Current Neurology and Neuroscience Reports (2019) 19: 88
https://doi.org/10.1007/s11910-019-1002-3

DEMYELINATING DISORDERS (J. BERNARD & M. CAMERON, SECTION EDITORS)

Exercise as Medicine in Multiple Sclerosis—Time for a Paradigm Shift: Preventive, Symptomatic, and Disease-Modifying Aspects and Perspectives

Ulrik Dalgas[1] · Martin Langeskov-Christensen[1] · Egon Stenager[2,3,4] · Morten Riemenschneider[1] · Lars G. Hvid[1]

Published online: 13 November 2019

Abstract

Purpose of Review For many years, exercise was controversial in multiple sclerosis (MS) and thought to exacerbate symptoms and fatigue. However, having been found to be safe and effective, exercise has become a cornerstone of MS rehabilitation and may have even more fundamental benefits in MS, with the potential to change clinical practice again. The aim of this review is to summarize the existing knowledge of the effects of exercise as primary, secondary, and tertiary prevention in MS.

Recent Findings Initial studies established exercise as an effective symptomatic treatment (i.e., tertiary prevention), but recent studies have evaluated the disease-modifying effects (i.e., secondary prevention) of exercise as well as the impact on the risk of developing MS (i.e., primary prevention).

Summary Based on recent evidence, a new paradigm shift is proposed, in which exercise at an early stage should be individually prescribed and tailored as "medicine" to persons with MS, alongside conventional medical treatment.

Keywords Training · Physical activity · Exercise therapy · Kinesiology · Clinical exercise physiology · Neurological disorder

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune-mediated, physically and cognitively debilitating disorder of the central nervous system (CNS), with no existing cure [1]. More than 2.3 million people live with MS worldwide [2], and it is the most prevalent non-traumatic neurological disorder in younger people [3], most frequently affecting women and has its onset around age 20–40 [4]. Since life expectancy in MS patients is reduced by 6–10 years when compared to the general population [5, 6], approximately 80% of patients will live with MS for more than 35 years [7]. The vast majority of these patients will experience the deleterious physical and cognitive consequences associated with the disease [8], which will ultimately affect their quality of life. Looking beyond the individual patient perspective toward an economic societal perspective, MS is further associated with substantial health care costs [9, 10]. Altogether, identification of effective symptomatic treatments (attenuating symptoms of the disease, i.e., tertiary prevention [11]), disease-modifying treatments (decreasing the severity of MS or slowing/halting progression of the disease by affecting the underlying pathology/pathophysiology, i.e., secondary prevention [11]), and potentially even preventive treatments (preventing development of the disease or stopping individuals from becoming at high risk, i.e., primary prevention [11]) is therefore highly warranted in MS.

So far, 16 disease-modifying drugs, primarily aimed at reducing relapse rates, have been approved [12]. However, these disease-modifying drugs are only partially effective in reducing progression and affecting symptoms of MS, such as impaired physical function [13]. In fact, symptoms such as fatigue [14] and cognition [15] are most often unaffected by medical treatment. Moreover, disease-modifying drugs are

Topical Collection on *Demyelinating Disorders*

✉ Ulrik Dalgas
dalgas@ph.au.dk

[1] Department of Public Health, Section for Sport Science, Aarhus University, Aarhus, Denmark

[2] Department of Neurology, Hospital of Southern Jutland, Sønderborg, Denmark

[3] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark

[4] MS Clinics of Southern Jutland (Sønderborg, Esbjerg, Kolding), Hospital of Southern Jutland, Sønderborg, Denmark

often associated with substantial side effects [16]. Therefore, effective non-pharmacological treatments with few side effects are of particular interest in MS, with one of the most promising candidates being exercise [17]. This is in line with the current international focus, in which exercise prescription is now considered "medicine" for 26 chronic conditions [18]. However, this paradigm shift has yet to gain momentum in MS, as addressed in a recent editorial [19]. This is likely because exercise was, for many years, a controversial intervention thought to exacerbate symptoms and fatigue in these patients [20]. Today, it is known that exercise is safe [21••] and that the incidental exacerbation of symptoms during exercise is a transient phenomenon that is normally fully reversed within 30 min after exercise cessation [22]. Furthermore, exercise may improve chronic fatigue rather than worsen it [23]. Consequently, previous concerns related to exercise in MS are unfounded.

Over the past 15 years, strong scientific interest in exercise has arisen, resulting in a substantial body of new research and evidence. While the initial studies considered exercise as an interesting symptomatic treatment (i.e., tertiary prevention), more recent work has started to evaluate aspects of exercise as also being disease-modifying—slowing/halting disease progression (i.e., secondary prevention) [24•] and even reducing the risk of MS (i.e., primary prevention) [25••]. Despite holding the potential to change clinical practice, no previous review paper has collected and summarized the existing knowledge on the effects of exercise as primary, secondary, and tertiary prevention against MS, which is therefore the aim of the present narrative review. Based on this summary, we will propose a paradigm shift in which exercise at an early stage should be individually prescribed and tailored as "medicine" for persons with MS, along with conventional medical treatment.

Definitions and Exercise Framework

According to Caspersen et al., physical activity is defined as "any bodily movement produced by skeletal muscles that result in energy expenditure." Physical activity in daily life can be categorized as occupational, sports, conditioning, household, or other activities, whereas exercise is defined as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective – the improvement or maintenance of physical fitness" [26]. While many different types of exercise exist, these can be classified according to the relative content of the two extremes of physical exercise modalities: resistance training and aerobic training [27]. Resistance training is characterized by a limited number of muscle contractions against heavy loads, primarily taxing the neuromuscular system [28]. Aerobic training is characterized by a large number of muscle contractions against low-resistance loads, primarily taxing the cardiovascular system [29]. While resistance and aerobic training (or combinations of the two) have been extensively evaluated in MS [30, 31], other exercise modalities, including yoga [32], Pilates [33], and balance training [34], have also attracted attention. No matter the type of exercise, the foundation of prescription is composed of four underlying exercise principles: (1) individual tailoring, (2) application of specific exercises (adhering to the goal of the exercise program), (3) progressive overload, and (4) regular and continuous moderate-to-high intensity efforts to sustain effects [35].

As exercise is only a subset of physical activity, an interesting, yet non-investigated, aspect is whether physical activity and exercise lead to comparable effects (i.e., preventive, symptomatic, and/or disease-modifying effects) following an intervention period. To avoid any unfounded conclusions on the potential superiority of either, we here use the conception that physical activity containing moderate-to-vigorous activities and moderate-to-high intensity exercise have comparable effects, as has been shown for outcomes of physical function in older healthy individuals [36].

Exercise (and Physical Activity) as Primary Prevention in MS—Risk Reduction

A combination of genetic and environmental factors have been shown to be associated with MS [37]. Modifiable lifestyle risk factors, such as smoking and obesity, have also gained attention [38], and, in recent years, much interest has been directed toward physical activity and exercise as well. While two small-scale case-control studies did not find an association between physical activity (subjectively evaluated) and the risk of developing MS [39] or the first clinical demyelinating event [40], two large-scale case-control studies provided evidence that physical activity is associated with a reduced risk of MS. The EnviMS study [25••]—a multinational case-control study—showed a significant inverse association between the level of vigorous physical activity (subjectively evaluated) and the risk of MS (crude odds ratio (95% CI) = 0.74 (0.63–0.87); odds ratio = 0.72 (0.59–0.87) when adjusted for infectious mononucleosis, body size, smoking, and outdoor activity). In support, a study of almost the entire male Norwegian population (born 1950–1975) showed a significant inverse association between cardiorespiratory fitness (objectively assessed, yet indirectly determined from a 3000-m maximal run test) and the relative risk of MS (relative risk = 0.69 (0.55–0.88)) [41]. Of note, this study provided indirect evidence that a high cardiorespiratory fitness level is most likely achieved through participation in moderate-to-vigorous physical activities and/or moderate-to-high intensity aerobic exercise training.

