Multiple Sclerosis and Exercise: A Literature Review

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Abstract

Multiple sclerosis (MS) is the most common autoimmune disabling neurological conditions of young adults and affects more than 2.3 million people worldwide. Given the high likelihood for disability and decreased neurological function, there have been concerns about the role of exercise in MS patients with a fear of increased injury. This article looks at recent articles evaluating the role of exercise in MS and can hopefully be used by patients, caregivers, and health care providers to guide decision making about the role of exercise in patients with MS.

Introduction

Multiple sclerosis (MS) is an immune-mediated, demyelinating disease that affects the central nervous system (CNS)—leading to considerable physical disability (1). MS currently affects more than two million people worldwide according to the National Multiple Sclerosis Society, and current estimates state that more than 400,000 individuals are affected in the United States (1). Recent data show that MS affects more women than men by a two-to-one ratio (2). Patient age at diagnosis is traditionally between 20 and 50 yr (1).

Numerous hypotheses exist as to which individuals get MS, but most experts agree that it is a combination of genetic and environmental factors. Genetic factors comprise mainly ethnicity and sex, with current research directed toward specific single-nucleotide polymorphisms and histocompatibility complexes (3,4). Environmental factors include geography and vitamin D exposure: generally, the closer that patients live to the equator, the less likely they are to get MS; additionally, higher levels of vitamin D are thought to be protective against MS (5–7). The role of exercise in MS has been controversial, with some thinking that it could lead to increased morbidity due to injuries, but new research is showing benefits of exercise regardless of disability level secondary to MS (8). The purpose of this article is to review new research relating to this topic and to consider new recommendations for our patients with MS.

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1537-890X/1701/31–35
Current Sports Medicine Reports

Diagnosis

The diagnostic criteria for MS have gradually changed over the years; however, the general principle has remained the same: CNS lesions must be disseminated both in time and space. These can be demonstrated either clinically or with radiographic imaging, typically magnetic resonance imaging (MRI). The McDonald criteria, first developed in 2001, and have since undergone two revisions, is the best evidence-based tool that clinicians have for the diagnosis of MS (9). For the 2010 revision to the McDonald criteria, the goal was to simplify the ability to show lesions in space and time with the help of MRI. Dissemination in space requires one or more lesions in at least two regions of the CNS on a T2-weighted MRI, or clinical demonstration of attacks involving two distinct areas of the CNS. Dissemination in time requires two separate, distinct, clinical attacks or presence of new lesions on MRI on follow-up scans (9). There are additional or supplemental requirements that must be met for those patients whose clinical course are more complicated or in those whose diagnosis is not certain/unclear, but that is beyond the scope of this article.

Multiple sclerosis is classically divided into four phenotypes: clinically isolated syndromes (CIS), Relapsing-remitting, secondary progressive, and primary progressive (10). These revisions were made in 2013 with CIS being a new addition. Clinically isolated syndrome is the first attack of a condition typically seen with MS (*i.e.*, optic neuritis) that has yet to fulfill McDonald MS criteria via a lack of demonstration of lesions in space or time. The odds of progression to MS depend on MRI findings during the first attack and which areas of the CNS are affected. For example, if there are positive MRI findings after an attack of optic neuritis, odds of progression to MS are 56%, with a normal MRI of 22% (11). Relapsing-remitting MS is defined by attacks and relapses with clearly defined intervals of time between attacks, whereby the patient may or may not return to complete baseline. This accounts for 80% to 90% of MS cases (12). Secondary progressive MS is when

the patient initially has relapsing remitting type, followed by gradual worsening and progression of disease without remissions. Primary progressive MS is characterized by progression from the onset with only temporary plateaus.

