

Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training

U Dalgas^{1,2,3}, E Stenager³ and T Ingemann-Hansen¹

This review summarizes the existing knowledge regarding the effects of physical exercise in patients suffering from multiple sclerosis (MS). Furthermore, recommendations are given regarding exercise prescription for MS patients and for future study directions. Previously, MS patients were advised not to participate in physical exercise. During recent years, it has been increasingly acknowledged that exercise benefits MS patients. The requirement for exercise in MS patients is emphasized by their physiological profile, which probably reflects both the effects of the disease *per se* and the reversible effects of an inactive lifestyle. To date the effects of exercise have only been studied in moderately impaired MS patients with an EDSS score of less than 7. Evidence exists for recommending participation in endurance training at low to moderate intensity, as the existing literature demonstrates that MS patients can both tolerate and benefit from this training modality. Also, resistance training of moderate intensity seems to be well tolerated and to have beneficial effects on MS patients, but the methodological quality of the existing evidence is in general low and the number of studies is limited. Only two studies have evaluated the effects of combined resistance- and endurance training, making solid conclusions regarding this training modality impossible. *Multiple Sclerosis* 2008; 14: 35–53. <http://msj.sagepub.com>

Key words: aerobic training; cardiovascular training; exercise recommendations; muscle strength; physiological profile; strength training

Introduction

For many years, patients with multiple sclerosis (MS) have been advised not to participate in physical exercise. This advice was given in part because some patients were reported to experience symptom instability during exercise as a consequence of increased body temperature [1,2]. A further argument was that avoiding exercise would preserve energy and thereby result in less fatigue, leaving more energy for activities of daily living. During the last decade, it has been more common to recommend exercise for MS patients, because of its recently proven beneficial effects in these patients [3–5]. Furthermore, it has recently been shown that the

worsening of the number and/or intensity of sensory symptoms, which is experienced by more than 40% of all MS patients after exercise, is temporal, and will be normalized within half an hour after exercise cessation in most (85%) patients [6]. Since 1990 several reviews [3–5,7–11] and meta-analyses [12,13] have been published regarding different aspects of exercise and MS. However, the still growing body of evidence calls for updated reviews. Resistance- and endurance training constitutes the two extremes of basic physical exercise. Recently it has become popular to engage in training programs that combine both resistance- and endurance training (combined training). Consequently, the main purpose of this review is to outline the existing evidence for

¹Department of Sport Science, University of Aarhus, Aarhus N, Denmark

²Department of Neurology, Aarhus University Hospital, Aarhus C, Denmark

³MS-clinic of southern Denmark (Sonderborg, Vejle, Esbjerg), Department of Neurology, Sonderborg Hospital, Sonderborg, Denmark

Author for correspondence: U Dalgas, Department of Sport Science, University of Aarhus, Kathrinebjergvej 89C, 8200 Aarhus N, Denmark. E-mail: dalgas@idraet.au.dk

Received 30 October 2006; accepted 21 March 2007

recommending MS patients to participate in either endurance-, resistance- or combined training, and to give recommendations for the practical use of these various training modalities. A secondary purpose is to clarify the rationale for the use of exercise in MS patients by briefly summarising the physiological and health profile of MS patients.

Methods and materials

The first part of this review briefly summarizes evidence regarding a possible reversion of some of the impairments seen in MS patients, as an effect of exercise. This is followed by a brief description of selected parts of the physiological and health profile of MS patients compared to healthy controls.

The second part of the review is based on a comprehensive literature search (PubMed, SweMed +, Embase, Cochrane library, PEDro, Sport Discus and ISI Web of Science) that was performed in order to identify articles and conference abstracts regarding multiple sclerosis and exercise until January 2007. The search was performed using the words 'exercise', 'exercise therapy' or 'training' in combination with 'multiple sclerosis'. This search yielded 1122 publications. Only studies using a longitudinal design in the evaluation of an exercise intervention were included. A screening of the 1122 publications based on title and abstract revealed 96 publications relevant for further reading. The reference lists of these 96 publications were checked for further relevant publications that were not captured by the search. This resulted in further 20 publications and in a total of 116 closely read publications. Only studies using training interventions that could be categorized as either endurance-, resistance- or combined training were included. Studies evaluating the effects of expiratory training ($n = 5$), physiotherapy ($n = 7$), tai chi ($n = 1$), yoga ($n = 1$), water therapy ($n = 1$) and studies that showed to have no or a nondefined training intervention ($n = 12$) were therefore excluded. Also articles not written in English ($n = 13$), case studies ($n = 7$), comments ($n = 10$), metaanalysis ($n = 2$), reviews ($n = 8$), book chapters ($n = 5$) and conference abstracts that were followed by an article ($n = 10$) were excluded from the final analysis. This left nine abstracts and 25 articles describing a total of 23 different studies of which 12 used a randomized controlled trial (RCT) design. Based on the type of the training intervention, the localized articles and abstracts were divided into one of three groups:

1) The first group comprises abstracts and articles that evaluate the effects of resistance training, ie, few muscle contractions against heavy loads

(13 publications, eight articles + five abstracts, eight different studies, two RCT).

- 2) The second group comprises studies that evaluate the effects of endurance training, ie, multiple muscle contractions against low loads (17 publications, 14 articles + three abstracts, 14 different studies, eight RCT).
- 3) The third group comprises studies that evaluate the effects of combined endurance- and resistance training (four publications, three articles + one abstract, two different studies, two RCT).

Results

Reversibility of impairments

Impairments seen in MS patients could be a result of the disease process *per se* (ie, demyelination and axonal degeneration in CNS [14]), and or it could be a consequence of the reduced physical activity level seen in MS patients compared to matched healthy subjects [15–18]. It is still unresolved to what extent the impairments can be reversed in MS patients [19]. This may depend on the extent of the impairment being a result of the disease *per se*, or whether it is a consequence of inactivity secondary to the disease. Impairments resulting from the disease *per se* are probably not reversible subsequent to exercise, whereas impairments developed as a consequence of inactivity, probably are [8]. As noted by other authors [20,21], and due to the fact that several studies have shown marked improvements in almost all aspects of the physiological profile of MS patients after exercise, it seems likely that a substantial part of the impairments is a result of inactivity, rather than a result of non-reversible tissue injury. This assumptions combined with the fact that exercise is a non-pharmacological intervention, makes exercise a very interesting tool in MS rehabilitation. Furthermore, the approved medical treatments have only shown moderate effects on relapse rate and to a lesser extent on disability progression, which is why MS rehabilitation remains the major strategy to improve disability and maintain functional status [9]. Recently, it has been suggested that exercise might have a disease-modifying anti-inflammatory effect, and therefore perhaps poses the potential to slow down the disease process [9,22]. However, to date only animal studies in experimental auto-immune encephalomyelitis have addressed this important question [22].

Physiological and health profile of MS patients

In healthy people physical inactivity is known to impose a serious health risk [23]. Inactivity is

known to raise the risk of chronic conditions such as cardiovascular diseases, obesity, Type-II diabetes, cancer, osteoporosis [23] and fatigue [24]. In MS patients there is an increased incidence of osteoporosis [25–27] (reduced bone mineral density), depression [28], fatigue [29] and death from cardiovascular diseases [30]. This increased incidence could be associated with the low level of daily activity seen in these patients. Furthermore, inactivity is known to be associated with reduced aerobic capacity [31], atrophy and loss of muscle strength [32] in otherwise healthy people. Aerobic capacity, in terms of maximal oxygen consumption (VO₂-max), has been shown to be reduced among MS patients [21,33]. Other cardiovascular parameters like resting heart rate [34] and diastolic blood pressure [35] have been shown to be elevated in MS patients. However, other studies could not confirm neither the increased resting heart rate [21,35,36] nor the increased diastolic blood pressure [36]. Also maximal muscle strength measured during both isokinetic [37–40] and isometric [17–20,37,41–45] muscle contractions as well as the rate of force development [19,41,45], has been shown to be reduced among MS patients. However one study [42] could not confirm the impaired rate of force development. It should also be noted that the strength impairment seems particular distinct in the lower extremity as compared to the upper extremity [43]. The mechanisms underlying the observed strength deficit in MS patients is probably of both morphological (peripheral) and neural (central) origin. Some studies [17,18,26], but not all [19,40,46], have indicated a loss of muscle mass in MS patients. At the whole body level Formica *et al.*

[26] demonstrated a small (5%) but significant lowering of fat free mass (FFM), in a large study comparing female MS patients with healthy controls. One study [46] could, however, not confirm this finding. Although a FFM of 67.1% in female MS patients versus 71.3% in healthy females was reported, this difference was not significant. At the whole muscle level, Kent-Braun *et al.* [18] showed a 30% reduction in the fat free cross sectional area (CSA) of the anterior compartment of the lower leg, whereas Ng *et al.* [19], failed to demonstrate a significant difference between the CSA of the ankle dorsiflexor muscles in MS patients and healthy subjects. Finally, histochemical analysis of biopsies from *m. tibialis anterior* have shown a reduction (26%) of the average muscle fibre area in MS patients compared to healthy subjects [18]. This finding was supported by Garner *et al.* [17] who, using the single fibre electrophoresis technique, found smaller Type 1 (–8%) and Type IIa (–13%) muscle fibre areas in MS patients as compared to healthy controls. However it should be noted that findings from another small study [40] including both histochemical analysis and single fibre electrophoresis (*m. vastus lateralis*) could not confirm the finding of atrophy in MS patients.