Although the direction of causality can be questioned, these large-scale studies taken together suggest that physical activity and exercise are factors that can be associated with a lower risk of developing MS in some individuals. However, whether they act as preventive factors by reducing the relative risk of MS or whether they simply postpone the onset of the deleterious physical and cognitive symptomatic changes leading to diagnosis is difficult to ascertain. In two prospective cohorts of women in the Nurses Health Studies, Dorans and colleagues [42] found a 27% lower incidence of MS when comparing quartiles with the highest versus the lowest levels of physical activity at baseline. However, this lower incidence was not found when the same cohorts were assessed at follow-up 6 years later. This suggests that (1) baseline findings may have been due to a subclinical reduction in the physical activity level and/or (2) physical activity and exercise do not prevent MS per se, but simply postpone the deleterious physical and cognitive symptomatic changes leading to diagnosis. Related to this, we introduce here the *exercise-induced postponement theory*, which is illustrated in Fig. 1. This theory suggests that long-term regular moderate-to-high intensity exercise (and/or moderate-to-vigorous physical activity) can potentially postpone the onset of clinical MS diagnosis and postpone the occurrence of disease activity and progression (including symptoms) in those who have MS. This is supported by the positive effects of physical activity and exercise on MS symptoms and disease activity, which will be presented and discussed in the following sections.

Exercise as Secondary Prevention in MS—Disease-Modifying Effects

While the existing evidence to support exercise (and physical activity) as offering MS risk reduction is scarce and still in its infancy, another line of recent research has investigated the hypothesis that exercise and physical activity may have neuroprotective effects that ultimately impact the progression of MS [24•] (i.e., secondary prevention [11]). Encouragingly, this notion has also been voiced by leading experts within the field of exercise and MS and has been emphasized in numerous reviews presenting exercise as a potentially disease-modifying treatment (i.e., affecting the underlying pathology/pathophysiology of the disease) and/or as an adjunct neuroprotective treatment [17, 43–46].

The basic idea—that exercise and physical activity hold neuroprotective capabilities—is predominantly founded in studies originating from basic sciences, but more recent clinical studies have also offered some support. The basic sciences involved studies investigating widely used animal models of

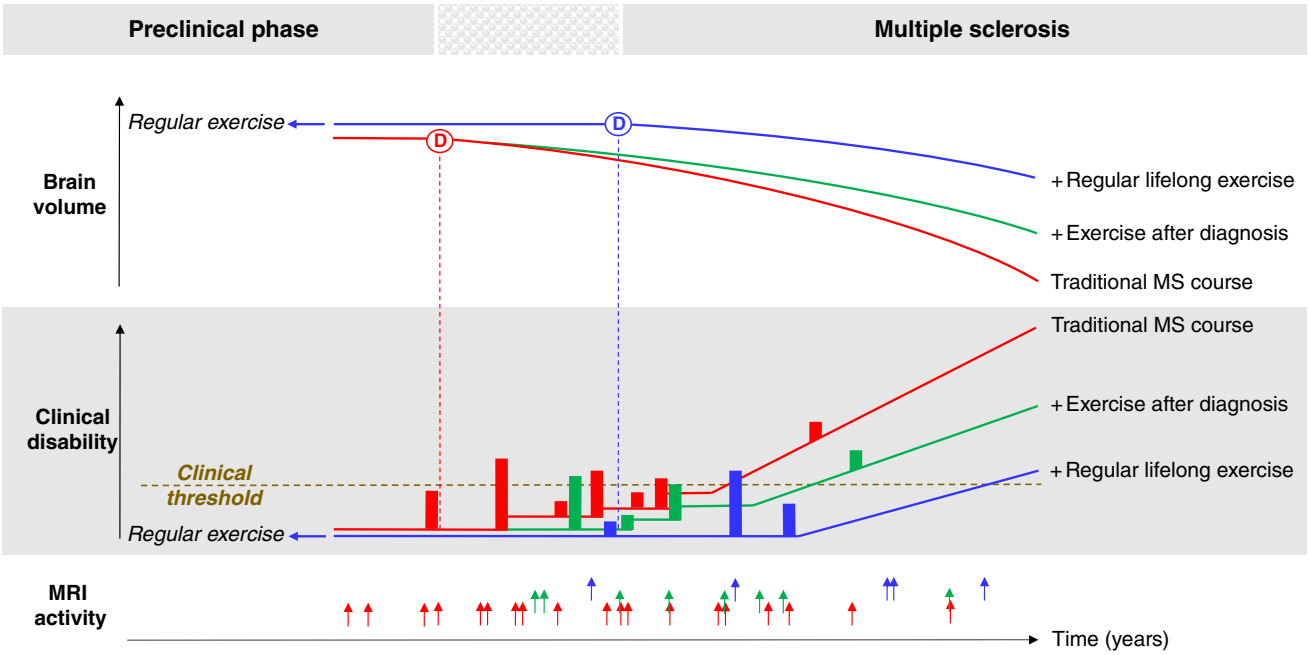

Fig. 1 Conceptualization of "exercise-induced postponement theory" showing the MRI activity, clinical disability, and brain volume development for patients following a traditional course of MS (red lines), for patients engaging in exercise after diagnosis (green lines), and for patients who have been engaged in regular lifelong exercise (blue lines, i.e., MS patients doing exercise throughout their life and thus long before the time of diagnosis). The green and blue lines thus visualize the "exercise-induced postponement theory" presented in the main text. Arrows denote new or active lesions, whereas vertical bars denote relapses. Time of diagnosis is shown as the vertical dotted lines originating from the encircled symbol D, which occur at a later point in MS patients doing regular exercise. The horizontal "clinical threshold" line denotes the hypothetical threshold for performing activities of daily living, i.e., when clinical disability (≈ EDSS score) has worsened to an extent where the ability to walk, rise from chairs, etc. has deteriorated significantly.

MS that, similar to MS, involve inflammatory neurodegeneration. Using these models, several studies have added consistent support to a neuroprotective effect of both aerobic training [47••, 48, 49, 50] and resistance training [47••], as well as of increased physical activity achieved through "enriched environments" [51]. In brief, these studies demonstrate that exercise impacts the main pathological hallmarks of MS: demyelination and axonal injury [47••, 48–51]. Consequently, (non-medicated) exercising animals develop a less severe neurological disease score/course and, in line with the proposed exercise-induced postponement theory, a later onset of disease than sedentary animals [48]. Of note, the exercise intervention is often initiated on the same day as, or prior to [47••], disease inducement, providing an early treatment regime, which adds further support to the exercise-induced postponement theory. Furthermore, a recent study suggested that high-intensity exercise might have greater benefits than moderate-intensity exercise on attenuating the progression and pathological hallmarks of MS [50]. By translating such results to human pathology, it seems evident that promoting engagement in moderate-to-vigorous physical activity and exercise in persons with MS may be a non-pharmacological tool that can help control disease progression [49]. However, while such findings point toward the neuroprotective effects of exercise and physical activity in MS, it is important to acknowledge the fundamental limitations of the existing animal exercise research, which limits the potential translation to humans [52]. As an example, the "exercising animals" were often compared with sedentary control animals, resulting in a comparison between "normal" behaving animals and sedentary animals [48]. Furthermore, the aforementioned early exercise intervention, with exercise being initiated on the same day as, or prior to [47••], disease inducement, is very hard to copy in humans.

The existing human clinical studies that have investigated the disease-modifying effects of exercise include cross-sectional [53–56], (pilot/exploratory) interventional [24•, 57–60], and review studies [61–64] primarily addressing EDSS (expanded disability status scale) scores, relapse rates, and magnetic resonance imaging [65] outcomes as markers of disease activity/progression. Notably, none of these studies was designed to assess these outcomes, thus limiting the impact of the study findings. In the cross-sectional studies, cardiorespiratory fitness was suggested as a predictor of cortical plasticity [53] and was associated with gray matter volume [54], deep gray matter structures [56], and white matter integrity [54]. Moreover, measures of muscle strength were associated with brain corticospinal tract pathology/sensorimotor disability [66, 67]. In the interventional studies, progressive aerobic training [60], combined exercise (aerobic training and resistance training) [59], and balance exercise [58] led to improved functional connectivity [59], viscoelasticity [60], and white matter plasticity in people with MS [58]. These findings are supported by studies demonstrating improvements in neuromuscular activation—a proxy measure of neural plasticity—following progressive resistance training [68–70]. Such findings suggest that exercise-induced neural plasticity is possible despite MS being a chronic CNS disease.

