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The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: Systematic review and meta-analysis

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease affecting the myelinated axons of the central nervous system causing neurological deterioration. People living with MS have a poor quality of life (QOL) because of the symptoms caused by the disease and there are various types of treatments to manage the symptoms aside from medication.
Objective: This meta-analysis examines the effect of exercise, yoga and physiotherapy on the physical, mental and social QOL among individuals living with MS.
Setting: A systematic review with meta-analysis was conducted using PubMed, Medline, and Scopus from 1990 to 2017. The standard mean difference scores were computed in each study for the domains of physical, mental and social functioning.
Results: Eighteen studies met the inclusion criteria for this meta-analysis. Aerobic exercise was effective in improving satisfaction with physical functioning,$d = 0.35$ (95% CI = 0.08 to 0.62), mental functioning $d = 0.42$ (95% CI = 0.11 to 0.72), and social functioning $d = 0.42$ (95% CI = 0.15 to 0.69). Physiotherapy was also found to be effective for physical functioning $d = 0.50$ (95% CI 0.19 to 0.80), mental functioning $d = 0.44$ (95% CI 0.14 to 0.75) and social functioning $d = 0.60$ (95% CI 0.21 to 0.90). However yoga and combination of exercises did not have a significant effect on any of the QOL domains.
Conclusion: These findings suggest that aerobic exercise and physiotherapy improves the satisfaction of MS patients with their physical, mental and social functioning and may be included as normal practice in the treatment of MS.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease which affects the myelinated axons in the central nervous system causing neurological deterioration over time.[1] MS is more common among individuals of Northern European descent.[2] It is usually diagnosed between the ages of 20–50 years of age.[3] The disease causes a wide variety of symptoms including muscle weakness, fatigue, ataxia, impaired speech, vision impairment, cognitive dysfunction and paralysis.[4] The Quality of Life (QOL) measures the satisfaction of individuals with their physical, mental and social wellbeing. Improving the QOL of MS patients has been recognized as important in secondary prevention of MS.[5–7] Health related QOL is based on the perspectives of the individual and how they feel in the various areas of their life such as their physical, mental and social health and is usually measured using a variety of questionnaires.[7] Individuals with MS have consistently shown to have lower QOL scores.[8]

Exercise training in general has been recognized as a useful intervention to alleviate some of the symptoms of MS[9–14] Meta-analysis studies that have investigated the possible association between exercise and QOL among individuals with MS have focused on an overall QOL score as opposed to investigating the different types of exercise methods and their impact on the various domains of QOL.[4,15,16] Endurance training, resistance training and combination of both[17] are the main categories of exercise that have been investigated for their effectiveness with respect to MS in experimental studies.

Yoga is an ancient practice that is used to bring balance and health to the individual and has been used as a therapeutic method to relieve symptoms caused by many illnesses.[18] It has been shown to help relieve stress and anxiety among individuals with neuropsychiatric disorders, however the impact of it among individuals with MS has not been systematically investigated across QOL domains.[19–23] Esmonde and

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Long (2008) state that yoga is among the six most effective complementary therapies for managing symptoms of MS.[24] Yoga has many therapeutic effects on QOL and help to improve many MS symptoms, including weakness, fatigue and mental impairments.[24–27] It also helps in the reduction of persistent pain and stress as well as in reducing the symptoms of cancer along with prevention of cardiovascular disease.[24–27] The different types of movements involved in yoga may improve QOL by relieving spasticity, balance and proprioception, cognitive impairment and mental stress as well as increasing physical and motor functions.[28]

Physiotherapy interventions consist of education, consultation, therapeutic exercise, and cardiorespiratory techniques[29] Physiotherapy has been known to help in the recovery from MS especially in problems associated with balance and gait.[30] It has also been used to help with urinary incontinence which is a common symptom of MS.[31] Besides helping people with balance, gait and urinary incontinence, not much research has been done on the benefits of physiotherapy and the effect it has on individual domains of QOL.

Although systematic reviews on interventions to alleviate symptoms of MS has been conducted, the comparative effectiveness of various types of interventions and impact of these interventions on specific domains of QOL have not been systematically assessed. This systematic review investigates the comparative effectiveness of various types of interventions such as aerobic exercise, anaerobic exercise, mixed exercise, yoga and physiotherapy on the domains of QOL (physical, mental and social).