Muscle fibre type composition have also been shown to differ in MS patients compared to healthy controls, but the findings are inconsistent. Kent-Braun *et al.* [18] reported a shift in fibre type composition from Type 1 fibres toward a greater proportion of Type IIa and IIax fibres. This shift in fibre type composition resembles the pattern seen in healthy subjects exposed to immobilization [47]. On the other hand Garner *et al.* [17] reported a

Table 1 Summary of differences between MS patients and healthy subjects

	MS patients versus healthy subjects	Ref. no.
Daily activity level	Decreased	15–18
VO ₂ -max	Decreased	21, 33
Blood pressure (rest)		
Systolic	No difference	35, 36
Diastolic	No difference or increased	36 or 35
Resting heart rate	No difference or increased	21, 35, 36 or 34
Muscle strength		
Isokinetic strength	Decreased	37–40
Isometric strength	Decreased	19, 41–43
Rate of force development	No difference or decreased	42 or 19, 41, 43
Muscle mass (% FFM)	No difference or decreased	46 or 26
Muscle fibre area	No difference or decreased	40 or 17, 18
Muscle activation	Decreased	19, 42, 44
Function (ADL)	Decreased	51–53
CVD risk	Increased	30
Bone mineral density (BMD)	Decreased	25–27, 97
Depression risk	Increased	28
Fatigue	Increased	29
HRQOL	Decreased	54

ADL: activities of daily living, BMD: bone mineral density, CVD: cardiovascular diseases, FFM: fat free mass, HRQOL: health related quality of life, VO₂-max: maximum oxygen consumption.

smaller proportion of fibres expressing the myosin heavy chain (MHC) IIa isoform, whereas Carroll *et al.* [40] could only demonstrate a larger proportion of hybrid fibres expressing MHC I/IIa/IIx in MS patients.

Also neural mechanisms are responsible for the strength deficit seen in MS patients. Studies in MS patients have shown a reduced ability to fully activate motor units in the thigh and lower leg muscles (47–93%) during maximal voluntary contractions as compared to healthy controls (94–100%) [19,42,44,45]. However a study by de Ruyter *et al.* [14] did not find any differences in the activation of *m. adductor pollicis* between MS patients and healthy controls. This study adds further support to the clinical experience that lower limb muscle strength is more or earlier affected than upper limb muscle strength. Additionally, decreases in maximal motor unit firing rates, which can impair voluntary muscle strength, have been reported in MS patients [44]. Furthermore, the central motor drive is increased during voluntary submaximal muscle contractions in MS patients [48].

In healthy elderly it is well documented that muscle strength is related to the functional capacity during activities of daily living [49,50]. In MS patients a relationship between gait speed and muscle strength has been established [51]. As would be expected Thoumie *et al.* [51] reported that both comfortable and maximal gait velocity were reduced in MS patients, which have been confirmed in other studies [43,52]. In concordance with these results it has also been demonstrated that MS patients walked significantly slower than healthy subjects during a six minute walk test [53]. Particularly, these physical aspects of the disease have been shown to be the main reason for the lower level of health related quality of life (HRQOL) seen in MS patients [54].

In summary, MS patients are at increased risk of developing a number of conditions known to be related to inactivity. The physiological profile of MS patients is characterised by inappropriate reductions in both aerobic capacity and muscle strength, which further translates into impaired functional capacity and reduced quality of life. The physiological profile seen in MS patients is probably caused by both the non-reversible effects of the disease *per se* and by the reversible effects of an inactive lifestyle. Table 1 summarizes the data describing the physiological and health profile of MS patients.

Resistance training

As shown in Table 2 only eight articles [55–58] and five abstracts [59–63] describing a total of eight different studies, can be retrieved. In general the

studies have examined only small sample sizes and only two studies have applied a RCT design [55,58]. Furthermore the home-based resistance training intervention in the RCT study by DeBolt *et al.* [55], was not supervised. Although a non-supervised home-based training programme represents a very realistic training approach, it lowers the methodological quality of the study because self reported training volume and intensity may be encumbered with uncertainty. In addition to this problem the other RCT study by Harvey *et al.* [58] also suffers from low statistical power because only seven MS patients were included in the resistance training group. Aimet *et al.* [63] conducted a large study but have not stated how the MS patients were divided into groups. However the size of the three groups in the study ($n = 75$, $n = 12$ and $n = 7$) do not point towards the use of a randomization procedure. The remaining five studies [57,59,61,62,64] suffers from the lack of a control group in the design and from low statistical power because of small sample sizes. Whereas two of the studies [57,64] have been described in several further publications [56,65–67], the remaining four have only been described in abstracts [59–63] which for logical reasons limits the amount of information that can be gathered from these studies. Based on the existing studies it is therefore difficult to draw solid conclusions regarding the effects of resistance training in subjects suffering from MS. However, a few clinical relevant findings seem to be consistent across the studies. First of all resistance training seems to be well tolerated by MS patients. None of these studies report any problems or unpleasant experiences related to resistance training. Another consistent finding, except in one study [58], is an improvement in muscle strength [55–57,59,60, 62–64] after resistance training. Although Harvey *et al.* [58] reported improvements in quadriceps maximum voluntary contraction (MVC) of 28–47%, this was not significant, which is probably a result of a small sample size ($n = 7$). White *et al.* [57] reported a significant 7.4% increase in maximal isometric knee extensor strength after 8 weeks of biweekly resistance training of the lower extremity. Kasser *et al.* [59] evaluated maximal dynamic knee extensor strength at both slow (60°/s) and fast (120°/s) velocities and found increases of 16.3% and 29.6%, respectively, after 10 weeks of biweekly whole body resistance training. In concordance with these results Taylor *et al.* [64] reported increases of 14% and 32% in one repetition maximum (1RM) strength of the arm and leg press exercise, respectively. Aimet *et al.* [63] tested two different training intensities in a short term (4–6 weeks) study with two to three weekly training sessions of unilateral leg training. The study showed a larger improvement in leg muscle strength after the

Table 2 Studies evaluating the effects of resistance training in MS patients

Study	Sample size	Design	Disability (EDSS)	Type of MS	Duration (weeks)	Frequency (days/week)	Intensity	Training regime	Main findings
'La Trobe group' (Dodd <i>et al.</i> , 2006 [65] and Taylor <i>et al.</i> , 2006 [64])	n = 9 RT: 9	Non-controlled	NR	NR	10 (+4 weeks of familiarization)	2	60–80% of 1 RM	Two sets of 10–12 reps. 3 machine exercises aiming at both upper and lower extremities	Muscle strength: 1 RM leg/arm press: +32%/14% Muscle endurance: Leg press endurance: +171% Arm press endurance: NS Function: Gait: 10 m/2 min: +6%/NS Stair climbing: NS Qualitative measures: Physical, psychological and social benefits. Muscle strength and CSA: KE and PF strength: +7%/52% KE and KF CSA: NS Function: Step: +9% Gait velocity: NS Stride length: +8% Fatigue: MFIS: –24% Resting cytokine conc.: IL-4 and IL-10: –54%/–43% IL-2, IL-6, TNF- α : NS CRP and IFN- γ : –28%/–52% Muscle strength: RT1 KE: +10% RT2 KE: +16%
'Florida group' (White <i>et al.</i> , 2006 [66], White <i>et al.</i> , 2006 [67], White <i>et al.</i> , 2004 [57], Gutierrez <i>et al.</i> , 2005 [56])	n = 12 (8–12) RT: 12	Non-controlled	2.5–5.5	RR	8	2	Week 1: 50% MVC Week 2: 60% MVC Weeks 3–8: 70% MVC When 15 reps was performed intensity was increased by 2–5% MVC	Week 1: 1 set, 6–10 reps. Week 2–8: 1 set, 10–15 reps. 5 machine exercises aiming at the lower extremities	
Aimet <i>et al.</i> , 2006 [63] (abstract only)	n = 94 RT1: 75 RT2: 12 C: 7	CRT	NR	NR	4–6	2–3	RT1: 40% of 1 RM RT2: 70% of 1 RM	Unilateral training of weakest KE. RT1: 3 set, 20–30 reps. RT2: 3 set, 8–12 reps.	
DeBolt <i>et al.</i> , 2004 [55]	n = 36 RT: 19 C: 17	RCT	1.0–6.5	B, CP, RR, P	8	3	Initial load: 0.5% of body weight. Progression obtained using weight west, 0.5–2% body weight increases every 2 weeks	Home-based RT using weight west, 5 exercises aiming at the lower extremities, 2 or 3 sets of 8–12 reps.	Muscle strength: Leg extensor power: +37% Function: Balance: NS Up and go: NS Spasticity: MAS: NS