Providing further encouraging support, an MS case study [57] involving 12 weeks of aerobic training demonstrated increased hippocampal volume, while a recent pilot RCT, involving 24 weeks of high-intensity progressive resistance training [24], showed increased thickness in several cortical regions and a trend toward preserved total brain volume. When compared to medical imaging studies that often apply total brain volume change as an essential paraclinical outcome [71–73], the latter finding is of great interest and justifies long-term trials further investigating this effect of exercise on brain morphology, which is likely a slowly responding tissue. Such long-term studies will help expose whether exercise can indeed complement disease-modifying medical therapies by further slowing or reversing total brain atrophy in MS patients—a primary target in halting disability progression in MS [73].

In further support of a disease-modifying effect of exercise—although the reporting of this outcome is inconsistent given its secondary role in most studies—previous literature reviews have identified a markedly reduced relapse rate in intervention groups, when compared with control groups across existing MS exercise studies [61, 62]. Although the pathways underlying the potential (long-term) effects of exercise on MS pathophysiology are incompletely understood [17], these findings suggest that exercise is capable of exerting a prophylactic effect on factors mediating disease activity in MS (see section "Potential Pathophysiological Effects Underlying the Exercise-Induced Postponement Theory" below for further details). Lastly, a recent systematic review investigated the pooled effect of exercise interventions on EDSS scores but did not find a benefit compared to untreated control groups [63]. However, using baseline-adjusted data for a sensitivity analysis, the results favored the exercise intervention groups, but the combination of the low-quality evidence underlying this result and the psychometric properties of the EDSS (i.e., insensitive to change [74]) must be kept in mind when interpreting this finding [63].

Despite the current absence of solid evidence from long-term large-scale human studies, the combination of consistent findings in animal models of MS and the overall effect of exercise on relapse rates in MS patients supports exercise as a potential disease-modifying treatment in MS. This is illustrated in Fig. 1 as a postponement of MRI activity and a slower rate of brain atrophy in persons with MS who are exercising.

Exercise as Tertiary Prevention in MS—Symptomatic Treatment

A large number of studies have examined the effects of exercise as a symptomatic treatment. A hallmark of MS is that the disease manifests with a wide variety of symptoms [1]. The combination and severity of symptoms differ and depend on the size, location, and number of lesions [75], but the physical activity level of the patients is also of importance [76, 77]. Importantly, the physical activity level of MS patients is substantially lower than that of matched healthy controls [78, 79]. Therefore, most MS symptoms could be the result of either the disease process per se (i.e., demyelination and axonal degeneration in the CNS [80]), the reduced physical activity levels per se, or a combination of the two. Exercise likely affects the combination of the two, eliciting improvements among the most frequent and (from a patient perspective) disabling symptoms of MS [81, 82•], such as fatigue, pain, mobility, and cognition. Table 1 summarizes existing reviews and/or meta-analyses of the effects of exercise on different symptoms, taking exercise modality into account [17].

As seen in Table 1, the overall pattern shows that general exercise (i.e., reviews and meta-analyses that pool different exercise modalities) can positively impact most of the listed symptoms, which are rated among the most important bodily functions by persons with MS [81, 82•]. When separated by exercise modality, the picture is less clear, although aerobic and resistance training show overall positive effects leading to a reduction (or even a normalization) of most listed symptoms. Exercise modalities such as Pilates and yoga have become more popular and have attracted recent research interest, but the existing evidence is still scarce [32, 33, 100]. So far, yoga has shown minor positive effects on fatigue and mood in MS patients, although the effects could not be confirmed in a subsequent sensitivity analysis controlling for selection and attrition bias [32]. In addition, a study of Pilates in MS patients suggested a positive impact on balance and pain, whereas no effect was found on quality of life, mood, and functional capacity [33].

The fact that the existing studies do not support an effect of a certain exercise modality on specific symptoms may not mean that the exercise modality is unable to impact the specific symptom. As an example, only two studies have investigated the effects of resistance training on balance, which applied different outcomes, had balance as a secondary outcome, and enrolled patients who were not necessarily characterized by balance impairments at baseline [34]. In fact, most of the cited reviews listed in Table 1 note two noteworthy limitations. First, most studies evaluated the short-term effects of exercise on a specific symptom as a secondary outcome rather than as the primary outcome, suggesting that many studies may have been underpowered. Second, most studies did not enroll participants based on their baseline status of a particular symptom. Consequently, not all participants may have suffered from, for example, clinical fatigue or impaired cognition at baseline. In patients free of a symptom of interest

Table 1 Summary of the effects of different exercise modalities on disabling symptoms, physiological impairments, and disease activity/progression. Only findings from reviews and/or meta-analyses are shown

	General exercise**	Aerobic training	Resistance training	Yoga and Pilates
Symptoms				
Fatigue*	↑ [23, 83, 84]	↑ [23]	→ [23]	↑ [32], → [33]
Pain*	↑ [85]	→ [85]		↑ [33]
Depressive symptoms	↑ [86, 87]	↑ [86]	↑ [86]	↑ [32], → [33]
Functional capacity (walking)*	↑ [88–90]	↑ [31, 88, 90]	↑ [88, 91, 92], → [90]	→ [32, 33]
Balance/falls	↑ [34, 90], ↑ [93]	→ [34]	↑ [91], → [34]	↑ [33]
Cognition*	→ [94, 95]			→ [32]
Physiological impairments				
Muscle strength	↑ [96]	→ [31, 96], ↑ [97]	↑ [90–92, 96, 98]	↑ [33]
Aerobic capacity (VO2-max)	↑ [96]	↑ [31, 96, 97]	→ [91, 96]	
Disease activity/progression				
Relapse rate	↑ [21••]			
Disease progression (EDSS)	→ [63]		→ [91]	
Health-related quality of life (HrQoL)				
HrQoL	↑ [99]	↑ [99]	→ [91]	→ [32, 33]

↑ = beneficial effect of exercise on the listed parameter; → = no effect of exercise on the listed parameter; empty field = no evidence could be located

*Symptoms being rated among the most important bodily functions by persons with MS [81, 82•]

**General exercise covers studies that pool findings from different exercise modalities or that use exercise interventions combining different modalities

at baseline, there is likely not much room for a meaningful improvement (ceiling effect), which would therefore dilute the potential effects seen in patients having that symptom at baseline. Nonetheless, in summarizing the effects of exercise on most symptoms across the existing studies, the general finding is that exercise has beneficial effects on most of the symptoms listed in Table 1 and induces a postponement of clinical disability, as illustrated in Fig. 1. Furthermore, there is evidence supporting the beneficial effects of resistance training or aerobic training on many symptoms, allowing more tailored interventions to be delivered.

Potential Pathophysiological Effects Underlying the Exercise-Induced Postponement Theory

A number of studies have looked into the explanatory factors/pathways believed to be involved in mediating the exercise-induced symptomatic, disease-modifying, and primary preventive effects in persons with MS. This is often termed *neuroprotection*, as assessments have exclusively focused on exercise-induced effects on the CNS/brain. While this is a complex area of research involving a myriad of potential factors that interact with each other, most research has focused on factors associated with inflammation and/or neurodegeneration—both hallmarks of the pathology of MS [101].