2. Methods

2.1. Data sources and searches

We performed a comprehensive search using the databases PubMed, Medline and Scopus using key words" multiple sclerosis" AND "exercise “OR "physical activity" OR "physical therapy “OR "aerobic" OR "anaerobic" OR "strength" OR "flexibility" OR "yoga" AND "quality of life" from 1990 to 2017. The inclusion criteria were: 1) study must have either a randomized control design, pre-test post-test design, quasi experimental design or cross over design 2) should be testing the effectiveness of either exercise, physiotherapy or yoga interventions, and 3) should have a standard recognized QOL outcome measure including specific measures of the subdomains of physical functioning, mental/emotional functioning and social role functioning. Two researchers were involved in the title and abstract screening and differences were resolved through discussions. Articles that had comparisons between a complementary therapy and control where the control had an exercise component were included in the meta-analysis as a separate study. Thus, a single study could have two types of treatment. We excluded articles that did not have measures of QOL domains or those that did not have cases and controls. Systematic reviews, literature reviews, meta-analysis and case studies were also excluded. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observations Studies in Epidemiology (MOOSE) guidelines were adhered to.[32,33]

2.2. Effect sizes and statistical analysis

Quality of life (QOL) was categorized into three domains: a) physical, b) mental and c) social health. Articles that did not have these components were not included in the meta-analysis. For each QOL category, mean differences based on the type of exercise or therapy (aerobic, anaerobic, mix of aerobic and anaerobic, yoga or physiotherapy) were calculated. We computed standard mean difference using Cohen's d for physical, mental and social health scores for each study.[34] The standard mean difference was calculated based on the mean difference between the treatment and control group divided by the pooled standard deviation. For randomized controlled trials, we used the difference between the treatment and control group, and for pre-test post-test studies, we used the post-test as the intervention and used pre-test as the control. The aggregated or pooled standard mean difference was computed using a random effects model where heterogeneity was found and weighted by using the sample size for each study. Heterogeneity was evaluated using the DerSimonian and Laird I^2 statistics.[35] When heterogeneity was absent, a fixed effect model was used. A standard mean difference (SMD) of 0.20 indicated a small effect, SMD of 0.50 indicated a medium effect and an SMD of 0.80 or greater indicated a large effect.[36] In order to assess publication bias, funnel plots and forest plot's test were used.[37] The assessment of study quality was conducted using the modified PEDro scale, which can be found in Appendix A. Sensitivity analysis was carried out in order to assess the impact of each study on the overall estimates. This was done by removing each study one at a time and by recalculating the standard mean difference. Meta-regression was used to assess heterogeneity and study quality. All analyses was conducted using STATA IC 13.

3. Results

There were 1015 articles initially identified through database searches in PubMed, Medline and Scopus. After duplicate titles were removed, 586 titles remained. Another 443 potential articles were removed after title review. After abstract review, full texts were reviewed for 84 articles and 18 articles were used in the analysis based on inclusion and exclusion criteria. Fig. 1 shows the process in selection of the articles.

Table 1 shows the characteristics of the studies that were included in the meta-analysis.

The majority of studies included in the analysis were carried out in USA with the most common instruments used to measure QOL were the SF-36 and the MSQOL-54. The majority of study designs used randomized controlled trials with some pretest post-test and repeated measures. There were 4 different types of quantitative measures of QOL: Medical Outcomes Survey Short Form-36, Multiple Sclerosis Quality of Life-54 Questionnaire (MSQOL-54), Multiple Sclerosis QOL Inventory (MSQLI) and World Health Organization QOLBREF (WHOQOL-BREF).

3.1. Effects of aerobic exercise on MS patients' QOL domains

There were seven studies of aerobic exercise interventions (low to high intensity such as walking, cycling, running etc.) with physical QOL health scores.[38–44] Five studies which had mental health scores.[39–41,43,44] and seven studies with social health scores.[38–44] Aerobic exercise intervention studies showed that aerobic exercise had a small effect on physical health of MS patients. These studies reported a standard mean difference SMD of $d = 0.351$ (95% CI = 0.08 to 0.62, p = 0.012, $I^2 = 48.1\%$). A funnel plot and Egger's test showed no small study effect bias (p = 0.100). Fig. 2 shows the forest and funnel plot for this analysis.

A small to medium effect found was found for the impact of aerobic exercise on mental health, $d = 0.417$ (95% CI = 0.112 to 0.721, p = 0.007, $I^2 = 54.2\%$). The funnel plot and Egger's test showed no small study effect bias (p = 0.315). Fig. 3 shows the results of the analysis.

Aerobic exercise also had a small effect on social health with an SMD of $d = 0.423$ (95% CI = 0.15 to 0.69, p = 0.002, $I^2 = 35.1\%$). Again the funnel plot and Egger's test did not show a small study effect bias (p = 0.851). These combined results clearly show that aerobic exercise has a significant impact on the physical, mental and social health of MS patients. Fig. 4 shows the forest plot along with the corresponding funnel plots.