(Continues)

Table 2 Studies evaluating the effects of resistance training in MS patients (*Continued*)

Study	Sample size	Design	Disability (EDSS)	Type of MS	Duration (weeks)	Frequency (days/week)	Intensity	Training regime	Main findings
Fischer et al., 2000 [62] (abstract only)	n = 16 RT: 16	Non-controlled	<6.5	NR	16	3	NR	Details NR Individually prescribed Duration: 1 h/day	Muscle strength: Upper and lower strength: +42–75% Function: Aerobic power: +16% 'Functional improvements': 8–14% Muscle strength and EMG: KE strength: NS KE surface EMG: NS Function: Chair transfer: 23% Gait: NS
Harvey et al., 1999 [58]	n = 19 RT: 7 PT: 7 C: 5	RCT	NR	RR	8	7	RT: Details NR	RT: Weighted leg raises, 2 set, 10 reps.	Muscle strength: KE and KF: +16–57% EE and EF: +6–29% SAB and SAD: 3–11%
Kasser and McCubbin, 1996 [59] (abstract only)	n = 8 RT: 9	Non-controlled	NR	RR	10	2	Details NR. Progressive increase in intensity	Details NR. RT for whole body. Combination of exercises performed in machines, with free weights and against bodyweight	Muscle strength: KE and KF: Improved EE and EF: Improved Function: Stairclimb: +21% and 26% Up and go: +17% and 14%
Kraft et al., 1996a and b [60,61] (abstract only)	n = 8 RT1: 4 RT2: 4	Non-controlled	RT1: <3 RT2: >6	NR	12	3	NR (progressive)	Details NR. RT for quadriceps, hamstrings, triceps and biceps	Muscle strength: KE and KF: Improved EE and EF: Improved Function: Gait: +11% and 2% Stairclimb: +21% and 26% Up and go: +17% and 14%

B: benign, C: control, CP: chronic progressive, CRP: C-reactive protein, CRT: controlled trial, CSA: cross sectional area, EDSS: expanded disability status scale, EE: elbow extensors, EF: elbow flexors, IFN: interferon, IL: interleukin, KE: knee extensors, KF: knee flexors, MAS: Modified Ashworth Scale, MFI: Modified Fatigue Impact Scale, MVC: maximum voluntary contraction, NR: not reported, NS: not significant, P: progressive, PF: plantar flexors, PT: physiotherapy, RCT: randomized controlled trial, RM: repetition maximum, RR: relapsing-remitting, RT: resistance training, SAB: shoulder abductors, SAD: shoulder adductors, SF: self reported, TNF: tumour necrosis factor.

most intense training regime (10% versus 16%). In four of the studies [55,57,58,63] the training intervention was solely aiming at the lower extremity, which is probably a consequence of the clinical observation of a more pronounced strength deficit in the lower extremity as compared to the upper extremity [43]. Notable improvements (3–29%) were however found in upper extremity muscle strength (elbow extensors, elbow flexors, shoulder abductors and shoulder adductors) in studies [59,60,64], exercising these muscle groups, indicating possible clinical meaningful strength improvements in the upper extremity as well. There is incomplete evidence regarding the effects of resistance training on functional capacity in MS patients. Harvey *et al.* [58], reported a 23% increase in 'chair transfer', whereas no change was seen in gait speed after 8 weeks of daily weighted leg raises. Kraft *et al.* [61] found increases in functional capacity during gait, stair climbing and 'timed up and go' after 12 weeks of resistance training three times a week. Taylor *et al.* [64] reported improvements (6%) in maximal gait velocity in a 10 m walktest after 10 weeks of biweekly training, but found no changes in 2 min walktest and stair climbing performance. White *et al.* [57] reported improved performance during a step test, but found no improvements in gait. Lastly DeBolt *et al.* [55] were not able to demonstrate a significant improvement in timed up and go after 8 weeks of home-based resistance training conducted three times a week. The heterogeneity of these findings is probably caused by differences in duration, mode and intensity of the resistance training regimes across the studies, by differences in study population, by small sample sizes ($n < 10$) in all except one study [55], or simply by lack of transfer to functional ability.

White *et al.* [57] found a marked (–24%) reduction in subjective feeling of fatigue as measured by the Modified Fatigue Impact Scale. This finding has recently earned further support from the study by Dodd *et al.* [65], who using a qualitative approach, reported reduced fatigue in seven out of nine patients after 10 weeks of biweekly training.

An important aspect that must be kept in mind during the interpretation of data from the resistance training studies is that all the evaluated training regimes comprise resistance training with only a moderate training intensity and a mild progression. If MS patients can tolerate a higher training intensity, a larger training volume and a faster progression, then larger and faster improvements would be expected from this training modality. Additionally, it must be noted that all studies, except a small study by Kraft *et al.* [60,61] included MS patients having an EDSS below 6.5. The study by Kraft *et al.* [60,61] showed that resistance training was well tolerated and had beneficial effects in

four MS patients having an EDSS larger than 6. The small sample size and the study description (abstract only) makes it impossible to draw any conclusions regarding the effects of resistance training in the most severely impaired group of MS patients.

In conclusion, only few studies have evaluated the application of resistance training among MS patients. In general these studies are of low methodological quality, which makes it difficult to draw solid evidence based conclusions regarding the effects of resistance training. However resistance training of moderate intensity seems to be well tolerated and to improve both muscle strength and some functional measures among moderately impaired MS patients. No conclusions can yet be drawn in regard to the application of resistance training among more severely impaired MS patients.

Endurance training

The effects of endurance training have been studied more extensively in MS patients compared to resistance training. As depicted in Table 3 a total of 14 articles [33,68–80] and three abstracts [81–83] comprising 14 studies, of which eight used a RCT design, have evaluated the effects of endurance training in MS patients. It should be noted that three studies [69,71,76] did not include a control group. Endurance training was conducted as bicycle ergometry [33,70–72,75,77,78], arm-leg ergometry [73,74,76], arm ergometry [83], aquatic exercise [68,69,80] and treadmill walking [79,83]. In general, the training regimes are insufficiently described. Another general methodological weakness is that the training intensity has been poorly controlled. However, some clinically important findings can be extracted from these studies. Endurance training with low to moderate intensity is well tolerated among MS patients. Furthermore, this training modality has a possible beneficial effect on both the physiological and psychological profile of MS patients. Five studies [33,73–75,78] have evaluated how endurance training affects aerobic capacity as measured by VO_2 -max. Petajan *et al.* [73] and Ponichtera-Mulcare *et al.* [74] found marked improvements (22% and 15%) in VO_2 -max after 15 and 24 weeks of arm-leg ergometry, training 3 days a week at an intensity of 55–60% of VO_2 -max. Measurements during the intervention period at week 5 and 10 [73] and at week 12 [74], showed significant improvements in VO_2 -max in these time intervals (9%, 19% and 10%, respectively). However studies that evaluated the effects of bicycle ergometry for 4 (5 days a week) [33] or 8 (2 days a week) [75,78] weeks at similar training intensities