Beyond MS, it has been argued that exercise can (1) normalize the imbalance between pro- and anti-inflammatory cytokines and thus reduce overall inflammation [102, 103] and (2) increase the levels of brain-derived neurotrophic factor (BDNF) and other neurotrophic factors (e.g., insulin-like growth factor 1, nerve growth factor, and neurotrophin-3 and neurotrophin-4/5 [102, 104]). Interestingly, studies using MS animal models provide strong evidence confirming that aerobic training and resistance training, along with increased levels of physical activity, can reduce inflammation and/or increase the expression of neurotrophic factors (BDNF in particular) within the CNS/brain, thereby mediating partial protection against demyelination and axonal injury [47••, 49–51, 105]. These positive exercise-induced effects of cytokines and neurotrophic factors on the CNS/brain are believed to be of both central and peripheral origin. In the former, direct effects occur in the brain, plausibly due to increased neuronal activity [106]. In the latter, indirect effects occur through the release of myokines (i.e., cytokines or peptides, such as cathepsin B, PGC1-alpha, and irisin) from exercising skeletal muscles, which are subsequently transported to the CNS/brain, where they increase levels of BDNF and other neurotrophic factors [104, 107].

However, recent systematic reviews summarizing the existing randomized controlled exercise studies in persons with MS reveal that both resistance and aerobic training have minor or negligible effects on acute/chronic systemic levels of pro- and anti-inflammatory cytokines [108] and neurotrophic factors (BDNF in particular) [64]. Consequently, the current evidence in persons with MS does not support the evidence from MS animal studies, which strongly support a pathogenic relationship between exercise-induced changes in neurotrophic/inflammatory factors and preservation of CNS/brain structure and function [47••, 49, 50, 105]. Several aspects likely explain this discrepancy, including small study sample sizes, short durations of intervention periods that do not induce chronic effects, and the fact that blood samples are used as surrogate markers to interpret neuroprotective effects occurring within the CNS/brain. Different research groups—including ours—have voiced their concerns over the latter [109, 110], i.e., whether blood samples/biomarkers are sufficiently precise/sensitive in reflecting events taking place in the cerebrospinal fluid. As an example, recent studies have reported that handling of blood samples (clotting time and centrifugation strategy) [111] and available blood sample kits vary in precision, sensitivity, and detection range [112], which markedly influence the magnitude and direction of changes in systemic BDNF levels.

Among other potential factors, a growing interest in the blood-brain barrier (BBB) and cerebral perfusion have emerged, as both factors are vital for CNS/brain structure and function [113–116]. Specifically, BBB and cerebral perfusion play important roles in maintaining homeostasis within the CNS/brain, with the former controlling the entry of peripheral mediators (e.g., myokines/cytokines and neurotrophic factors) and the latter ensuring adequate delivery of oxygen and nutrients along with the removal of waste products [117, 118]. As with inflammation and/or neurodegeneration, BBB disruption and cerebral hypoperfusion are also common and viewed as hallmarks of MS [113, 114, 117, 119–121]. Importantly, both BBB disruption and cerebral hypoperfusion are present in very early MS and likely precede symptoms and changes in brain morphology/volume [120–122].

In contrast to cytokines and neurotrophic factors, only a few studies have addressed the effects of exercise on BBB disruption and cerebral hypoperfusion in persons with MS. Studies that have examined markers of BBB function/disruption have reported divergent exercise-induced effects. Specifically, both neutral and positive findings have been reported for metalloproteinases [123, 124] along with positive findings for S100 calcium-binding protein B and neutral findings for neuron-specific enolase (but only in a subgroup of normal-weight persons with MS) [125]. While we were unable to identify any studies examining the effects of exercise on cerebral hypoperfusion in persons with MS, a study in older individuals with mild cognitive impairments—a population that also experiences neurodegeneration and deterioration of cognitive function—reported a normalization of cerebral blood flow that was associated with improvements in cognitive performance after 12 weeks of

moderate-intensity aerobic training [126]. Obviously, these findings need to be verified in persons with MS.

Taken together, evidence from animal studies strongly supports a pathogenic relationship between exercise-induced changes in both neurotrophic/inflammatory and brain homeostasis factors and the preservation of CNS structure and function, whereas the evidence from persons with MS is less clear. A general observation of the existing studies in persons with MS is that they are small, of short duration, and often inappropriately designed with regard to target mechanisms, and they rarely combine measures of explanatory factors (e.g., cytokines and neutrophic factors) with measures of neuroprotection (e.g., brain MRI outcomes). Interpretation is thus quite challenging, suggesting that future studies should apply more rigorous methodologies, e.g., by using study designs that are of much longer duration (we recommend more than a year) and specifically address the explanatory factors of interest (with relevant sample size calculations) concomitant with measures of neuroprotection.

Future Perspectives for Research and Clinical Practice

Over the past two decades, exercise (and physical activity) has shifted from being controversial and cautiously prescribed to being an integrated part of MS rehabilitation, due to the evident symptomatic benefits. Obviously, exercise effects will depend on the delivery of exercise stimulus that is sufficient in terms of frequency, intensity, time, and type and is aligned with the intended goals and the patient's current level. Here, much work still needs to be done to further understand dose–response relationships in different patient categories. Furthermore, the predominant focus on the symptomatic effects of exercise (i.e., tertiary prevention) has led to an unintentional knowledge gap, as all existing MS exercise studies have included patients with a mean disease duration of > 4.9 years—leaving an uninvestigated "window of opportunity" for exercise early in the disease course of MS [127]. Combining the potential early "window of opportunity" with the recent indications of preventive and disease-modifying effects of exercise (i.e., primary and secondary prevention, respectively) suggest that it is time for a paradigm shift in how exercise is applied in persons with MS.

First, if exercise holds the potential to modify the disease course of MS, it should be considered a standard treatment option supplementing medical treatment in clinical practice. One could argue that early-phase prescription of exercise should already be established as a standard recommendation based on the current knowledge, although definite high-quality evidence supporting the primary and secondary preventive effects of exercise in MS is still lacking. Given the many known beneficial effects of exercise [128], in combination with the well-established safety profile that includes few, if any, side effects [21••], there are no strong arguments against early exercise prescription in MS. As such, application of an inverted precautionary principle should be considered in this case. A further perspective arises when combining this with the knowledge that "time matters in MS" [129] and that early medical treatment initiation is superior to later treatment initiation [130, 131]. This offers additional support for prescribing exercise along with medical treatment as early as possible in the disease course to gain maximal exercise-induced postponement—although it is likely never too late to gain some effects [77].

Second, medical treatment and exercise can be hypothesized to act in a synergistic way through different pathways that address both the underlying pathophysiology and the most prominent symptoms of MS. Ultimately, the combination of early medical and exercise intervention will likely postpone disability progression (i.e., secondary prevention) more than medical treatment alone, as indicated by Kjølhede et al.'s study, in which all patients received first-line medical treatment but still saw the disease-modifying effects of exercise [24•]. To facilitate and support this shift in paradigm, continuous efforts should be made to further elucidate the potential disease-modifying effects of exercise and the underlying mechanisms, especially in the early window of opportunity. Finally, much work lies ahead to ensure long-term adherence to exercise interventions, as this seems to be one of the major challenges for successful implementation of exercise in the daily lives of MS patients [132].

Conclusion

Exercise is a safe and well-recognized symptomatic treatment option that has beneficial effects on a variety of symptoms (i.e., tertiary prevention) in persons with MS. However, recent evidence suggests that exercise may also have disease-modifying effects (i.e., secondary prevention) in persons with MS and may even have preventive effects by lowering the disease risk (i.e., primary prevention). By incorporating this knowledge, we here propose the exercise-induced postponement theory and suggest that long-term regular moderate-to-high intensity exercise (and/or moderate-to-vigorous physical activity) can potentially postpone the onset of clinical MS diagnosis and postpone the occurrence of disease activity and progression (including occurrence and worsening of prominent symptoms) in those who have MS. We therefore propose a paradigm shift in which tailored exercise should be prescribed from an early stage as "medicine" to persons with MS, alongside conventional medical treatment.