3.2. Effects of anaerobic exercise on MS patients' QOL domains

There were four anaerobic exercise studies that had physical health

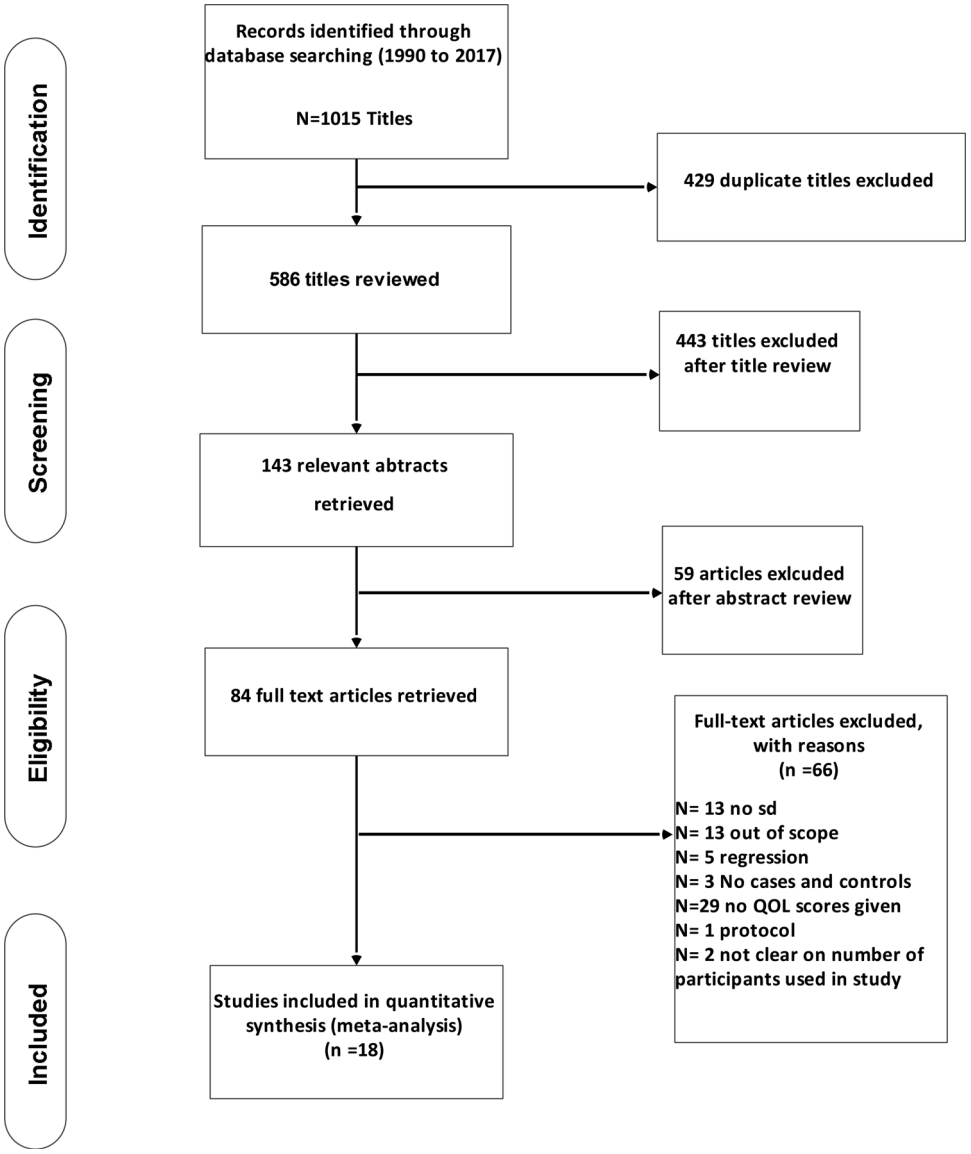

Fig. 1. PRISMA flow diagram for the process of selecting articles to be included in this review.

QOL scores [39,45–47]: two studies reported mental health scores [39,47] and two studies reported social health scores.[39,46] Anaerobic exercise in MS patient groups did not have a significant effect on either physical, mental or social health. The SMD scores were for physical health QOL was d = -0.02 (95% CI = -0.30 to 0.26 p = 0.90, I^2 = 0%), mental health: d = -0.10 (95% CI = -0.47 to 0.28, p = 0.61, I^2 = 61.5%) and social health: d = -0.18 (95% CI = -0.81 to 0.45, p = 0.573). Funnel plots and Egger's did not show any small study effect bias (p = 0.94) for the physical QOL studies.