Treatment

Treatment of MS is divided into two categories with very different pharmacotherapy: acute attacks and disease-modifying agents. For acute attacks, used mainly to combat relapses in relapse-remitting MS, high-dose glucocorticoids are the mainstay of therapy (13). This is typically done via a 3- to 7-d course of intravenous (IV) methylprednisone or oral prednisone with or without a short prednisone taper. In regard to disease-modifying agents, these are different forms of immunomodulatory agents that can be given via differing routes depending on patient preference and disease activity. The goal of disease-modifying agent therapy is to decrease the risk of long-term disease progression and the amount of relapses (14). Which agent to use should be a choice between the patient and their neurologist, tailored to the patient's goals of therapy. Currently, there are three main classes of disease-modifying agents used (15). One is infusion therapy with natalizumab. This therapy is more targeted to patients who desire effectiveness over safety and convenience. Two is an injectable medication (interferon beta) that patients can do at home once a week. This therapy is targeted to patients who prefer safety over convenience and maximum efficacy because these are some of the best-studied disease-modifying medications. The last class is for patients who prefer convenience, that is, daily oral disease-modifying agents (dimethyl fumarate). The role of exercise in MS therapy is currently being explored, and current literature will be reviewed in the coming sections.

Resistance Training in MS

Resistance training is an exercise that causes muscles to contract against a form of resistance, such as lifting weights or using exercise bands. There are various types of resistance training, but most have the purpose of increasing the strength and function of the muscles exercised. Previous advice for patients with MS was to avoid exercise (endurance and resistance) all together with fear that it may worsen or accelerate disease progression. However, over the last 10 to 15 yr, there have been multiple studies examining the effects of resistance training in patients with MS. The research that has been done has shown promising results with the potential to improve the lives of patients suffering from MS. Most of the studies have been 8- to 12-wk programs with a progressive resistance training (PRT) program, meaning that the further they get into the program the more the resistance is increasing for the exercises. All of these studies have shown that patients who complete the PRT program have increased strength compared with the controls (16–24) as well as increasing muscle fiber size and the power generated from their muscles (16,17,24,25). The research also has shown that resistance training programs in patients with MS improve their balance and functional ability while at the same time decreasing their disability status (16–23,26). A few studies also have looked at more intense resistance training with High-Intensity Interval Training (HIIT) and found similar outcomes to a PRT program with improved strength and quality of life (32) and found that it only took 3 wk of training to see these improvements (27). In resistance training programs that are solely home based without in person instruction, patients only saw increases in strength but not in balance and functional capacity (28). However, it also was shown that patients who completed a resistance training program, were able to successfully continue the training program at home and maintain their improved strength and quality of life (23).

Researchers also have studied resistance training in MS to see if there is any change on a physiological level. One study looked at a multitude of inflammatory markers before and after a 12-wk PRT program and found that there were no significant changes in either group, but a study in women with MS did show that yoga can improve inflammation showing decreased cortisol levels and increased ACTH levels (29). Another group did find increased cortical thickness on brain MRI after a 24-wk PRT, indicating that resistance training may have a neuroprotective or neuroregenerative effect on MS (20).

These studies have shown significant decreases in the patient's disability status by improving their strength, balance, and functional capacity. It is important to note that there were no significant setbacks or injuries shown in the patients in these studies meaning that not only can resistance training improve the quality of life in patients with MS it also is very safe. With a multitude of studies showing decreased disability scores, resistance training may serve as a therapy to delay functional deterioration in people with MS (17).

Aquatic Therapy and MS

Aquatic exercise and swimming have been particular topics of interest in regard to the MS literature because it theoretically has some advantages over equal exercise on land. The three main advantages of aquatic exercise are buoyancy, viscosity, and thermodynamics (30). Buoyancy is beneficial because it reduces weight on joints and creates a much smoother and lower impact exercise environment. Viscosity creates drag, and an environment in which exercises can be done in all directions rather than a single plane. Resistance is easily increased simply by increasing speed of movement. The third, thermodynamics, may play the most important role in MS patients, who often have difficulties with thermoregulation due to Uhthoff phenomenon. Uhthoff phenomenon is the worsening of MS symptoms in the setting of increasing temperature (31). Precooling MS patients before exercise can prevent the crossing of the critical temperature threshold and improve exercise tolerance (32). Aquatic exercise programs can more precisely maintain a patient's body temperature during exercise due to the water's high heat capacity and rate of heat transfer compared with air.