Compliance with Ethical Standards

Conflict of Interest Ulrik Dalgas has received research support, travel grants, and/or teaching honoraria from Biogen Idec, Merck Serono, Novartis, Bayer Schering, and Sanofi Aventis, as well as honoraria from serving on the scientific advisory boards of Biogen Idec and Genzyme. Martin Langeskov-Christensen has received teaching honoraria from Novartis. Lars G. Hvid has received research support, travel grants, and/or teaching honoraria from Biogen and Sanofi Genzyme. Egon Stenager andMorten Riemenschneider each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372(9648):1502–17.
2. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV, et al. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurology. 2014;83(11):1022–4. https://doi.org/10.1212/Wnl.0000000000000768.
3. Pilz G, Wipfler P, Ladurner G, Kraus J. Modern multiple sclerosis treatment - what is approved, what is on the horizon. Drug Discov Today. 2008;13(23–24):1013–25.
4. Liguori M, Marrosu MG, Pugliatti M, Giuliani F, De RF, Cocco E, et al. Age at onset in multiple sclerosis. Neurol Sci. 2000;21(4 Suppl 2):S825–S9.
5. Scalfari A, Neuhaus A, Daumer M, Ebers GC, Muraro PA. Age and disability accumulation in multiple sclerosis. Neurology. 2011;77(13):1246–52. https://doi.org/10.1212/WNL.0b013e318230a17d.
6. Lunde HMB, Assmus J, Myhr KM, Bo L, Grytten N. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psychiatry. 2017;88(8):621–5. https://doi.org/10.1136/jnnp-2016-315238.
7. Koch-Henriksen N, Bronnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. J Neurol Neurosurg Psychiatry. 1998;65(1):56–9.
8. Kister I, Bacon TE, Chamot E, Salter AR, Cutter GR, Kalina JT, et al. Natural history of multiple sclerosis symptoms. International Journal of MS care. 2013;15(3):146–58. https://doi.org/10.7224/1537-2073.2012-053.
9. Gyllensten H, Kavaliunas A, Alexanderson K, Hillert J, Tinghog P, Friberg E. Costs and quality of life by disability among people with multiple sclerosis: a register-based study in Sweden. Multiple Sclerosis Journal - Experimental, Translational and Clinical. 2018;4(3):2055217318783352. https://doi.org/10.1177/2055217318783352.
10. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J, Group MS, et al. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017;23(8):1123–36. https://doi.org/10.1177/1352458517694432.
11. World Health Organization. Neurological disorders : public health challenges. Geneva: World Health Organization; 2006.
12. De Angelis F, John NA, Brownlee WJ. Disease-modifying therapies for multiple sclerosis. BMJ. 2018;363:k4674. https://doi.org/10.1136/bmj.k4674.
13. Cohen JA, Krishnan AV, Goodman AD, Potts J, Wang P, Havrdova E, et al. The clinical meaning of walking speed as measured by the timed 25-foot walk in patients with multiple sclerosis. JAMA Neurol. 2014;71(11):1386–93. https://doi.org/10.1001/jamaneurol.2014.1895.
14. 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;2014:798285–12. https://doi.org/10.1155/2014/798285.
15. Amato MP, Langdon D, Montalban X, Benedict RH, DeLuca J, Krupp LB, et al. Treatment of cognitive impairment in multiple sclerosis: position paper. J Neurol. 2013;260(6):1452–68. https://doi.org/10.1007/s00415-012-6678-0.
16. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol. 2019. https://doi.org/10.1007/s00415-019-09395-w.
17. Motl RW, Sandroff BM, Kwakkel G, Dalgas U, Feinstein A, Heesen C, et al. Exercise in patients with multiple sclerosis. Lancet Neurol. 2017;16(10):848–56. https://doi.org/10.1016/S1474-4422(17)30281-8.
18. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25(Suppl 3):1–72. https://doi.org/10.1111/sms.12581.
19. KM Z. Exercise as medicine in multiple sclerosis - moving beyond compensatory benefits. US Neurology. 2017;13(1):2. https://doi.org/10.17925/USN.2017.13.02.70.
20. Tallner A, Maurer M, Pfeifer K. Multiple sclerosis and physical activity : an historical perspective. Nervenarzt. 2013;84(10):1238–44.
21.•• Pilutti LA, Platta ME, Motl RW, Latimer-Cheung AE. The safety of exercise training in multiple sclerosis: a systematic review. J Neurol Sci. 2014;15(343 (1-2)):3–7 **Comprehensive review showing that exercise is safe in MS and that exercise positively impact relapse rate.**
22. Smith RM, ey-Steel M, Fulcher G, Longley WA. Symptom change with exercise is a temporary phenomenon for people with multiple sclerosis. Arch Phys Med Rehabil. 2006;87(5):723–7.
23. Heine M, Van dP I, Rietberg MB, van Wegen EE, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. Cochrane Database Syst Rev. 2015;9:CD009956.
24.• Kjolhede T, Siemonsen S, Wenzel D, Stellmann JP, Ringgaard S, Pedersen BG et al. Can resistance training impact MRI outcomes in relapsing-remitting multiple sclerosis? Multiple sclerosis (Houndmills, Basingstoke, England). 2018;24(10):1356-65. https://doi.org/10.1177/1352458517722645. **First randomised controlled exercise study to include MRI outcomes in MS.**
25.•• Wesnes K, Myhr KM, Riise T, Cortese M, Pugliatti M, Bostrom I, et al. Physical activity is associated with a decreased multiple sclerosis risk: the EnvIMS study. Mult Scler. 2018;24(2):150–7. https://doi.org/10.1177/1352458517694088 **Large study linking increased physical activity to a decreased MS risk.**
26. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.
27. Dalgas U. Rehabilitation and multiple sclerosis: hot topics in the preservation of physical functioning. J Neurol Sci. 2011;311(S1):S43–S7.
28. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009;41(3):687–708.