3.3. Effects of yoga on MS patients' QOL domains

Three studies examined the effect of yoga interventions on physical health of MS patients[43,48,49] Yoga did not have a significant effect on physical health d = 0.11 (95% CI = -0.26 to 0.48, p = 0.57, I^2 = 0%). A funnel plot and Egger's test showed no small study effect bias for yoga on physical health (p = 0.247). The three studies that assessed the effect of yoga on mental health found no significant effect d = 0.46 (95% CI = -0.24 to 1.17, p = 0.19, I^2 = 0.46 (95% CI = -0.24 to 1.17, p = 0.19.[43]

3.4. Effects of physiotherapy on MS patient's QOL domains

Three studies used physiotherapy as an intervention and reported on physical and mental health outcomes[50–52] Physiotherapy did have a significant medium effect on physical health d = 0.50 (95% CI = 0.19 to 0.80 p = 0.001, I^2 = 0%). An Egger's test and funnel plot showed no small study effects bias (p = 0.945). Similarly physiotherapy was found to have a significant effect on mental health outcomes d = 0.44 (95% CI = 0.14 to 0.75, p = 0.004, I^2 = 0%). Egger's tests and funnel plot indicated that there was no small study effect bias for mental health (p = 0.174). The one physiotherapy intervention study that reported social health scores found that physiotherapy had a medium to large effect d = 0.60 (95% CI = 0.21 to 0.90, p = 0.002).[50] Figs. 5 and 6 shows the forest and funnel plot for the analysis.

3.5. Combination of exercises on MS patient's QOL domains

There were five studies of combination of exercise interventions with physical and mental health QOL scores [44,47,53–55] and three studies reporting social health scores.[44,47,53] Combination of exercises has a combination of various types of aerobic, anaerobic and flexibility or strength training exercises. No significant effect was found for the

Table 1
Description of studies that were included in the meta-analysis.

	Author, Study year	Country	N	Study design	Instrument Used	Intervention	Exercise type
1	Ahmadi et al. 2010	Iran	10	RCT	MSQOL-54	Treadmill training	Aerobic
2	Cakit et al. 2010	Turkey	23	RCT	SF-36	Cycling progressive resistance training	Aerobic
	Cakit et al. 2010	Turkey	19	RCT	SF-36	Home based anaerobic exercise	Anaerobic
3	Cohen et al. 2017	USA	14	Repeated measures	MSQLI	Yoga program	Yoga
4	Dodd et al. 2011	Australia	71	RCT	WHOQOL-BREF	Progressive resistance training	Anaerobic
5	Gobbi et al. 2016	Italy	8	Pretest post test	SF-36	Combination of aerobic and strength training sessions	Aerobic and anaerobic
6	Husinga et al. 2011	USA	26	Pretest post test	SF-36	Elliptical exercise training	Aerobic
7	Jackson et al. 2012	USA	26	Single group repeated measures	MSQOL-54	Kickboxing program	Aerobic and anaerobic
8	Kargarfard et al. 2012	Iran	21	RCT	MSQOL-54	Aquatic exercise	Aerobic
9	Kerling et al. 2015	Germany	18	RCT	SF-36	Combined workout	Aerobic and anaerobic
	Kerling et al. 2015	Germany	38	RCT	SF 36	Endurance workout	Aerobic
10	Mutluay et al. 2008	Turkey	43	RCT	MSQOL-54	Group exercise (calisthenics)	Anaerobic
11	Oken et al. 2004	USA	42	RCT	SF-36	Yoga	Yoga
	Oken et al. 2004	USA	35	RCT	SF-36	Aerobic exercise	Aerobic
12	Patti et al. 2002	UK	111	RCT	SF 36	Rehabilitation treatment	Physiotheraphy
13	Pilutti et al. 2016	USA	10	RCT	MSQOL-54	Total body recumbent stepper training	Aerobic
14	Ray et al. 2013	USA	21	Quasi experimental before after trial	SF-36	Progressive resistance respiratory muscle training	Anaerobic
15	Romberg et al. 2005	Finland	91	RCT	MSQOL-54	Progressive resistance training	Anaerobic
16	Salgado et al. 2013	USA	22	Pretest post test	SF-36	Yoga	Yoga
17	Solari et al. 1999	Italy	54	RCT	SF-36	Physical rehab	Physiotheraphy
18	Sutherland et al. 2001	Australia	22	RCT	MSQOL	Water aerobics	Aerobic

combination exercises on physical QOL; $d = 0.06$ (95% CI = -0.21 to 0.32, p = 0.66, $I^2 = 0\%$), mental QOL: $d = 0.59$ (95% CI = -0.15 to 1.33, p = 0.12, $I^2 = 83.7$), or social QOL: $d = 0.07$ (95% CI = -0.24 to 0.39, p = 0.65, $I^2 = 4.1\%$). Funnel plots and Egger's tests showed no small study effect bias for physical (p = 0.08) and mental scores (p = 0.14) but did show for social scores (p = 0.01).