Aquatic exercise therapy has several studies not only looking at patient function and reported subjective improvements but also in animal studies and at an immunologic and biochemical level. One study showed improvement in short-term memory in rats and another showed increased serum levels of brain-derived neurotrophic factor (BDNF) in humans (33,34). Two small cohort studies have shown mixed results which appear to be related to the number of aquatic exercise sessions attended. Roehrs and Karst (35) showed

very minor improvements in Modified Social Support Survey (MSSS) and Modified Fatigue Impact Scale (MFIS), but overall minimal changes in a 12-wk aquatic exercise program which had high dropout and low attendance to exercise sessions (over half withdrew or attended <50% of sessions). Salem *et al.* (36) showed significant improvements in 10-m walk test, Berg Balance Scale (BBS), and Timed Up and Go (TUG) test, and had much better attendance (88%) during a 5-wk program.

Several randomized controlled trials have been done looking at aquabiking, aquatic aerobics, and Ai-Chi. Ai-Chi is a combination of Tai-Chi and Qigong, and is performed in water. Bansi *et al.* (34,37) published two articles showing improvements in exercise tolerance and cardiorespiratory values with aquabiking compared with stationary bike for 3 wk, but did not improve fatigue scores during daily life. Two studies looked at aquatic aerobics. One study showed improvements in fatigue and quality of life compared with control after 8 wk of aquatic exercise (38). Another study found the aquatic aerobic cohort's improvements to be equivalent to land-based Pilates (39). Two studies have looked at Ai-Chi versus strength exercises combined with abdominal breathing exercises (40,41). Both studies were small, but with promising results. Bayraktar *et al.* (40) showed improvement in TUG, one leg stance, 6-min walk, and fatigue severity scores after an 8-wk program. Castro-Sanchez *et al.* (41) showed improvements in pain scores with 20 wk of Ai-Chi which were sustained 4 wk after stopping the exercise and still improved from baseline 10 wk later. These patients also had improvements in disability, depression, and fatigue.

In all studies, both aquatic- and land-based exercises were beneficial. It is still debatable whether the aquatic aspect is significantly better, though the studies do lean toward suggesting aquatic exercise is more beneficial. The main advantage appears to be the thermoregulatory benefits of water. None of the studies specifically monitored body temperature during exercise, and this could potentially be a further area of research

MS and Aerobic exercise

There are numerous studies that highlight the benefits of exercise in the setting of MS with many of them having limitations in terms of number of participants, subjective scoring systems, and duration of study. As this field has evolved, especially over the last decade, many papers have been published showing the benefits of exercise in patients with MS across a litany of quality of life measures. As such, we will review some of the more interesting, poignant, and applicable papers here, with an emphasis on meta-analyses and systemic reviews because these significantly increase the power of our data.

Leavitt *et al.* (42) conducted a study that showed increased hippocampal volume in an MS patient who underwent a 3-month aerobic exercise program. They cite numerous studies that show an increase in hippocampal volume in nonhuman animals after exercise, and their comparison between two MS patients showed a 16.5% increase in hippocampal volume and 53.7% increase in memory (assessed with verbal and nonverbal tasks (California Verbal Learning Test-second edition [CVLT-II], Brief Visual Memory Test Revised [BVMT-R]) in the patient who went through the exercise program.

A systematic review and meta-analysis of 11 studies done by Paltamaa *et al.* (43) showed improvements in balance for MS patients with mild and moderate disabilities after implementing an aerobic exercise program. There was no statistically significant difference for patients with severe disabilities before starting an exercise program. In the conclusion of their article, they discuss the need for many more studies as the studies they included ranged from 4 to 40 participants.

In another systematic review assessing fatigue management and impact of different modalities of therapy on fatigue, Asano and Finlayson (44) reviewed 25 articles and came to the conclusion that aerobic exercise therapy had a more significant impact on reducing patient-reported levels of fatigue compared with fatigue education and pharmacotherapies. Similarly, in a comprehensive Cochrane review, which resulted in 45 included studies, Heine *et al.* (45) showed a statistically significant difference between exercise and control groups when it came to fatigue reduction. On average, fatigue was reduced to 53% across all studies. This study also addresses some of the previously perceived negative side effects of exercise. They showed that there was no difference in number of relapses between the intervention and control groups, although the authors' acknowledge this was not reported in all of the studies included. Additionally, there was only one fall across all studies, which encompassed over 2000 patients.