Table 3 Studies evaluating the effects of endurance training in MS patients

Study	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)	Frequency (days/week)	Intensity	Training regime	Main findings
Van den Berg <i>et al.</i> , 2006 [79]	n = 16 ET: 8 C: 8	RCOT	NR	NR	4	3	55–85% of age predicted max HR	Treadmill walking Duration: max 30 min with max 3 rest periods	Function: 10 m walk time: -17% 2 min walk dist: NS Fatigue: FSS: NS Function: VO ₂ peak/kg: NS Watt/kg: +12% Fatigue: MFS: -11% Depression and HRQOL: BDIS: +24% MSQOL: +10 Function: Duration: 30 min 10 m walk time: NS 6 min walk distance: +16% Fatigue: FSS: NS Spasticity and disability: GNDS: -38% MAS: NS Fatigue: MFI: -8% Depression and HRQOL: CESD-10: NS POMS: NS SF36 (Energy and fatigue): -16% Function: Gait: Improved
Rasova <i>et al.</i> , 2006 [75]	n = 95 ET: 36 PT: 24 PT + ET: 19 C: 16	CRT	1–6.5	NR	8	2	60% of VO ₂ -max	Ergometer bicycling Duration: Initial phase 2–10 min Duration was increased progressively until study end where it was 10–30 min	Function: VO ₂ -max: NS Gait: NS Balance: Improved coordination: Improved
Killeff and Ashburn, 2005 [71]	n = 8 ET: 8	Non controlled	4–6	NR	12	2	60–80% of HR reserve	Ergometer bicycling	Fatigue: MFS: NS Depression and HRQOL: POMS: NS HAQUAMS: +11%
Oken <i>et al.</i> , 2004 [72]	n = 69 ET: 21 YT: 26 C: 22	RCT	<6	NR	26	1 (and encouraged to exercise at home)	Intensity not reported in details. 'Light and moderate intensity'	Ergometer bicycling. Periodically Swiss ball training. Duration: Until fatigue or until reaching personal goal	Function: VO ₂ -max: NS Gait: NS Balance: Improved coordination: Improved
Koudouni <i>et al.</i> , 2004 [82] (abstract only)	n = 40 ET: 40 HC: 50	CRT	NR	NR	20	1	NR	Details NR. Duration 40–45 min	Function: VO ₂ -max: NS Gait: NS Balance: Improved coordination: Improved
'Hamburg group' Schulz <i>et al.</i> , 2004 [78] and Hesse <i>et al.</i> , 2003 [70]	n = 28/39 ET: 15/23 C: 13/16 HC: 20 (two studies with different inclusion criteria)	RCT	<5	RR, PP and SP	8	2	60% of VO ₂ -max	Ergometer bicycling Interval training Duration: 30 min	Fatigue: MFS: NS Depression and HRQOL: POMS: NS HAQUAMS: +11%

(Continues)

Table 3 Studies evaluating the effects of endurance training in MS patients (Continued)

Study	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)	Frequency (days/week)	Intensity	Training regime	Main findings
O Connell <i>et al.</i> , 2003 [81] (abstract only)	n = 11 ET: 5 C: 6	RCT	NR	RR	12	3	NR	Circuit training Two times a week with supervision and one time at home.	Blood measures: Lactate: -16% ACTH and cortisol: NS Nor- and epinephrine: NS BDNF, NGF, IL-6, sIL-6R: NS Function: Gait velocity: NS Gait cadence: Improved MGET: Improved HRQOL: FAMS: Improved MSIS: NS Function: VO ₂ -max: NS Aerobic threshold: +12% FVC: +12% Fatigue: FSS: NS HRQOL: SF36: Vitality: +46% SF 36: Social functioning: +36%
Mostert and Kesseling, 2002 [33]	n = 26 ET: 13 C: 13 HC/HET	RCT	1-6.5	RR, CP, B	3-4	5	Aerobic threshold corresponding to approx-60% of VO ₂ -max	Ergometer bicycling Duration: 30 min	
Sutherland <i>et al.</i> , 2001[80]	n = 22 ET: 11 C: 11	RCT	NR	NR	10	3	NR	Water aerobics Duration: NR	HRQOL: Energy and vigour: Improved Fatigue and pain: Reduced Function: ET1: VO ₂ -max +19% ET2: VO ₂ -max +7% ET1 + 2: VO ₂ -max +15% C: VO ₂ -max -12% Gait velocity: -9% Cadence: 13% Function: VO ₂ -max: +22% Max power output: +48% Muscle strength: UE: +17% LE: +11%
'Baltimore group' Ponichtera-Mulcare <i>et al.</i> , 1997 [74] and Rodgers <i>et al.</i> , 1999 [76]	n = 23 ET1: 11 ET2: 8 C: 4	CRT	1-4.5 5-6.5	NR	24	3	55-60% of VO ₂ -max	Arm/leg ergometer bicycling Duration: 30 min	
Petajan <i>et al.</i> , 1996 [73],	n = 46 ET: 21 C: 25	RCT	< 6	NR	15	3	60% of VO ₂ -max	Arm and leg ergometry: Duration: 40 min	

(Continues)

Table 3 Studies evaluating the effects of endurance training in MS patients (Continued)

Study	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)	Frequency (days/week)	Intensity	Training regime	Main findings
Schapiro <i>et al.</i> , 1988[77]	n = 50 E1: 25 C: 25	RCT	1-6	NR	16	4-5	65-80% of max HR	Ergometer bicycling Duration: 15-30 min Lectures on exercise, nutrition and stress management.	Fatigue: FSS: NS HRQOL and disability: POMS: Improved at week 5 and 10 SIP: Improved at week 10 Blood measures: TG: -17% TC, HDL, LDL: NS Function: Work load: +11% GET: +5% Grip strength: NS Low EDSS ppt. had larger improvements Blood measures: TC/HDL/LDL/TG: NS Function: Work load: Improved Endurance capacity: Improved Function: Gait: NS Muscle strength: KE and KF: NS Swimbench: Force UE: +47-85% Swimbench: Work UE/KE: +82%/330% Fatigue: LE: -14%
March <i>et al.</i> , 1986[83] (abstract only)	n = 17 E1: 17	Non controlled	3-7	NR	4	2-3	70% of max HR	Arm ergometry or treadmill. Duration: 30 min.	
Gehlsen <i>et al.</i> , 1984[68] and Gehlsen <i>et al.</i> , 1986[69]	n = 10 E1: 10	Non controlled	3-6	NR	10	3	~60-75% of max HR	Aquatic exercise. Freestyle swimming and callisthenics in 25-27.5&dec;/C water. Duration: 1 h	

ACTH: adrenocorticotrophic hormone, B: benign, BDIS: Beck Depression Inventory Score, BDNF: brain-derived neurotrophic factor, C: control, CESD: Centre for Epidemiologic Studies Depression Scale, CP: chronic progressive, CRT: controlled trial, EDSS: expanded disability status scale, ET: endurance training, FAMS: functional assessment in multiple sclerosis, FVC: forced vital capacity, FSS: fatigue severity scale, GET: graded exercise time, GNDS: Guys Neurological Disability Scale, HAQUAMS: Hamburg Quality of Life Questionnaire for MS, HC: healthy control group, HDL: high density lipoprotein, HET: healthy endurance training group, HR: heart rate, HRQOL: health related quality of life, KE: knee extensors, KF: knee flexors, LDL: low density lipoprotein, LE: lower extremity, MFI: multidimensional fatigue inventory, MFIS: modified fatigue impact scale, MSIS: multiple sclerosis impact scale, MSQOL: multiple sclerosis quality of life, NGF: nerve growth factor, NR: not reported, NS: not significant, POMS: profile of mood states, PP: primary progressive, PT: physiotherapy, RCOT: randomized crossover trial, RCT: randomized controlled trial, RR: relapsing-remitting, sIL-6R: soluble IL-6 receptor, SIP: sickness impact profile, SP: secondary progressive, TC: total cholesterol, TG: triglyceride, UE: upper extremity, VO₂-max: maximal oxygen consumption, Y1: yoga training.

could not demonstrate significant improvements in $\text{VO}_2\text{-max}$. This suggests that training at least 3 days a week would seem crucial if improvements in $\text{VO}_2\text{-max}$ should be attained within the first 8 weeks of training using a moderate (55–60% of $\text{VO}_2\text{-max}$) training intensity. Furthermore this questions whether training at that intensity for 2 days a week will provide an adequate stimulus for improving $\text{VO}_2\text{-max}$. It should however be noted that although the study by Mostert and Kesselring [33] could not show an improvement in $\text{VO}_2\text{-max}$, 5 weeks of bicycle ergometry actually did result in a rightward placement of the aerobic threshold indicating an improvement in aerobic capacity when working at submaximal intensities.

Fatigue is a common clinical symptom in MS and as many as 40% of the patients describe it as the single most disabling symptom exceeding complaints about weakness, spasticity, motor problems or bowel or bladder problems [84]. Interventions that can reduce fatigue in MS patients are therefore of particular interest. Several studies have tested endurance training as an intervention against fatigue. The findings show inconsistency due to the fact that some studies show an effect [72,75], whereas others do not [33,71,73,78,79]. With only one exception [78] all the studies that could not demonstrate an effect of endurance training on fatigue, used the unidimensional Fatigue Severity Scale (FSS). On the other hand, the studies that reported an effect of endurance training on fatigue, used either the multidimensional Modified Fatigue Impact Scale (MFIS) [75] or the Multidimensional Fatigue Inventory (MFI) [72]. This could imply that the FSS is not measuring fatigue in a sufficiently sensitive manner to capture improvements in the various areas of the fatigue phenomenon. This is supported by the fact that one of the studies that could not demonstrate any change in the FSS, actually did find a significant improvement in the profile of mood states (POMS) measure of fatigue [73]. The study by Schulz *et al.* [78] did not find any effect of endurance training on fatigue using the MFIS. However, this study in general showed no or only modest effects of the training intervention.