Based on the sensitivity analysis, there was no significant change made to the combined results by any single study indicating that the results were reliable. Meta-regression did not find specific variables that caused heterogeneity, but there could be other factors associated with the heterogeneity present in the study such as methodological issues with randomization within individual studies. However, random effect models were used when heterogeneity was present in our study. The study quality was assessed using the modified PEDro scale (Appendix A). Based on the scale, the studies ranged from 5 to 9 with the majority of the studies in the 9's. This indicated that the majority of studies that were selected were of high quality.

3.6. Summary of results

Table 2 summarizes the impact in terms of effect size of each treatment type on MS patients QOL domains. For all domains of QOL, aerobic exercise was found to have a small significant effect. Anaerobic exercise, combinations of exercises and yoga did not have a significant effect on QOL. Physiotherapy was found to be most effective for the physical, mental and social domains in comparison to other types of complementary treatments.

4. Discussion

This systematic review and meta-analysis extends previous findings by showing that aerobic exercise interventions had a small significant effect in improving MS patients physical, mental and social QOL. These results were consistent with a previous review conducted on the effect of exercise as a treatment for MS that found aerobic exercise helps with psychological problems such as depression.[56] In general, studies have shown that aerobic exercise such as jogging, swimming, cycling and

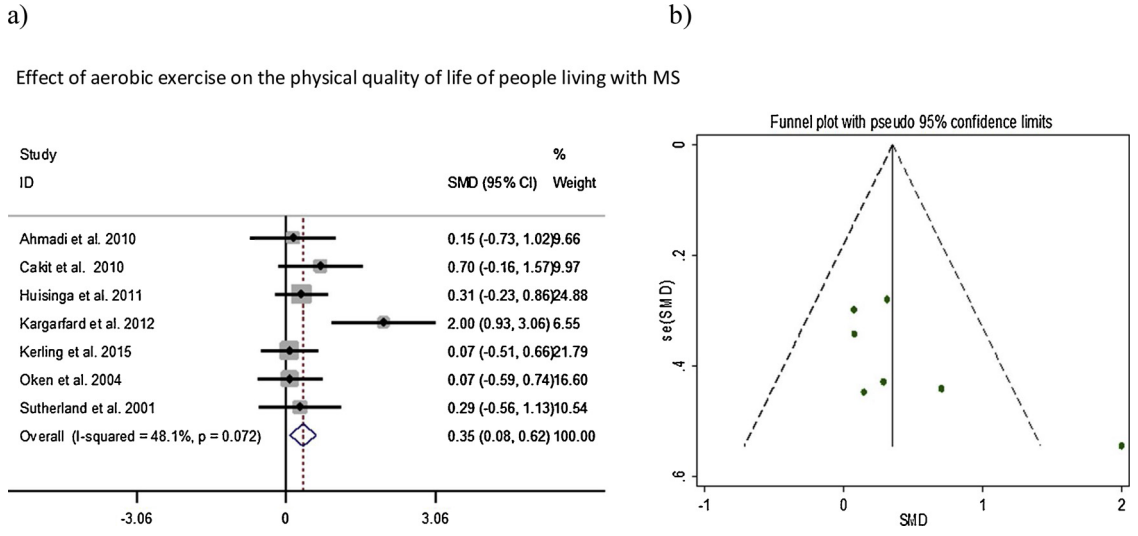

Fig. 2. a) The effect of aerobic exercise on the physical health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for aerobic exercise.

