerosis. Holist Nurs Midwifery J 26(1):30–40
43. Attar Sayyah AE, Hoseini Kakhk SAR, Hamedinia MR et al (2014) Effect of 8-week combined training (resistance and proprioceptive neuromuscular facilitation) on fatigue and quality of life in multiple sclerosis patients. Q Horizon Med Sci 22(1):43–50
44. Nasiriziba F, Askarizadeh A, Mohammadi N (2014) The effect of stretching exercise on physical health composite in patients with multiple sclerosis. Sci Res J Shahed Univ 21(109):1–7
45. Ghafari S, Ahmadi F, Nabavi S (2008) Effects of applying hydrotherapy on fatigue in multiple sclerosis patients. J Mazandaran Univ Med Sci (JMUMS) 18(66):71–81
46. Shanazari Z, Marandi SM, Minasian V (2013) Effect of 12-week pilates and aquatic training on fatigue in women with multiple sclerosis. J Mazandaran Univ Med Sci (JMUMS) 23(98):257–264
47. Eftekhari E, Nikbakht H, Rabiei K et al (2008) Effect of endurance training on aerobic power and quality of life in female patients with multiple sclerosis. Olympic 16(1):37–46
48. Ghasemi GA, Rahimi N, Zolaktaf V et al (2013) The effect of one period selected exercise program on knee torque, functional performance and quality of life in women with multiple sclerosis. Sport Rehabil 1(1):9–19
49. Hedges LV, I Olkin (1985) Statistical methods for meta {analysis. Academic Press, Orlando (Flor.)
50. Asadizaker M, Majdinasab N, Atapour M et al (2010) Effect of exercise on walking speed, fatigue and quality of life in patients with multiple sclerosis. Jundishapur Sci Med J 9(2):190–198
51. Rafeeyan Z, Azarbarzin M, Moosa FM et al (2010) Effect of aquatic exercise on the multiple sclerosis patients' quality of life. Iran J Nurs Midwifery Res 15(1):43–47
52. Kargarfard M, Etemadifar M, Asfarjani F et al (2010) Changes in quality of life and fatigue in women with multiple sclerosis after 8 weeks of aquatic exercise training. J Fundam Mental Health 12(3):562–573
53. Negahban H, Rezaie S, Goharpey S (2013) Massage therapy and exercise therapy in patients with multiple sclerosis: a randomized controlled pilot study. Clin Rehabil 27(12):1–11
54. Ahmadi A, Nikbakh M, Arastoo A et al (2010) The effects of a yoga intervention on balance, speed and endurance of walking, fatigue and quality of life in people with multiple sclerosis. J Human Kinet 23:71–78
55. Kjølhede T, Vissing K, Dalgas U (2012) Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler 18(9):1215–1243
56. Pilutti LA, Greenlee TA, Motl RW et al (2013) Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med 75(6):575–580
57. Kantele S, Karinkanta S, Sievänen H (2015) Effects of long-term whole-body vibration training on mobility in patients with multiple sclerosis: a meta-analysis of randomized controlled trials. J Neurol Sci 358(1):31–37
58. Paltamaa J, Sjögren T, Peurala SH et al (2012) Effects of physiotherapy interventions on balance in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. J Rehabil Med 44(10):811–823
59. Pearson M, Dieberg G, Smart N (2015) Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. Arch Phys Med Rehabil 96(7):1339–1348. e1337
60. Van Den Akker LE, Heine M, van der Veldt N et al (2015) Feasibility and safety of cardiopulmonary exercise testing in multiple sclerosis: a systematic review. Arch Phys Med Rehabil 96(11):2055–2066
61. Motl RW, McAuley E, Snook EM (2005) Physical activity and multiple sclerosis: a meta-analysis. Mult Scler 11(4):459–463

62. Cramer H, Lauche R, Azizi H et al (2014) Yoga for multiple sclerosis: a systematic review and meta-analysis. PLoS One 9(11): e112414
63. Motl RW (2014) Benefits, safety, and prescription of exercise in persons with multiple sclerosis. Expert Rev Neurother 14(12): 1429–1436
64. Cruickshank TM, Reyes AR, Ziman MR (2015) A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson disease. Medicine 94(4):e411
65. Latimer-Cheung AE, Ginis KAM, Hicks AL et al (2013) Development of evidence-informed physical activity guidelines for adults with multiple sclerosis. Arch Phys Med Rehabil 94(9): 1829–1836. e1827
66. Pilutti LA, Platta ME, Motl RW et al (2014) The safety of exercise training in multiple sclerosis: a systematic review. J Neurol Sci 343(1):3–7
67. Dalgas U, Stenager E, Ingemann-Hansen T (2007) Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance-and combined training. Mult Scler 14(1):35–53
68. Motl RW, McAuley E (2009) Pathways between physical activity and quality of life in adults with multiple sclerosis. Health Psychol 28(6):682–689