Endurance training seems to positively influence psychological measures regarding both health related quality of life scores like SF36 [33,72], multiple sclerosis quality of life (MSQOL) [75], Hamburg quality of life questionnaire for MS (HAQUAMS) [78] and mood measured by POMS [73,80]. Improvements have been found in items regarding vitality [33], social functioning [33,78], mood [78], energy [72,80], fatigue [72,73,80], anger [73], sexual function [80] and depression [73]. Depression has also been measured by Becks Depression Inventory showing a positive impact of

endurance training on symptoms of depression in MS patients [75].

The reported effects of endurance training on functional capacity are inconsistent. Several studies evaluating the effects of both bicycle ergometry [75,77] and arm-leg ergometry [73] have reported improvements in endurance performance (watt or duration) during maximal testing on the ergometer used for training. Not all studies [78] have reported this improvement indicating that the training period was too short (8 weeks), the intensity was too low (60% of $\text{VO}_2\text{-max}$) or that the training frequency (2 days a week) was too low. Several studies have investigated how endurance training influenced gait velocity, and the findings show great diversity as it has been reported that gait velocity was either reduced [76], unaffected [68,70,81] or improved [71,79]. This suggests that endurance training at best results in modest improvements in activities of daily living (ADL) reflecting that such activities are more dependent on muscle strength than on endurance. This would agree with the fact that no [69] or only modest improvements (11%) [73] in lower extremity muscle strength will result from endurance training.

All cited studies evaluating the effects of endurance training have studied MS patients having an EDSS score below 7. This means that knowledge are insufficient regarding the application of endurance training among the most severely disabled patients. However, several studies [33,73,74,77] have evaluated the relationship between degree of training adaptation and neurological disability. Based on the EDSS score Shapiro *et al.* [77] divided their MS patients into a low (EDSS < 3.5) and a high (EDSS: 4–6) disability group. The data showed that the MS patients in the low disability group showed a larger (10%) increase in exercise time during a graded bicycle test after the training period. Similarly, Ponicthera-Mulcare *et al.* [74] divided their MS patients into two groups based on the EDSS score (group 1: EDSS < 4.5 and group 2: EDSS 5–6.5). The data showed that 24 weeks of arm-leg ergometry resulted in a significant larger improvement in $\text{VO}_2\text{-max}$ in the low EDSS group (19% versus 7%). This led to the suggestion that the level of training adaptation is influenced by the level of neurological impairment. The studies by Mostert and Kesselring [33] and Petajan *et al.* [73] were, however, not able to confirm this relationship. In fact, the findings by Mostert and Kesselring [33] indicated that the most disabled patients actually experienced the largest improvements, whereas Petajan *et al.* [73] found equal improvements in $\text{VO}_2\text{-max}$ when the MS patients were classified in this manner. Consequently findings regarding the relationship between disability

level and the adaptability to endurance training in MS patients are inconsistent.

In summary, only the effects of endurance training of low to moderate intensity have been evaluated in MS patients. MS patients having an EDSS lower than 7 have been studied and it has unambiguously been shown that endurance training is well tolerated. Endurance training induces improvements in aerobic capacity and in measures regarding health related quality of life, mood and depression in MS patients. Inconsistent findings regarding the impact of endurance training on fatigue might be related to the selected fatigue scale. Endurance training of low to moderate intensity has no or only a modest effect on functional capacity evaluated as gait velocity. It is also unclear whether the more severely impaired MS patients exhibit impaired adaptation to the effects of endurance training.

Combined training

Carter *et al.* [85] was the first to evaluate combined training, however, the results were only reported in an abstract despite the use of an RCT design. The study showed that 12 weeks of twice weekly combined training were well tolerated, that muscle strength was improved, and that the level of effort of walking was reduced. Recently a large study has evaluated the effects of combined training [86]. This publication was followed by two articles [87,88] based on data from the same study. The study used a RCT design, a large sample size (95 subjects) and a long-term training intervention lasting 26 weeks. After a 3 week in-patient rehabilitation programme the intervention group completed 23 weeks of home based combined training. The home based training intervention consisted on a weekly basis of 3–4 days of resistance training and 1 day of endurance training. An important finding was that combined training was well tolerated by MS patients. Surprisingly, none or only small (10%) improvements were seen in knee extensor and knee flexor muscle strength after the training intervention, and no significant differences were noted when compared to the control group. However, this may be explained by several conditions. Data from the subjects training diaries showed a total training adherence of 93%, where the adherence to resistance training was 59% and the adherence to endurance training was 185%. Consequently, the resistance- and endurance training constituted a similar proportion of the completed training, and resistance training was therefore on average performed about two times per week instead of the planned three to four times. Furthermore, the conducted resistance training applied a low training

intensity and a slow progression. In addition to this, home-based and non supervised training suffers from the fact that the reported training volume, intensity and progression speed are based on self reports, which not necessarily reflects the training actually conducted. Finally, combined resistance- and endurance training has to some degree been shown to compromise the effects of each other in healthy subjects [89] which also could be the case in MS patients. Taken together, only modest strength improvements would be expected from the training intervention used in this study. This conclusion is further supported by the fact that no change of aerobic capacity was observed. Despite the small or non-existent change in muscle strength and VO₂-max, some functional improvements were found. Walking time during a short (7.62 m) and a long (500 m) test showed improvements of 12% and 6% respectively [87]. No significant change was seen in the MSQOL, depression score (Centre for Epidemiologic Studies Depression Scale) [88] and fatigue (FSS) [86].

In summary, only two studies have examined the effects of combined training in MS patients, which makes it difficult to draw solid conclusions regarding the effects of this training modality. However, the studies showed that combined training was well tolerated, and that small improvements were found in muscle strength and functional capacity (gait velocity). No change was observed in aerobic capacity, depression, fatigue and HRQOL after combined training. The findings are summarized in Table 4.

Exercise recommendations

MS patients should consult an expert (eg, a physiotherapist or an exercise physiologist) before starting a new exercise programme [10]. It is important that the programme is designed and prescribed on an individual basis so that individual capabilities and impairments as well as environmental conditions can be taken into account. It must therefore be emphasized that the following recommendations only serve as basic guidelines that should be considered in relation to every MS patient. The following recommendations are limited to MS patients with an EDSS score of less than 7, because too little is known about the effects of exercise in the more severely impaired group of MS patients

Recommendations for resistance training

Solid evidence based recommendations regarding optimal resistance training in MS patients can not be given based on the scientific literature.

Table 4 Studies evaluating the effects of combined training using MS patients

Study	Sample size	Design	Disability (EDSS)	MS courses	Duration (weeks)	Frequency (days/week)	Intensity	Training regime	Main findings
'Masku group' (Romberg <i>et al.</i> , 2004 [87], Romberg <i>et al.</i> , 2005 [88] and Surakka <i>et al.</i> , 2004 [86])	n = 95 CT: 47 C: 48	RCT	1-5.5	All	26	Weeks 1-3: RT: 5 ET: 5 Weeks 4-26: RT: 3-4 ET: 1	Not described in details. Stiffer elastic band at week 15.	Week 1-3: Inpatient rehabilitation program. Weeks 4-26: RT: Circuit training, 10 exercises for whole body, 2 sets, 10-15 reps. ET: Aquatic training or preferred mode of ET	Function: 7.62 m walk time: -12% 500 m walk time: -6% Balance: NS VO ₂ -peak: NS MSFC: Improved Muscle strength: KE: NS KF: 10% Disability, HRQOL and Depression: EDSS: NS FIM: NS MSQOL-54: NS CES-D: NS Fatigue: FSS: NS Function: PCI: -19% Muscle strength: LE: Improved
Carter <i>et al.</i> , 2003 [85] (abstract only)	n = 16 CT: NR C: NR	RCT	NR	NR	12	2 (+1)	NR	Details NR. Supervised RT + ET + Flexibility training + one unsupervised session	

C: control, CESD: Centre for Epidemiologic Studies Depression Scale, CT: combined training, EDSS: Expanded Disability Status Scale, ET: endurance training, FIM: functional independence measure, FSS: Fatigue Severity Scale, KE: knee extensors, KF: knee flexors, LE: lower extremity, MSFC: multiple sclerosis functional composite, MSQOL: multiple sclerosis quality of life, PCI: physiological cost index, RCT: randomized controlled trial, RT: resistance training.

Consequently, the following recommendations are a composite based on the general resistance training recommendations [90,91] and the sparse literature dealing with resistance training in MS.