29. Hughes JR. Psychological effects of habitual aerobic exercise: a critical review. Prev Med. 1984;13(1):66–78.
30. Kjolhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler. 2012;18(9):1215–28.
31. Langeskov-Christensen M, Heine M, Kwakkel G, Dalgas U. Aerobic capacity in persons with multiple sclerosis: a systematic review and meta-analysis. Paper submitted. 2014.
32. Cramer H, Lauche R, Azizi H, Dobos G, Langhorst J. Yoga for multiple sclerosis: a systematic review and meta-analysis. PLoS One. 2014;9(11):e112414. https://doi.org/10.1371/journal.pone.0112414.
33. Sanchez-Lastra MA, Martinez-Aldao D, Molina AJ, Ayan C. Pilates for people with multiple sclerosis: a systematic review and meta-analysis. Multiple Sclerosis and Related Disorders. 2019;28:199–212. https://doi.org/10.1016/j.msard.2019.01.006.
34. Gunn H, Markevics S, Haas B, Marsden J, Freeman J. Systematic review: the effectiveness of interventions to reduce falls and improve balance in adults with multiple sclerosis. Arch Phys Med Rehabil. 2015;96(10):1898–912. https://doi.org/10.1016/j.apmr.2015.05.018.
35. Stathopoulos E, Felson DJ. History and principles of exercise-based therapy: how they inform our current treatment. Semin Speech Lang. 2006;27(4):227–35. https://doi.org/10.1055/s-2006-955113.
36. Van Roie E, Delecluse C, Opdenacker J, De Bock K, Kennis E, Boen F. Effectiveness of a lifestyle physical activity versus a structured exercise intervention in older adults. J Aging Phys Act. 2010;18(3):335–52.
37. Ascherio A, Munger KL, Lunemann JD. The initiation and prevention of multiple sclerosis. Nat Rev Neurol. 2012;8(11):602–12. https://doi.org/10.1038/nrneurol.2012.198.
38. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol. 2017;13(1):25–36. https://doi.org/10.1038/nrneurol.2016.187.
39. Abdollahpour I, Nedjat S, Mansournia MA, Sahraian MA, van der Mei I. Lifestyle factors and multiple sclerosis: a population-based incident case-control study. Mult Scler Relat Disord. 2018;22:128–33. https://doi.org/10.1016/j.msard.2018.03.022.
40. Ponsonby AL, Lucas RM, Dear K, van der Mei I, Taylor B, Chapman C, et al. The physical anthropometry, lifestyle habits and blood pressure of people presenting with a first clinical demyelinating event compared to controls: the Ausimmune study. Mult Scler. 2013;19(13):1717–25. https://doi.org/10.1177/1352458513483887.
41. Cortese M, Riise T, Bjornevik K, Myhr KM. Multiple Sclerosis Conscript Service Database Study G. Body size and physical exercise, and the risk of multiple sclerosis. Mult Scler. 2018;24(3):270–8. https://doi.org/10.1177/1352458517699289.
42. Dorans KS, Massa J, Chitnis T, Ascherio A, Munger KL. Physical activity and the incidence of multiple sclerosis. Neurology. 2016;87(17):1770–6. https://doi.org/10.1212/WNL.0000000000003260.
43. Dalgas U, Stenager E. Exercise and disease progression in multiple sclerosis: can exercise slow down the progression of multiple sclerosis? Ther Adv Neurol Disord. 2012;5(2):81–95. https://doi.org/10.1177/1756285611430719.
44. Motl RW. Physical activity and irreversible disability in multiple sclerosis. Exerc Sport Sci Rev. 2010;38(4):186–91. https://doi.org/10.1097/JES.0b013e3181f44fab.
45. White LJ, Castellano V. Exercise and brain health - implications for multiple sclerosis: part 1 - neuronal growth factors. Sports Med. 2008;38(2):91–100.
46. White LJ, Castellano V. Exercise and brain health–implications for multiple sclerosis: part II–immune factors and stress hormones. Sports medicine (Auckland, NZ). 2008;38(3):179–86 doi:3831.
47.•• Souza PS, Goncalves ED, Pedroso GS, Farias HR, Junqueira SC, Marcon R, et al. Physical exercise attenuates experimental autoimmune encephalomyelitis by inhibiting peripheral immune response and blood-brain barrier disruption. Mol Neurobiol. 2017;54(6):4723–37. https://doi.org/10.1007/s12035-016-0014-0 **Comprehensive analysis of mechanisms underlying the disease modifying effects of exercise observed in the animal model of MS.**
48. Pryor WM, Freeman KG, Larson RD, Edwards GL, White LJ. Chronic exercise confers neuroprotection in experimental autoimmune encephalomyelitis. J Neurosci Res. 2015;93(5):697–706. https://doi.org/10.1002/jnr.23528.
49. Mandolesi G, Bullitta S, Fresegna D, De Vito F, Rizzo FR, Musella A, et al. Voluntary running wheel attenuates motor deterioration and brain damage in cuprizone-induced demyelination. Neurobiol Dis. 2019;129:102–17. https://doi.org/10.1016/j.nbd.2019.05.010.
50. Xie Y, Li Z, Wang Y, Xue X, Ma W, Zhang Y, et al. Effects of moderate- versus high- intensity swimming training on inflammatory and CD4(+) T cell subset profiles in experimental autoimmune encephalomyelitis mice. J Neuroimmunol. 2019;328:60–7. https://doi.org/10.1016/j.jneuroim.2018.12.005.
51. Bonfiglio T, Olivero G, Vergassola M, Di Cesare ML, Pacini A, Iannuzzi F, et al. Environmental training is beneficial to clinical symptoms and cortical presynaptic defects in mice suffering from experimental autoimmune encephalomyelitis. Neuropharmacology. 2019;145(Pt A):75–86. https://doi.org/10.1016/j.neuropharm.2018.01.026.
52. Burrows DJ, McGown A, Jain SA, De Felice M, Ramesh TM, Sharrack B, et al. Animal models of multiple sclerosis: from rodents to zebrafish. Mult Scler. 2019;25(3):306–24. https://doi.org/10.1177/1352458518805246.
53. Prakash RS, Snook EM, Erickson KI, Colcombe SJ, Voss MW, Motl RW, et al. Cardiorespiratory fitness: a predictor of cortical plasticity in multiple sclerosis. Neuroimage. 2007;34(3):1238–44. https://doi.org/10.1016/j.neuroimage.2006.10.003.
54. Prakash RS, Snook EM, Motl RW, Kramer AF. Aerobic fitness is associated with gray matter volume and white matter integrity in multiple sclerosis. Brain Res. 2010;1341:41–51. https://doi.org/10.1016/j.brainres.2009.06.063.
55. Motl RW, McAuley E. Association between change in physical activity and short-term disability progression in multiple sclerosis. J Rehabil Med. 2011;43(4):305–10. https://doi.org/10.2340/16501977-0782.
56. Motl RW, Pilutti LA, Hubbard EA, Wetter NC, Sosnoff JJ, Sutton BP. Cardiorespiratory fitness and its association with thalamic, hippocampal, and basal ganglia volumes in multiple sclerosis. NeuroImage Clinical. 2015;7:661–6. https://doi.org/10.1016/j.nicl.2015.02.017.
57. Leavitt VM, Cirnigliaro C, Cohen A, Farag A, Brooks M, Wecht JM, et al. Aerobic exercise increases hippocampal volume and improves memory in multiple sclerosis: preliminary findings. Neurocase. 2014;20(6):695–7. https://doi.org/10.1080/13554794.2013.841951.
58. Prosperini L, Fanelli F, Petsas N, Sbardella E, Tona F, Raz E, et al. Multiple sclerosis: changes in microarchitecture of white matter tracts after training with a video game balance board. Radiology. 2014;273(2):529–38. https://doi.org/10.1148/radiol.14140168.
59. Tavazzi E, Bergsland N, Cattaneo D, Gervasoni E, Lagana MM, Dipasquale O, et al. Effects of motor rehabilitation on mobility and brain plasticity in multiple sclerosis: a structural and functional MRI study. J Neurol. 2018;265(6):1393–401. https://doi.org/10.1007/s00415-018-8859-y.