In a comprehensive review assessing multiple modalities to combat fatigue, Rottoli *et al.* (46) came to a conclusion that exercise plays a key role in preventing and treating fatigue in MS patients. In their review, they state that 80% of all MS patients suffer from fatigue, regardless of disability level, and 55% of patients report that it is the most debilitating symptom they suffered from. Of note, the fatigue scales used in their systematic review varied greatly among the included studies; however, they conclude that the best therapeutic approach to fatigue in MS patients includes exercise as part of a multidisciplinary approach.

Conclusion

Overall, it can be reasonably concluded based on current research that exercise should be a mainstay of treatment for patients with MS. Each type of exercise listed above was shown to have positive impacts across a variety of symptoms typically encountered by patients with MS, most prominently fatigue and balance. This leads to a perceived increase in the quality of life without any negative effects as all studies that have tracked adverse outcome show no increase in falls or accidents. Of note, exercise does not seem to prevent or cause a decreased frequency of relapses, but this has been poorly studied so far. This should be a more focused area of research going forward as studies that have relapse rates have an inadequate number of patients and inadequate duration of study to make significant conclusions.

When it comes to trying to determine if one form of exercise is superior compared with others, there are very few studies that have attempted to evaluate this. One article, done by Kerling *et al.* (47) attempted to assess if there was a difference between aerobic exercise and a combined program of

aerobic exercise plus resistance training on the impact of quality of life and fatigue. They showed that, although each group that exercised showed statistically significant differences from the control group of no exercise, there was no significant difference between the two groups. As stated above, aqua therapy is an evolving field with great potential in patients with MS due to its ability to allow for a well-rounded exercise regimen, all while keeping body temperature lower than similar exercise on land. This thereby reduces chances of MS patients having to stop exercise due to flair ups of symptoms relating to increased body temperature.

This is still an evolving area of study, but there has been much progress in the last 5 to 10 yr regarding evidenced-based approaches to exercise in MS patients. We would recommend further research include multicenter studies to have a significantly higher number of patients in one study that uses that same subjective measures for fatigue, depression, quality of life evaluation, and so on. It also would be best for studies to use the same subjective measures to allow for greater comparison across studies, which would thereby improve the quality of meta-analyses. Additionally, these studies all typically range from 2 to 6 months in duration, and current evidence is lacking if effects of exercise plateau after a certain duration, or maybe even decrease over time; as such, longer-duration studies are necessary. Regardless, the evidence is clear that exercise, in addition to appropriate pharmacotherapy, should be a part of a multidisciplinary approach in the treatment of MS.

The authors declare no conflict of interest and do not have any financial disclosures.