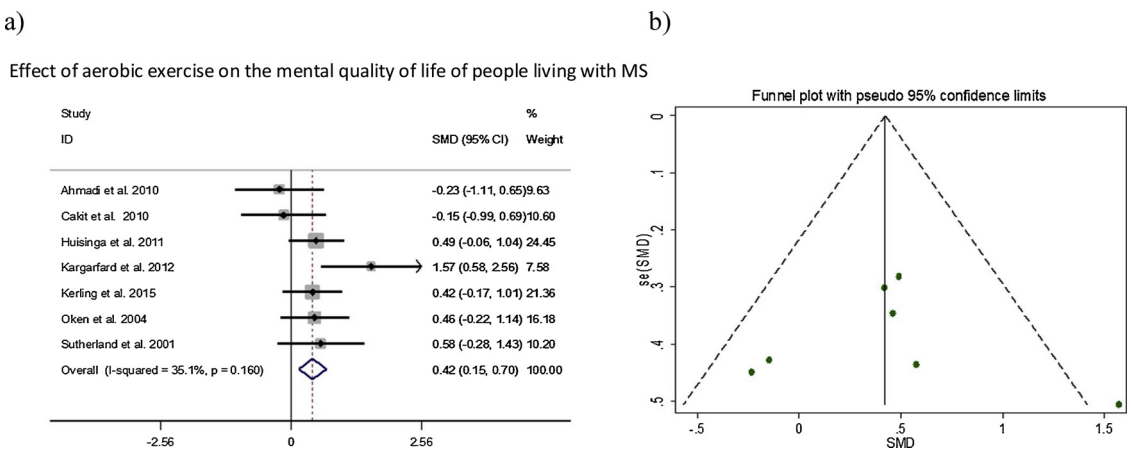

Fig. 3. a) The effect of aerobic exercise on the mental health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for aerobic exercise.

walking reduces anxiety and depression in individuals.[57–60] It is hypothesized that exercise stimulates activity in the sympathetic nervous system (SMS) and activates the parasympathetic nervous system activity (PNS) which causes acetylcholine to be released resulting in a calming effect.[61] Our results are consistent with previous reviews where aerobic exercise have been found to show a slight improvement in physical and mental health since it decreases fatigue and pain which are two main symptoms of MS.[4,62,63]

Pain is common among patients living with MS and it is one of the reasons behind poor QOL[64] There are several types of pain that were reported by patients living with MS such as extremity pain, trigeminal neuralgia, Lhermitte's sign, painful tonic spasms, back pain and headache.[64] The prevalence of pain in MS have ranged from 29% to 86% and managing pain has been one of the difficult tasks for people living with MS.[64] In addition to pain, fatigue is considered another disabling symptom of MS and is associated with inflammation, demyelination or axonal loss.[65] However fatigue could also be considered secondary and can be caused by sleep problems or as side effects of medications used to treat MS.[65]

In a systematic review conducted by Latimer-Cheung et al. 2013, it was found that aerobic exercise training could improve walking endurance in people living with MS.[4] In their paper, they indicate mixed evidence for aerobic exercise and its impact on the health related QOL of people living with MS which could be due to differences in the type of exercise carried out during the trials.[4] One randomized controlled trial (RCT) showed that thrice weekly moderate-intensity aerobic exercise such as treadmill training, elliptical training and cycling had a significant effect on improving the mental composite scores.[66] Another RCT showed that aerobic and resistance training 2 times per week for 8 weeks helped improve physical functioning.[39] However other experimental studies showed no or minimal effect of aerobic exercise on health related QOL.[43,67] Other meta-analysis literature has shown that exercise training in general resulted in small improvements in QOL among individuals living with MS. Similar findings were shown by Motl et al. 2008 and Motl et al. 2009 where both articles indicated the benefits of aerobic exercise where individuals who were more physically active reported lower level of disability, depression, fatigue and pain.[7,15] In addition patients reported higher levels of social support and increased self-efficacy for managing MS.[7,15]

Physiotherapy was also found to be beneficial in improving the physical and mental QOL of people living with MS where it was found to have a medium effect on physical QOL and small effect on mental health. This was consistent with a randomized controlled trial that assessed the effect of physiotherapy at home vs outpatient program vs no therapy program. Based on the study, it was found that physiotherapy improved mobility, subjective wellbeing and mood in people living with MS.[68] Another study that investigated the benefits of physiotherapy found similar results in that physiotherapy helped to improve balance and gait.[69] Incorporating therapeutic exercise into physiotherapy programs was found to be beneficial for people living with MS as well as other neurological conditions.[70]

Based on our analysis aerobic exercise and physiotheraphy were effective for improving QOL. The improvement reported by patients could be due to feeling better when using CAM as opposed to when