An important aspect is that resistance training must be performed under supervision from experienced personnel, until the MS patient is comfortable with the training programme. In addition to the safety issue, data from healthy subjects shows, that supervised resistance training is superior to non supervised resistance training [92]. In the initial training phase general experience indicates, that the use of training machines (ie, closed kinetic chains) should be preferred instead of free weights (ie, open kinetic chains). If the use of training machines is not feasible, then home based training using elastic bands and/or exercises using body weight as load, represents an alternative. It is however often difficult to obtain the same effectiveness from this kind of training, as can be obtained using training machines. Intensities in the range of 8–15 repetition maximum (RM) is recommended. Intensities around 15 RM are recommended during the initial training phase and should be progressively (over several months) increased toward intensities around 8–10 RM. The number of sets should initially be in the range of 1–3, which can be increased toward 3–4 sets of every exercise after a few months. Rest periods between sets and exercises in the range of 2–4 min are recommended. A training frequency in the range of 2–3 days per week is well tolerated and results in meaningful improvements in MS patients. In general a whole body programme containing 4–8 exercises is recommended. Only in special cases where the training frequency is exceeding 3 times a week, a split programme should be considered. In general the exercise order should be planned so that large muscle group exercises are performed before small muscle group exercises, and multiple-joint exercises before single-joint exercises [90]. For MS patients lower extremity exercises should have high priority, because it has been shown that the extent of the strength deficit in the lower extremities is of greater magnitude than in the upper extremity [43].

Recommendations for endurance training

Several different modes of endurance training have been shown to induce favourable improvements in MS patients. Bicycle ergometry [33,70–72,75,77,78], arm-leg ergometry [73,74,76], arm ergometry [83] aquatic exercise [68,69,80] and treadmill walking [79] can all be recommended whereas running and rowing is suitable for well-functioning MS patients, only. A training frequency of two to three

sessions per week using an initial training intensity of 50–70% of $\text{VO}_2\text{-max}$ corresponding to 60–80% of maximum heart rate is recommended. An initial exercise duration of 10–40 min is recommended depending on the disability level of the MS patient. During the first 2–6 months progression should be obtained by increasing the training volume either by a longer training duration or by adding an extra training day. After this period it should be tested whether a higher training intensity is tolerated. This can be done by replacing one training session with interval training using intensities of up to 90% of $\text{VO}_2\text{-max}$.

Recommendations for combined training

As described earlier very little is known about combined training in MS patients which makes it difficult to provide evidence-based recommendations regarding this training modality. Combined training has been shown to be well tolerated in MS patients. Combined training based on equal proportions of resistance- and endurance training performed on alternate days is recommended. It has been shown that two weekly days of resistance training only and two weekly days of endurance training only is well tolerated by MS patients [87]. Based on this, two days of resistance training and two days of endurance training is recommended as the maximal initial training frequency on a weekly basis. The two bouts of resistance training as well as the two bouts of endurance training should be separated by an interval of 24–48 h for recovery. The recommendations described earlier regarding resistance- and endurance training should be followed when designing both the resistance- and the endurance training programme.

Discussion

Endurance- and resistance training is known to have beneficial effects on different aspects of the physiological profile (Table 5). Endurance training results in profound adaptations of the cardiorespiratory and neuromuscular systems that enhance the delivery of oxygen from the atmosphere to the mitochondria and enable a tighter regulation of muscle metabolism [93]. Resistance training is on the other hand known to increase muscle mass and to improve neural activation [91]. It is obvious that MS patients have deficits in various areas of the physiological profile. In theory, optimal rehabilitation aiming at a normalization of the physiological profile would therefore require the application of both endurance and resistance training. Presently, the concept of combined

Table 5 Summary of the effects of either endurance training (1) or resistance training (2) in MS patients

	1) Effects of endurance training	Ref. no.	2) Effects of resistance training	Ref. no.
Daily activity level	Benefit ^a	98	Benefit ^a	99
VO ₂ -max	No benefit or benefit	33, 75, 78 or 73, 74	No benefit ^a or benefit ^a	102
Blood pressure (rest)				
Systolic	Benefit ^a	100	Benefit ^a	103
Diastolic	No benefit ^a	100	Benefit ^a	103
Resting heart rate	Benefit ^a	101	No benefit ^a or benefit ^a	102
Muscle strength				
Isokinetic strength	No benefit	69	No benefit or benefit	58 or 55, 59
Isometric strength	Benefit	73	Benefit	57
Rate of force development	NR		Benefit ^a	105
Muscle mass (%FFM)	No benefit	73	No benefit	57
Muscle fiber area	No benefit ^a	104 89	Benefit ^a	106
Muscle activation	No benefit ^a	104	No benefit	57
Function (ADL)	No benefit or benefit	76 68, 70, 81 or 71, 79	No benefit or benefit	55 or 57, 58, 61, 64
CVD risk	Benefit ^a	107, 108	Benefit ^a	110
Bone mineral density (BMD)	Benefit ^a	109	Benefit ^a	111
Depression risk	Benefit ^b	75	Benefit ^{a,b}	112
Fatigue	No benefit or benefit	71, 73, 78, 79 or 72, 75	Benefit	57, 65
HRQOL	Benefit	33, 72, 73, 75, 78	Benefit ^a	110

^aNo data from MS patients exists. Data obtained from healthy subjects.

^bThe training modality can reduce the severity of symptoms.

NR: not reported.

training is however so sparsely investigated in MS patients that solid evidence-based recommendations can not be provided.

Although the amount of studies evaluating the effects of resistance training among MS patients is limited, there are several observations that favour the use of this training modality. First of all exercise has been reported to trigger symptom exacerbations in more than 40% of the MS patients during and immediately after exercise [6]. The condition, which is known to be temporal and to be normalized within half an hour after exercise for most (85%) patients [6], seems to be related to the increase seen in core temperature during exercise [2]. However resistance training is not accompanied by the same increases in core temperature, as is seen during endurance training. It is therefore likely that resistance training more rarely than endurance training will cause unpleasant experiences, because of increases in body temperature. However, no matter what training modality being applied in MS patients factors affecting core temperature should always be considered and minimized, in order to make exercise as pleasant as possible [2]. Another important aspect of resistance training has been pointed out by White *et al.* [10]. Patients suffering from major strength deficits may be unable to benefit from endurance training because endurance training of sufficient duration and intensity cannot be performed. A period of prior resistance training can probably make efficient endurance training possible for some MS patients suffering from these problems.

Physical exercise in the form of resistance or endurance training represents a very effective means to attain improvements in the physiological profile, but many MS patients do not apply this possibility. In an attempt to promote compliance, the training programme should be individually varied and include regular testing and adjustment. Another way to improve motivation and thereby adherence to a training programme is by including alternate training selected by the MS patient in the training programme. It should also be considered whether the training should be conducted on an individual basis or as group training. In the study by Romberg *et al.* [88] individual home-based combined training did not result in any improvement in HRQOL. The authors speculate that the social isolation and the lack of support from other exercisers might have contributed to this. Evidence from healthy older sedentary subjects supports this notion [94].

In a long term perspective exercise poses the potential to prolong the period of independent living of MS patients. This is an important aspect because it is known that quality of life is strongly influenced by loss of independency [95].

Future perspectives

In general many of the previous studies have applied short training interventions (<10 weeks). From classical exercise physiology it is known that a training intervention lasting 12 weeks or longer makes it more likely to obtain measurable cardiovascular, morphological and neural adaptations [96]. A training intervention lasting 12 weeks or more is recommended for future training studies of MS patients, regardless of the training modality being investigated. Another general feature of the existing literature is that MS patients having an EDSS of more than 7 have not been studied. Consequently future training studies should include more impaired MS patients. In general more accurate descriptions regarding the tested training regime are also warranted.

Concerning the different training modalities it is clear, that there is a need for future RCT studies that evaluate different resistance training protocols. Particularly studies that systematically evaluate programme parameters like training frequency, mode, intensity and volume are needed. Also studies evaluating the effects of combined training are warranted in order to establish some guidelines for MS patients regarding this training modality. These studies should focus on the proportion of resistance training compared to endurance training, training frequency, intensity and volume. Finally, it would be of great interest to find out whether MS patients can tolerate more intense endurance training. If so, faster and larger training improvements are to be expected and this would probably also prevent a fast plateau in training improvements caused by to little overload. In this context the application of systematic interval training is a possibility allowing higher training intensities combined with breaks that can perhaps reduce the effects of thermosensitivity seen in some patients. To obtain these perspectives it is important that the training intensity will be better controlled and described in future studies.

Conclusions

Physical exercise is an important non-pharmacological tool in MS rehabilitation. Contrary to earlier beliefs, exercise is well tolerated and induces beneficial effects in MS patients. Studies examining resistance training are in general of low methodological quality, which makes it difficult to draw solid conclusions regarding the effects of this training modality. However, resistance training with moderate intensity seems to be well tolerated and to have beneficial effects among moderately impaired MS patients. The therapeutic effect of endurance training is better described. Endurance

training at low to moderate intensity is well tolerated and has beneficial effects in MS patients having an EDSS lower than 7. Combined resistance- and endurance training has only been evaluated in two studies but the results are promising. Future MS training studies should evaluate longer training periods (>12weeks), more severely impaired patients (EDSS > 6.5), various training intensities and primarily focus on resistance training and combined resistance or endurance training.