References

1. Noonan CW, Williamson DM, Henry JP, *et al*. The prevalence of multiple sclerosis in 3 US communities. *Prev. Chronic Dis.* 2010; 7:A12.
2. Who gets MS? (Epidemiology)[cited 2017 Feb 4]. *National Multiple Sclerosis Society website*. http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS.
3. Nischwitz S, Müller-Myhsok B, Weber F. Risk conferring genes in multiple sclerosis. *FEBS Lett.* 2011; 585:3789–97. doi: 10.1016/j.febslet.2011.03.037.
4. Yeo TW, De Jager PL, Gregory SG, *et al*. A second major histocompatibility complex susceptibility locus for multiple sclerosis. *Ann. Neurol.* 2007; 61:228–36.
5. Kampman MT, Brustad M. Vitamin D: a candidate for the environmental effect in multiple sclerosis—observations from Norway. *Neuroepidemiology.* 2008; 30:140–6. doi: 10.1159/000122330.
6. Munger KL, Levin LI, Hollis BW, *et al*. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006; 296:2832–8.
7. Islam T, Gauderman WJ, Cozen W, Mack TM. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. *Neurology.* 2007; 69:381–8.
8. Edwards T, Pilutti LA. The effect of exercise training in adults with multiple sclerosis with severe mobility disability: a systematic review and future research directions. *Mult Scler Relat Disord*. 2017; 16:31–9.
9. Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann. Neurol.* 2011; 69:292–302.
10. Lublin FD, Reingold SC, Cohen JA, *et al*. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology.* 2014; 83:278–86.
11. Beck RW, Trobe JD, Moke PS, *et al*. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. *Arch. Ophthalmol.* 2003; 121:944–9.
12. Weinshenker BG. Natural history of multiple sclerosis. *Ann. Neurol.* 1994; 36:S6–11.
13. Galea I, Ward-Abel N, Heesen C. Relapse in multiple sclerosis. *BMJ*. 2015; 350:h1765.
14. Lizak N, Lugaresi A, Alroughani R, *et al*. Highly active immunomodulatory therapy ameliorates accumulation of disability in moderately advanced and advanced multiple sclerosis. *J. Neurol. Neurosurg. Psychiatry.* 2017; 88:196–203.
15. Tramacere I, Del Giovane C, Salanti G, *et al*. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst. Rev.* 2015:CD011381.
16. Cruickshank T, Reyes A, Ziman M. A systematic review and meta-analysis of strength training in individuals with multiple sclerosis or Parkinson's disease. *Medicine*. 2015; 94.
17. de Souza-Teixeira F, Costilla S, Alan C, *et al*. Effects of resistance training in multiple sclerosis. *Int. J. Sports Med.* 2009; 30:245–50.
18. Eftekhari E, Mostahfezian M, Etemadifar M, *et al*. Resistance training and vibration improve muscle strength and functional capacity in female patients with multiple sclerosis. *Asian J Sports Med.* 2012; 3:279–84.
19. Jørgensen M, Dalgas U, Wens I, *et al*. Muscle strength and power in persons with multiple sclerosis—a systematic review and meta-analysis. *J. Neurol. Sci.* 2017; 376:225–41.
20. Kjølhede T, Siemonsen S, Wenzel D, *et al*. Can resistance training impact MRI outcomes in relapsing-remitting multiple sclerosis. *Mult. Scler.* 2017: 1352458517722645.
21. Kjølhede T, Vissing K, de Place L, *et al*. Neuromuscular adaptations to long-term progressive resistance training translates to improved functional capacity for people with multiple sclerosis and is maintained at follow-up. *Mult. Scler.* 2015; 21:599–611.
22. Moradi M, Sahraian MA, Aghsaie A, *et al*. Effects of eight-week resistance training program in men with multiple sclerosis. *Asian J Sports Med.* 2015; 6.
23. White LJ, McCoy SC, Castellano V, *et al*. Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult. Scler.* 2004; 10:668–74.
24. Zaenker P, Favret F, Lonsdorfer E, *et al*. High-intensity interval training combined with resistance training improves physiological capacities, strength and quality of life in multiple sclerosis patients: a pilot study. *Eur. J. Phys. Rehabil. Med.* 2017.
25. Dalgas U, Stenager E, Jakobsen J, *et al*. Muscle fiber size increases following resistance training in multiple sclerosis. *Mult. Scler.* 2010; 16:1367–76.
26. Sangelaji B, Kordi M, Banihashemi F, *et al*. A combined exercise model for improving muscle strength, balance, walking distance, and motor agility in multiple sclerosis patients: a randomized clinical trial. *Iran. J. Neurol.* 2016; 15:111–20.
27. Manca A, Dvir Z, Dragone D, *et al*. Time course of strength adaptations following high-intensity resistance training in individuals with multiple sclerosis. *Eur. J. Appl. Physiol.* 2017; 117:731–43.
28. DeBolt L, McCubbin J. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. *Arch. Phys. Med. Rehabil.* 2004; 85:290–7.
29. Najafi P, Moghadasi M. The effect of yoga training on enhancement of adrenocorticotropic hormone (ACTH) and cortisol levels in female patients with multiple sclerosis. *Complement. Ther. Clin. Pract.* 2017; 26:21–5.
30. Frohman AN, Okuda DT, Beh S, *et al*. Aquatic training in MS: neurotherapeutic impact upon quality of life. *Ann. Clin. Transl. Neurol.* 2015; 2:864–872. doi:10.1002/acn3.220.
31. Frohman TC, Davis SL, Beh S, *et al*. Uhthoff's phenomena in MS - clinical features and pathophysiology. *Nat. Rev. Neurol.* 2013; 9:535–40.
32. Davis SL, Wilson TE, White AT, *et al*. Thermoregulation in multiple sclerosis. *J. Appl. Physiol. (1985)*. 2010; 109:1531–7.
33. Jin J-J, Ko I-G, Kim S-E, *et al*. Swimming exercise ameliorates multiple sclerosis-induced impairment of short-term memory by suppressing apoptosis in the hippocampus of rats. *J. Exerc. Rehabil.* 2014; 10:69–74.
34. Bansi J, Bloch W, Gamper U, *et al*. Endurance training in MS: short-term immune responses and their relation to cardiorespiratory fitness, health-related quality of life, and fatigue. *J. Neurol.* 2013; 260:2993–3001.
35. Roehrs TG, Karst GM. Effects of an aquatics exercise program on quality of life measures for individuals with progressive multiple sclerosis. *J. Neurol. Phys. Ther.* 2004; 28:63–71.
36. Salem Y, Scott AH, Karpatkin H, *et al*. Community based group aquatic programme for individuals with multiple sclerosis: a pilot study. *Disabil. Rehabil.* 2011; 33:720–8.
37. Bansi J, Bloch W, Gamper U, *et al*. Training in MS: influence of two different endurance training protocols (aquatic versus overland) on cytokine and neurotrophin concentrations during three week randomized controlled trial. *Mult. Scler.* 2013; 19:613–21.