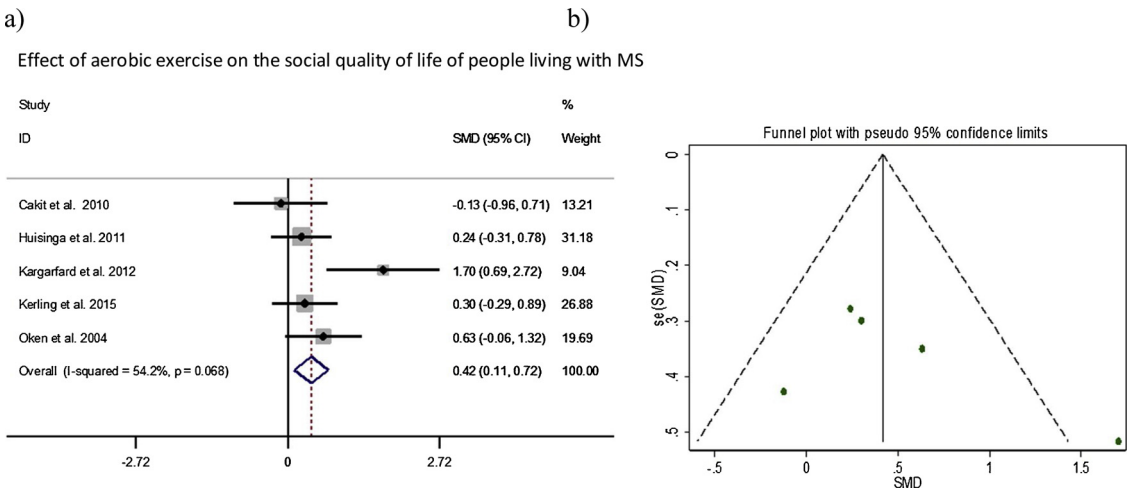

Fig. 4. a) The effect of aerobic exercise on the social health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for aerobic exercise.

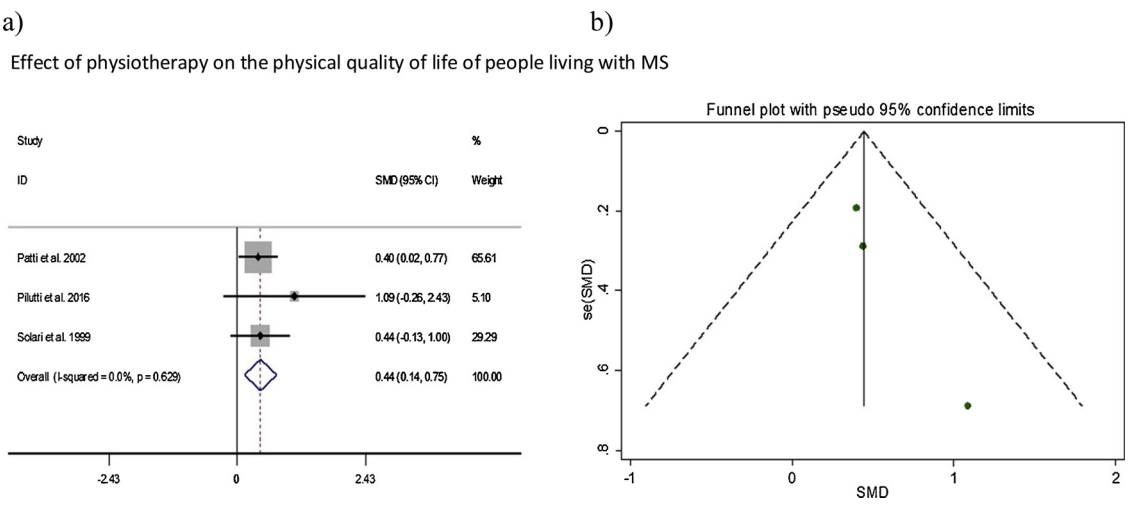

Fig. 5. a) The effect of physiotherapy on the physical health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for physiotherapy.

using traditional medications. This is evident in a study done on CAM use whereby individuals who used CAM reported that their stress was reduced and found improvements in their overall wellbeing.[71] One of the main reasons for using CAM was the ineffectiveness of conventional medical treatments in not providing symptomatic relief.[71] In addition to this, the longer people use CAMs, the less satisfied they were of conventional medicine.[72] Similar findings were found in another study, where exercise therapy was most frequently used as one of the CAM treatments.[73]

The strength of this systematic review is that it provides an effect size estimate for the impact of exercise, yoga and physiotherapy on the physical, mental and social QOL domains. A limitation of the analysis is that some studies could not be included in the meta-analysis because they either did not report physical, mental and social QOL scores or were published in languages other than English. Some articles did not report mean and standard deviations needed to calculate SMD and were therefore excluded. The exclusion criteria also did not allow for the use of other types of QOL scales such as fatigue impact scale which may have reduced the number of articles included in the meta-analysis. There was also some heterogeneity that were found in some of the analysis, which indicated variation in the degree of association between the type of intervention and its effect on the physical, mental and social health of individuals with MS. However we used a random effects model in our analysis when heterogeneity was present. Publication bias that was present when assessing the effect of combination of therapies on social health was probably due to small studies being included in the analysis. Since combination of therapies was not significant in our analysis, the results were negligible. There were few number of studies on yoga, which could not give a good estimate of the overall effect on QOL, one of the possible reasons for this is that yoga, and its effect on MS is starting to gain popularity in the last couple of years. Therefore, research in this area is scarce.