60. Sandroff BM, Johnson CL, Motl RW. Exercise training effects on memory and hippocampal viscoelasticity in multiple sclerosis: a novel application of magnetic resonance elastography. Neuroradiology. 2017;59(1):61–7. https://doi.org/10.1007/s00234-016-1767-x.
61. Pilutti LA, Platta ME, Motl RW, Latimer-Cheung AE. The safety of exercise training in multiple sclerosis: a systematic review. J Neurol Sci. 2014;343(1–2):3–7. https://doi.org/10.1016/j.jns.2014.05.016.
62. Tallner A, Waschbisch A, Wenny I, Schwab S, Hentschke C, Pfeifer K, et al. Multiple sclerosis relapses are not associated with exercise. Mult Scler. 2012;18(2):232–5. https://doi.org/10.1177/1352458511415143.
63. Hempel S, Graham GD, Fu N, Estrada E, Chen AY, Miake-Lye I, et al. A systematic review of the effects of modifiable risk factor interventions on the progression of multiple sclerosis. Mult Scler. 2017;23(4):513–24. https://doi.org/10.1177/1352458517690271.
64. Negaresh R, Motl RW, Zimmer P, Mokhtarzade M, Baker JS. Effects of exercise training on multiple sclerosis biomarkers of central nervous system and disease status: a systematic review of intervention studies. Eur J Neurol. 2019;26(5):711–21. https://doi.org/10.1111/ene.13929.
65. Grp PS, G UBCMA. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS (vol 55, pg 1628, 2001). Neurology. 2001;57(6):1146-.
66. Fritz NE, Keller J, Calabresi PA, Zackowski KM. Quantitative measures of walking and strength provide insight into brain corticospinal tract pathology in multiple sclerosis. Neuroimage Clin. 2017;14:490–8. https://doi.org/10.1016/j.nicl.2017.02.006.
67. Zackowski KM, Smith SA, Reich DS, Gordon-Lipkin E, Chodkowski BA, Sambandan DR, et al. Sensorimotor dysfunction in multiple sclerosis and column-specific magnetization transfer-imaging abnormalities in the spinal cord. Brain. 2009;132(Pt 5):1200–9. https://doi.org/10.1093/brain/awp032.
68. Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J. Enhanced neural drive after maximal strength training in multiple sclerosis patients. Eur J Appl Physiol. 2010;110(2):435–43. https://doi.org/10.1007/s00421-010-1519-2.
69. Dalgas U, Stenager E, Lund C, Rasmussen C, Petersen T, Sorensen H, et al. Neural drive increases following resistance training in patients with multiple sclerosis. J Neurol. 2013;260(7):1822–32.
70. Kjolhede T, Vissing K, de Place L, Pedersen BG, Ringgaard S, Stenager E 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. Multiple sclerosis (Houndmills, Basingstoke, England). 2014.
71. Vollmer T, Signorovitch J, Huynh L, Galebach P, Kelley C, DiBernardo A, et al. The natural history of brain volume loss among patients with multiple sclerosis: a systematic literature review and meta-analysis. J Neurol Sci. 2015;357(1–2):8–18. https://doi.org/10.1016/j.jns.2015.07.014.
72. Tsivgoulis G, Katsanos AH, Grigoriadis N, Hadjigeorgiou GM, Heliopoulos I, Kilidireas C, et al. The effect of disease modifying therapies on brain atrophy in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis. PLoS One. 2015;10(3):e0116511. https://doi.org/10.1371/journal.pone.0116511.
73. Favaretto A, Lazzarotto A, Margoni M, Poggiali D, Gallo P. Effects of disease modifying therapies on brain and grey matter atrophy in relapsing remitting multiple sclerosis. Multiple Sclerosis and Demyelinating Disorders. 2018;3(1):1. https://doi.org/10.1186/s40893-017-0033-3.
74. Hobart J, Freeman J, Thompson A. Kurtzke scales revisited: the application of psychometric methods to clinical intuition. Brain. 2000;123 (Pt 5)(Pt 5):1027–40.
75. Vellinga MM, Geurts JJ, Rostrup E, Uitdehaag BM, Polman CH, Barkhof F, et al. Clinical correlations of brain lesion distribution in multiple sclerosis. Journal of Magnetic Resonance Imaging : JMRI. 2009;29(4):768–73. https://doi.org/10.1002/jmri.21679.
76. Stephens S, Shams S, Lee J, Grover SA, Longoni G, Berenbaum T, et al. Benefits of physical activity for depression and fatigue in multiple sclerosis: a longitudinal analysis. J Pediatr. 2019;209:226–32.e2. https://doi.org/10.1016/j.jpeds.2019.01.040.
77. Rooney S, Riemenschneider M, Dalgas U, Jorgensen MK, Michelsen AS, Brond JC, et al. Physical activity is associated with neuromuscular and physical function in patients with multiple sclerosis independent of disease severity. Disabil Rehabil. 2019:1–8. https://doi.org/10.1080/09638288.2019.1634768.
78. Motl RW, McAuley E, Snook EM. Physical activity and multiple sclerosis: a meta-analysis. Mult Scler. 2005;11(4):459–63.
79. Kinnett-Hopkins D, Adamson B, Rougeau K, Motl RW. People with MS are less physically active than healthy controls but as active as those with other chronic diseases: an updated meta-analysis. Multiple Sclerosis and Related Disorders. 2017;13:38–43. https://doi.org/10.1016/j.msard.2017.01.016.
80. de HA, de Ruiter CJ, van der Woude LH, Jongen PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. Muscle Nerve 2000;23(10):1534–1541.
81. Green R, Cutter G, Friendly M, Kister I. Which symptoms contribute the most to patients' perception of health in multiple sclerosis? Multiple sclerosis journal - experimental, translational and clinical. 2017;3(3):2055217317728301. https://doi.org/10.1177/2055217317728301.
82.• Heesen C, Haase R, Melzig S, Poettgen J, Berghoff M, Paul F, et al. Perceptions on the value of bodily functions in multiple sclerosis. Acta Neurol Scand. 2018;137(3):356–62. https://doi.org/10.1111/ane.12881. **Study rating the importance of different bodily functions from a patient and physician perspective**.
83. Pilutti L, Greenlee T, Motl RW, Nickrent M, Petruzzello SJ. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med 2013;75(6):575–580.
84. Andreasen AK, Stenager E, Dalgas U. The effect of exercise therapy on fatigue in multiple sclerosis. Mult Scler. 2011;17(9):1041–54.
85. Demaneuf T, Aitken Z, Karahalios A, Leong TI, De Livera AM, Jelinek GA, et al. Effectiveness of exercise interventions for pain reduction in people with multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. Arch Phys Med Rehabil. 2019;100(1):128–39. https://doi.org/10.1016/j.apmr.2018.08.178.
86. Dalgas U, Stenager E, Sloth M, Stenager E. The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. Eur J Neurol. 2015;22(3):443–e34.
87. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. J Psychosom Res. 2014;76(6):465–71.
88. Pearson M, Dieberg G, Smart N. Exercise as a therapy for improvement of walking ability in adults with multiple sclerosis: a meta-analysis. Arch Phys Med Rehabil. 2015;96:1339–1348.e7.
89. Snook EM, Motl RW. Effect of exercise training on walking mobility in multiple sclerosis: a meta-analysis. Neurorehabil Neural Repair. 2008;23(108):116.
90. Charron S, McKay KA, Tremlett H. Physical activity and disability outcomes in multiple sclerosis: a systematic review (2011-2016). Multiple sclerosis and related disorders. 2018;20:169–77. https://doi.org/10.1016/j.msard.2018.01.021.
91. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training - a systematic review. Mult Scler. 2012;18(9):1215–28.