38. Kargarfard M, Etemadifar M, Baker P, *et al*. Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. *Arch. Phys. Med. Rehabil.* 2012; 93:1701–8.

39. Marandi SM, Nejad VS, Shanazari Z, *et al*. A comparison of 12 weeks of Pilates and aquatic training on the dynamic balance of women with multiple sclerosis. *Int. J. Prev. Med.* 2013; 4:S110–7.

40. Bayraktar D, Guclu-Gunduz A, Yazici G, *et al*. Effects of Ai-Chi on balance, functional mobility, strength and fatigue in patients with multiple sclerosis: a pilot study. *NeuroRehabilitation*. 2013; 33:431–7.

41. Castro-Sánchez AM, Matarán-Peñarrocha GA, Lara-Palomo I, *et al*. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. *Evid Based Complement Alternat Med*. 2012; 2012:473963.

42. Leavitt VM, Cirnigliaro C, Cohen A, *et al*. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: preliminary findings. *Neurocase*. 2014; 20:695–7.

43. Paltamaa J, Sjögren T, Peurala SH, *et al*. Effects of physiotherapy interventions on balance in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. *J. Rehabil. Med*. 2012; 44: 811–23.

44. Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. *Mult. Scler. Int*. 2014; 2014:798285.

45. Heine M, van de Port I, Rietberg MB, *et al*. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst. Rev.* 2015:CD009956.

46. Rottoli M, La Gioia S, Frigeni B, *et al*. Pathophysiology, assessment and management of multiple sclerosis fatigue: an update. *Expert Rev. Neurother.* 2017; 17:373–9.

47. Kerling A, Keweloh K, Tegtbur U, *et al*. Effects of a short physical exercise intervention on patients with multiple sclerosis. *Int. J. Mol. Sci.* 2015; 16:15761–75.

48. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Mult. Scler.* 2008; 14:35–53.

49. Deckx N, Wens I, Nuyts A, *et al*. 12 Weeks of combined endurance and resistance training reduces innate markers of inflammation in a randomized controlled clinical trial in patients with multiple sclerosis. *Mediators Inflamm.* 2016.

50. Silverman EP, Miller S, Zhang Y, *et al*. Effects of expiratory muscle strength training on maximal respiratory pressure and swallow-related quality of life in individuals with multiple sclerosis. *Mult Scler J Exp Transl Clin.* 2017; 3:2055217317710829.