Acknowledgements

This study was supported by the national Multiple Sclerosis Society. The authors would like to thank Johannes Jakobsen, Professor, MD, Jens Olesen, Physiotherapist and Kristian Overgaard, Ass. Professor, for qualified comments to the manuscript.

References

1. Uthoff W. Untersuchungen über die bei der Multiplen Herdsklerose vorkommenden Augenstörungen. *Arch Psychiat Nervenkrankh* 1889; 21: 55–410.
2. White AT, Wilson TE, Davis SL, Petajan JH. Effect of precooling on physical performance in multiple sclerosis. *Mult Scler* 2000; 6: 176–80.
3. Petajan JH, White AT. Recommendations for physical activity in patients with multiple sclerosis. *Sports Med* 1999; 27: 179–91.
4. Ponichtera-Mulcare JA. Exercise and multiple sclerosis. *Med Sci Sports Exerc* 1993; 25: 451–65.
5. Sutherland G, Andersen MB. Exercise and multiple sclerosis: physiological, psychological, and quality of life issues. *J Sports Med Phys Fitness* 2001; 41: 421–32.
6. 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: 723–27.
7. Brown TR, Kraft GH. Exercise and rehabilitation for individuals with multiple sclerosis. *Phys Med Rehabil Clin N Am* 2005; 16: 513–55.
8. Karpatkin H. Multiple sclerosis and exercise – a review of the evidence. *Int J MS Care* 2006; 7: 36–41.
9. Heesen C, Romberg A, Gold S, Schulz KH. Physical exercise in multiple sclerosis: supportive care or a putative disease-modifying treatment. *Expert Rev Neurother* 2006; 6: 347–55.
10. White LJ, Dressendorfer RH. Exercise and multiple sclerosis. *Sports Med* 2004; 34: 1077–100.
11. Poser CM, Ronthal M. Exercise and alzheimer's disease, parkinson's disease, and multiple sclerosis. *Physician Sportsmed* 1991; 19: 85–86, 88.
12. Rietberg M, Brooks D, Uitdehaag B, Kwakkel G. Exercise therapy for multiple sclerosis. *Cochrane Database Syst Rev* 2005; CD003980.
13. Baker NA, Tickle-Degnen L. The effectiveness of physical, psychological, and functional interventions in treating clients with multiple sclerosis: a meta-analysis. *Am J Occup Ther* 2001; 55: 324–31.
14. de Ruiter CJ, Jongen PJ, van der Woude LH, de Haan A. Contractile speed and fatigue of adductor pollicis muscle in multiple sclerosis. *Muscle Nerve* 2001; 24: 1173–180.
15. Ng AV, Kent-Braun JA. Quantitation of lower physical activity in persons with multiple sclerosis. *Med Sci Sports Exerc* 1997; 29: 517–23.
16. Stuifbergen AK. Physical activity and perceived health status in persons with multiple sclerosis. *J Neurosci Nurs* 1997; 29: 238–43.
17. Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. *Muscle Nerve* 2003; 27: 456–64.
18. Kent-Braun JA, Ng AV, Castro M, Weiner MW, Gelinias D, Dudley GA *et al.* Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *J Appl Physiol* 1997; 83: 1998–2004.
19. Ng AV, Miller RG, Gelinias D, Kent-Braun JA. Functional relationships of central and peripheral muscle alterations in multiple sclerosis. *Muscle Nerve* 2004; 29: 843–52.
20. Kent-Braun JA, Sharma KR, Weiner MW, Miller RG. Effects of exercise on muscle activation and metabolism in multiple sclerosis. *Muscle Nerve* 1994; 17: 1162–69.
21. Tantucci C, Massucci M, Piperno R, Grassi V, Sorbini CA. Energy cost of exercise in multiple sclerosis patients with low degree of disability. *Mult Scler* 1996; 2: 161–67.
22. Le Page C, Bourdoulous S, Beraud E, Couraud PO, Rieu M, Ferry A. Effect of physical exercise on adoptive experimental auto-immune encephalomyelitis in rats. *Eur J Appl Physiol Occup Physiol* 1996; 73: 130–35.
23. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports* 2006; 16(Suppl 1): 3–63.
24. Berlin AA, Kop WJ, Deuster PA. Depressive mood symptoms and fatigue after exercise withdrawal: the potential role of decreased fitness. *Psychosom. Med* 2006; 68: 224–30.
25. Cosman F, Nieves J, Komar L, Ferrer G, Herbert J, Formica C *et al.* Fracture history and bone loss in patients with MS. *Neurology* 1998; 51: 1161–65.
26. Formica CA, Cosman F, Nieves J, Herbert J, Lindsay R. Reduced bone mass and fat-free mass in women with multiple sclerosis: effects of ambulatory status and glucocorticoid Use. *Calcif Tissue Int* 1997; 61: 129–33.
27. Nieves J, Cosman F, Herbert J, Shen V, Lindsay R. High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. *Neurology* 1994; 44: 1687–92.
28. Zorzon M, de Masi R, Nasuelli D, Ukmar M, Mucelli RP, Cazzato G *et al.* Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects. *J Neurol* 2001; 248: 416–21.
29. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol* 1988; 45: 435–37.
30. Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain* 2004;
31. Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Med Sci Sports Exerc* 1997; 29: 191–96.
32. Convertino VA, Bloomfield SA, Greenleaf JE. An overview of the issues: physiological effects of bed rest and restricted physical activity. *Med Sci Sports Exerc* 1997; 29: 187–90.
33. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Mult Scler* 2002; 8: 161–68.
34. Olgiate R, Jacquet J, di Prampero PE. Energy cost of walking and exertional dyspnea in multiple sclerosis. *Am Rev Respir Dis* 1986; 134: 1005–10.
35. Anema JR, Heijnenbroek MW, Faes TJ, Heimans JJ, Lanting P, Polman CH. Cardiovascular autonomic function in multiple sclerosis. *J Neurol Sci* 1991; 104: 129–34.