92. Manago MM, Glick S, Hebert JR, Coote S, Schenkman M. Strength training to improve gait in people with multiple sclerosis: a critical review of exercise parameters and intervention approaches. Int J MS Care. 2019;21(2):47–56. https://doi.org/10.7224/1537-2073.2017-079.
93. Paltamaa J, Sjogren T, Peurala SH, Heinonen A. Effects of physiotherapy interventions on balance in multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. J Rehabil Med. 2012;44(10):811–23. https://doi.org/10.2340/16501977-1047.
94. Kalron A, Zeilig G. Efficacy of exercise intervention programs on cognition in people suffering from multiple sclerosis, stroke and Parkinson's disease: a systematic review and meta-analysis of current evidence. NeuroRehabilitation. 2015;37:273–89.
95. Sandroff BM, Motl RW, Scudder MR, DeLuca J. Systematic, evidence-based review of exercise, physical activity, and physical fitness effects on cognition in persons with multiple sclerosis. Neuropsychol Rev. 2016;26(3):271-294. doi:https://doi.org/10.1007/s11065-016-9324-2.
96. Platta ME, Ensari I, Motl RW, Pilutti LA. Effect of exercise training on fitness in multiple sclerosis: a meta-analysis. Arch Phys Med Rehabil. 2016;97(9):1564–72.
97. Campbell E, Coulter EH, Paul L. High intensity interval training for people with multiple sclerosis: a systematic review. Multiple sclerosis and related disorders. 2018;24:55–63. https://doi.org/10.1016/j.msard.2018.06.005.
98. Jorgensen M, Dalgas U, Wens I, Hvid LG. Muscle strength and power in persons with multiple sclerosis - a systematic review and meta-analysis. J Neurol Sci. 2017;376:225–41. https://doi.org/10.1016/j.jns.2017.03.022.
99. Motl RW, Gosney JL. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. Mult Scler. 2008;14(1):129–35.
100. Sanchez-Lastra MA, Martinez-Aldao D, Molina AJ, Ayan C. Corrigendum to 'Pilates for people with multiple sclerosis: a systematic review and meta-analysis' Multiple Sclerosis and Related Disorders 28 (2019)199-212. Multiple Sclerosis and related Disorders. 2019;32:139–40. https://doi.org/10.1016/j.msard.2019.04.027.
101. Friese MA, Schattling B, Fugger L. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. Nat Rev Neurol. 2014;10(4):225–38. https://doi.org/10.1038/nrneurol.2014.37.
102. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007;30(9):464–72. https://doi.org/10.1016/j.tins.2007.06.011.
103. Pedersen BK. Muscle as a secretory organ. Compr Physiol. 2013;3(3):1337–62. https://doi.org/10.1002/cphy.c120033.
104. Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. Cell Metab. 2013;18(5):649–59. https://doi.org/10.1016/j.cmet.2013.09.008.
105. Einstein O, Fainstein N, Touloumi O, Lagoudaki R, Hanya E, Grigoriadis N et al. Exercise training attenuates experimental autoimmune encephalomyelitis by peripheral immunomodulation rather than direct neuroprotection. Exp Neurol. 2018;299(Pt A):56–64. doi:https://doi.org/10.1016/j.expneurol.2017.10.008.
106. Thoenen H. Neurotrophins and neuronal plasticity. Science. 1995;270(5236):593–8. https://doi.org/10.1126/science.270.5236.593.
107. Pedersen BK. Physical activity and muscle-brain crosstalk. Nat Rev Endocrinol. 2019;15(7):383–92. https://doi.org/10.1038/s41574-019-0174-x.
108. Negaresh R, Motl RW, Mokhtarzade M, Dalgas U, Patel D, Shamsi MM, et al. Effects of exercise training on cytokines and adipokines in multiple sclerosis: a systematic review. Multiple Sclerosis and Related Disorders. 2018;24:91–100. https://doi.org/10.1016/j.msard.2018.06.008.
109. Damasceno A, Damasceno BP, Cendes F, Damasceno A, Moraes AS, Farias A, et al. Serum BDNF levels are not reliable correlates of neurodegeneration in MS patients. Multiple Sclerosis and Related Disorders. 2015;4(1):65–6. https://doi.org/10.1016/j.msard.2014.11.003.
110. Jorgensen MLK, Kjolhede T, Dalgas U, Hvid LG. Plasma brain-derived neurotrophic factor (BDNF) and sphingosine-1-phosphat (S1P) are NOT the main mediators of neuroprotection induced by resistance training in persons with multiple sclerosis-a randomized controlled trial. Multiple Sclerosis and Related Disorders. 2019;31:106–11. https://doi.org/10.1016/j.msard.2019.03.029.
111. Gejl AK, Enevold C, Bugge A, Andersen MS, Nielsen CH, Andersen LB. Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. Sci Rep. 2019;9(1):9655. https://doi.org/10.1038/s41598-019-45976-5.
112. Polacchini A, Metelli G, Francavilla R, Baj G, Florean M, Mascaretti LG, et al. A method for reproducible measurements of serum BDNF: comparison of the performance of six commercial assays. Sci Rep. 2015;5:17989. https://doi.org/10.1038/srep17989.
113. Spencer JI, Bell JS, DeLuca GC. Vascular pathology in multiple sclerosis: reframing pathogenesis around the blood-brain barrier. J Neurol Neurosurg Psychiatry. 2018;89(1):42–52. https://doi.org/10.1136/jnnp-2017-316011.
114. Martinez Sosa S, Smith KJ. Understanding a role for hypoxia in lesion formation and location in the deep and periventricular white matter in small vessel disease and multiple sclerosis. Clin Sci (Lond). 2017;131(20):2503–24. https://doi.org/10.1042/CS20170981.
115. Malkiewicz MA, Szarmach A, Sabisz A, Cubala WJ, Szurowska E, Winklewski PJ. Blood-brain barrier permeability and physical exercise. J Neuroinflammation. 2019;16(1):15. https://doi.org/10.1186/s12974-019-1403-x.
116. Boraxbekk CJ, Salami A, Wahlin A, Nyberg L. Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network-a multimodal approach. NeuroImage. 2016;131:133–41. https://doi.org/10.1016/j.neuroimage.2015.12.010.
117. Ortiz GG, Pacheco-Moises FP, Macias-Islas MA, Flores-Alvarado LJ, Mireles-Ramirez MA, Gonzalez-Renovato ED, et al. Role of the blood-brain barrier in multiple sclerosis. Arch Med Res. 2014;45(8):687–97. https://doi.org/10.1016/j.arcmed.2014.11.013.
118. Rempe RG, Hartz AMS, Bauer B. Matrix metalloproteinases in the brain and blood-brain barrier: versatile breakers and makers. J Cereb Blood Flow Metab. 2016;36(9):1481–507. https://doi.org/10.1177/0271678X16655551.
119. Alvarez JI, Cayrol R, Prat A. Disruption of central nervous system barriers in multiple sclerosis. Biochim Biophys Acta. 2011;1812(2):252–64. https://doi.org/10.1016/j.bbadis.2010.06.017.
120. D'Haeseleer M, Hostenbach S, Peeters I, Sankari SE, Nagels G, De Keyser J, et al. Cerebral hypoperfusion: a new pathophysiologic concept in multiple sclerosis? J Cereb Blood Flow Metab. 2015;35(9):1406–10. https://doi.org/10.1038/jcbfm.2015.131.
121. Wuerfel J, Paul F, Zipp F. Cerebral blood perfusion changes in multiple sclerosis. J Neurol Sci. 2007;259(1–2):16–20. https://doi.org/10.1016/j.jns.2007.02.011.
122. Kermode AG, Thompson AJ, Tofts P, MacManus DG, Kendall BE, Kingsley DP, et al. Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis. Pathogenetic and clinical implications. Brain J

Neurol. 1990;113(Pt 5):1477–89. https://doi.org/10.1093/brain/113.5.1477.

123. Deckx N, Wens I, Nuyts AH, Hens N, De Winter BY, Koppen G, 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. Mediat Inflamm. 2016;2016:6789276–13. https://doi.org/10.1155/2016/6789276.
124. Zimmer P, Bloch W, Schenk A, Oberste M, Riedel S, Kool J, et al. High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: a randomized controlled trial. Mult Scler. 2018;24(12):1635–44. https://doi.org/10.1177/1352458517728342.
125. Mokhtarzade M, Motl R, Negaresh R, Zimmer P, Khodadoost M, Baker JS, et al. Exercise-induced changes in neurotrophic factors and markers of blood-brain barrier permeability are moderated by weight status in multiple sclerosis. Neuropeptides. 2018;70:93–100. https://doi.org/10.1016/j.npep.2018.05.010.
126. Alfini AJ, Weiss LR, Nielson KA, Verber MD, Smith JC. Resting cerebral blood flow after exercise training in mild cognitive impairment. J Alzheimers Dis. 2019;67(2):671–84. https://doi.org/10.3233/JAD-180728.
127. Riemenschneider M, Hvid LG, Stenager E, Dalgas U. Is there an overlooked "window of opportunity" in MS exercise therapy? Perspectives for early MS rehabilitation. Mult Scler. 2018;24(7):886–94. https://doi.org/10.1177/1352458518777377.
128. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta A, Mackibbon KA, et al. The 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. 2013;94(9):1800–28.
129. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord. 2016;9(Suppl 1):S5–S48. https://doi.org/10.1016/j.msard.2016.07.003.
130. Ziemssen T, Derfuss T, de Stefano N, Giovannoni G, Palavra F, Tomic D, et al. Optimizing treatment success in multiple sclerosis. J Neurol. 2016;263(6):1053–65. https://doi.org/10.1007/s00415-015-7986-y.
131. Elovaara I. Early treatment in multiple sclerosis. J Neurol Sci. 2011;311(Suppl 1):S24–8. https://doi.org/10.1016/S0022-510X(11)70005-3.
132. Heesen C, Bruce J, Gearing R, Moss-Morris R, Weinmann J, Hamalainen P, et al. Adherence to behavioural interventions in multiple sclerosis: follow-up meeting report (AD@MS-2). Mult Scler J Exp Transl Clin. 2015;1:2055217315585333. https://doi.org/10.1177/2055217315585333.