5. Conclusions

This systematic review indicates that physical activity particularly aerobic exercise and physiotherapy had the greatest impact on physical, mental and social health as opposed to anaerobic exercise, combination of exercises or yoga. This review provides some evidence for carrying out exercise and doing physiotherapy to improve QOL. However, further studies need to be conducted in CAM treatments in terms of amount of treatment necessary in order for improvements to be noticed in physical, mental and social aspects of quality of life. The combination of CAM with traditional medications need to be explored in order to determine the overall safety and effectiveness of these treatments in relieving symptoms of MS.

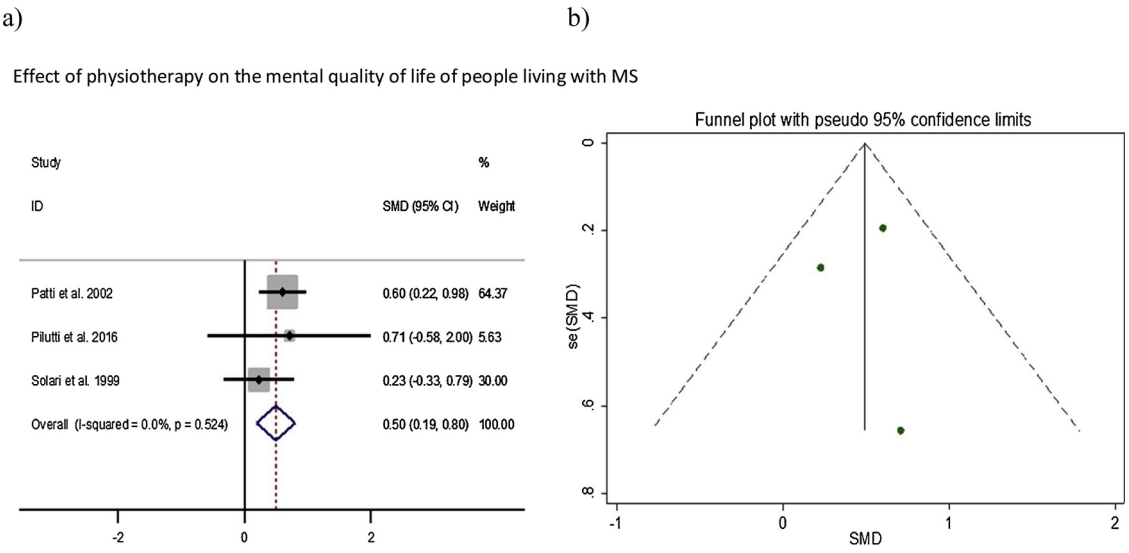

Fig. 6. a) The effect of physiotherapy on the mental health of people living with MS. b) Funnel plot with pseudo 95% confidence limits for physiotherapy.

Table 2
Effect size estimates for interventions based on domains of quality of life.

Domains	Type of Intervention	No of studies	Cohen's d	95% CI	p-value	Effect
Physical	Aerobic	7	0.35	0.08-0.62	0.01	Small effect
	Anaerobic	4	−0.02	−0.30-0.26	0.90	
	Combined	5	0.06	−0.21-0.32	0.66	
	Physiotherapy	3	0.50	0.19-0.80	p < 0.001	Medium effect
	Yoga	3	0.11	−0.26-0.48	0.57	
Mental	Aerobic	5	0.42	0.11-0.72	0.007	Small effect
	Anaerobic	2	−0.10	−0.47-0.28	0.61	
	Combined	5	0.59	−0.15-1.33	0.12	
	Physiotherapy	3	0.44	0.14-0.75	0.004	Small effect
	Yoga	3	0.46	−0.24-1.17	0.19	
Social	Aerobic	7	0.42	0.15-0.69	0.002	Small effect
	Anaerobic	2	−0.18	−0.81-0.45	0.57	
	Combined	5	0.07	−0.24-0.39	0.65	
	Physiotherapy	1	0.60	0.21-0.90	0.002	Medium to large effect
	Yoga	1	−0.28	−0.89-0.32	0.36	

$p < 0.05$ was used to identify significance.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.02.010.

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