36. Pepin EB, Hicks RW, Spencer MK, Tran ZV, Jackson CG. Pressor response to isometric exercise in patients with multiple sclerosis. *Med Sci Sports Exerc* 1996; **28**: 656–60.
37. Armstrong LE, Winant DM, Swasey PR, Seidle ME, Carter AL, Gehlsen G. Using isokinetic dynamometry to test ambulatory patients with multiple sclerosis. *Phys Ther* 1983; **63**: 1274–79.
38. Lambert CP, Archer RL, Evans WJ. Muscle strength and fatigue during isokinetic exercise in individuals with multiple sclerosis. *Med Sci Sports Exerc* 2001; **33**: 1613–19.
39. Ponichtera JA, Rodgers MM, Glaser RM, Mathews T. Concentric and eccentric isokinetic lower extremity strength in persons with multiple sclerosis. *J Orthop Sports Phys Ther* 1992; **16**: 114–22.
40. Carroll CC, Gallagher PM, Seidle ME, Trappe SW. Skeletal muscle characteristics of people with multiple sclerosis. *Arch Phys Med Rehabil* 2005; **86**: 224–29.
41. Chen WY, Pierson FM, Burnett CN. Force-time measurements of knee muscle functions of subjects with multiple sclerosis. *Phys Ther* 1987; **67**: 934–40.
42. de Haan A, de Ruiter CJ, Der Woude LH, Jongen PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. *Muscle Nerve* 2000; **23**: 1534–41.
43. Schwid SR, Thornton CA, Pandya S, Manzur KL, Sanjak M, Petrie MD et al. Quantitative assessment of motor fatigue and strength in MS. *Neurology* 1999; **53**: 743–50.
44. Rice CL, Vollmer TL, Bigland-Ritchie B. Neuromuscular responses of patients with multiple sclerosis. *Muscle Nerve* 1992; **15**: 1123–32.
45. Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Evidence of an abnormal intramuscular component of fatigue in multiple sclerosis. *Muscle Nerve* 1995; **18**: 1403–11.
46. Lambert CP, Lee AR, Evans WJ. Body composition in ambulatory women with multiple sclerosis. *Arch Phys Med Rehabil* 2002; **83**: 1559–61.
47. Hortobagyi T, Dempsey L, Fraser D, Zheng D, Hamilton G, Lambert J et al. Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. *J Physiol* 2000; **524**: 293–304.
48. Ng AV, Miller RG, Kent-Braun JA. Central motor drive is increased during voluntary muscle contractions in multiple sclerosis. *Muscle Nerve* 1997; **20**: 1213–18.
49. Buchner DM, Larson EB, Wagner EH, Koepsell TD, de Lateur BJ. Evidence for a non-linear relationship between leg strength and gait speed. *Age Ageing* 1996; **25**: 386–91.
50. Ferrucci L, Guralnik JM, Buchner D, Kasper J, Lamb SE, Simonsick EM et al. Departures from linearity in the relationship between measures of muscular strength and physical performance of the lower extremities: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci* 1997; **52**: M275–M285.
51. Thoumie P, Mevellec E. Relation between walking speed and muscle strength is affected by somatosensory loss in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002; **73**: 313–315.
52. Morris ME, Cantwell C, Vowels L, Dodd K. Changes in gait and fatigue from morning to afternoon in people with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2002; **72**: 361–65.
53. Savci S, Inal-Inc, Arikian H, Guclu-Gunduz A, Cetisli-Korkmaz N, Armutlu K et al. Six-minute walk distance as a measure of functional exercise capacity in multiple sclerosis. *Disabil Rehabil* 2005; **27**: 1365–71.
54. Miller A, Dishon S. Health-related quality of life in multiple sclerosis: the impact of disability, gender and employment status. *Qual Life Res* 2006; **15**: 259–71.
55. DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. *Arch Phys Med Rehabil* 2004; **85**: 290–97.
56. Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance training improves gait kinematics in persons with multiple sclerosis. *Arch Phys Med Rehabil* 2005; **86**: 1824–29.
57. White LJ, McCoy SC, Castellano V, Gutierrez G, Stevens JE, Walter GA et al. Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult Scler* 2004; **10**: 668–74.
58. Harvey L, Smith A, Jones R. The effect of weighted leg raises on quadriceps strength, EMG parameters and functional activities in people with multiple sclerosis. *Phys Ther* 1999; **85**: 154–61.
59. Kasser S, McCubbin JA. Effects of progressive resistance exercise on muscular strength in adults with multiple sclerosis. *Med Sci Sports Exerc* 1996; **28**: S143.
60. Kraft G, Alquist A, Lateur B. Effects of resistive exercise on strength in multiple sclerosis (MS). *Arch Phys Med Rehabil* 1996; **77**: 984.
61. Kraft G, Alquist A, Lateur B. Effects of resistive exercise on function in multiple sclerosis (MS). *Arch Phys Med Rehabil* 1996; **77**: 984.
62. Fisher NM, Lenox J, Granger CV, Brown-scheidle C, Jacobs L. Effects of an anti-fatiguing exercise program on fatigue and physiological function in patients with multiple sclerosis. *Neurology* 2000; **54**: A338.
63. Aimeta M, Lampichlera J, Musila U, Spiesbergera R, Pelikana J, Schmida J et al. High and moderate intensities in strength training in multiple sclerosis. *Isokin Exerc Sci* 2006; **14**: 153.
64. Taylor NF, Dodd KJ, Prasad D, Denisenko S. Progressive resistance exercise for people with multiple sclerosis. *Disabil Rehabil* 2006; **28**: 1119–26.
65. Dodd KJ, Taylor NF, Denisenko S, Prasad D. A qualitative analysis of a progressive resistance exercise program for people with multiple sclerosis. *Disabil Rehabil* 2006; **28**: 1127–34.
66. White LJ, McCoy SC, Castellano V, Ferguson MA, Hou W, Dressendorfer RH. Effect of resistance training on risk of coronary artery disease in women with multiple sclerosis. *Scand J Clin Lab Invest* 2006; **66**: 351–56.
67. White LJ, Castellano V, McCoy SC. Cytokine responses to resistance training in people with multiple sclerosis. *J Sports Sci* 2006; **24**: 911–14.
68. Gehlsen G, Beekman K, Assmann N, Winant D, Seidle M, Carter A. Gait characteristics in multiple sclerosis: progressive changes and effects of exercise on parameters. *Arch Phys Med Rehabil* 1986; **67**: 536–39.
69. Gehlsen GM, Grigsby SA, Winant DM. Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis. *Phys Ther* 1984; **64**: 653–57.
70. Heesen C, Gold SM, Hartmann S, Mladek M, Reer R, Braumann KM et al. Endocrine and cytokine responses to standardized physical stress in multiple sclerosis. *Brain Behav Immun* 2003; **17**: 473–81.
71. Killeff J, Ashburn A. A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis. *Clin Rehabil* 2005; **19**: 165–69.
72. Oken BS, Kishiyama S, Zajdel D, Bourdette D, Carlsen J, Haas M et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology* 2004; **62**: 2058–64.
73. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* 1996; **39**: 432–41.
74. Ponichtera-Mulcare JA, Mathews T, Barret PJ, Gupta SC. Change in aerobic fitness of patients with multiple

- sclerosis during a 6 month training program. *Sports Med Train Rehabil* 1997; 7: 265–72.
75. Rasova K, Havrdova E, Brandejsky P, Zalisova M, Foubikova B, Martinkova P. Comparison of the influence of different rehabilitation programmes on clinical, spirometric and spiroergometric parameters in patients with multiple sclerosis. *Mult Scler* 2006; 12: 227–34.
 76. Rodgers MM, Mulcare JA, King DL, Mathews T, Gupta SC, Glaser RM. Gait characteristics of individuals with multiple sclerosis before and after a 6-month aerobic training program. *J Rehabil Res Dev* 1999; 36: 183–88.
 77. Schapiro RT, Petajan JH, Kosich D. Role of cardiovascular fitness in multiple sclerosis: a pilot study. *J Neurol Rehabil* 1988; 2: 43–49.
 78. Schulz KH, Gold SM, Witte J, Bartsch K, Lang UE, Hellweg R *et al*. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. *J Neurol Sci* 2004; 225: 11–18.
 79. van den Berg M, Dawes H, Wade DT, Newman M, Burridge J, Izadi H *et al*. Treadmill training for individuals with multiple sclerosis: a pilot randomised trial. *J Neurol Neurosurg Psychiatry* 2006; 77: 531–33.
 80. Sutherland G, Andersen MB, Stoove MA. Can aerobic exercise training affect health-related quality of life for people with multiple sclerosis? *J Sport Exerc Psych* 2007; 23: 122–35.
 81. ÓConnell R, Murphy RM, Hutchinson M, Cooke G, Coote S. A controlled study to assess the effects of aerobic training on patients with multiple sclerosis. *14th International World Confederation for Physical Therapy, Barcelona* 2003; RR-PL-2105.
 82. Koudouni A, Orologas A. Contribution of aerobic exercise to the improvement of quality of life in persons suffering from multiple sclerosis. *Mult Scler* 2004; 10: S132.
 83. Marsh H, Alexander J, Costello E. Short-term exercise programme effect on physical work capacity. *Arch Phys Med Rehabil* 1986; 67: 644.
 84. Bakshi R. Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult Scler* 2003; 9: 219–227.
 85. Carter P, White CM. The effect of general exercise training on effort of walking in patients with multiple sclerosis. *14th International World Confederation for Physical Therapy, Barcelona* 2003; RR-PL-1517.
 86. Surakka J, Romberg A, Ruutiainen J, Aunola S, Virtanen A, Karppi SL *et al*. Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial. *Clin Rehabil* 2004; 18: 737–46.
 87. Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi SL, Vaara M *et al*. Effects of a 6-month exercise program on patients with multiple sclerosis: a randomized study. *Neurology* 2004; 63: 2034–38.
 88. Romberg A, Virtanen A, Ruutiainen J. Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. *J Neurol* 2005; 252: 839–45.
 89. Kraemer WJ, Patton JF, Gordon SE, Harman EA, Deschenes MR, Reynolds K *et al*. Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. *J Appl Physiol* 1995; 78: 976–89.
 90. Kraemer WJ, Adams K, Cafarelli E, Dudley GA, Dooly C, Feigenbaum MS *et al*. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2002; 34: 364–80.
 91. Kraemer WJ, Ratamess NA. Fundamentals of resistance training: progression and exercise prescription. *Med Sci Sports Exerc* 2004; 36: 674–88.
 92. Mazzetti SA, Kraemer WJ, Volek JS, Duncan ND, Ratamess NA, Gomez AL *et al*. The influence of direct supervision of resistance training on strength performance. *Med Sci Sports Exerc* 2000; 32: 1175–84.
 93. Jones AM, Carter H. The effect of endurance training on parameters of aerobic fitness. *Sports Med* 2000; 29: 373–86.
 94. Cox KL, Burke V, Gorely TJ, Beilin LJ, Puddey IB. Controlled comparison of retention and adherence in home- vs center-initiated exercise interventions in women ages 40–65 years: The S.W.E.A.T. Study (Sedentary Women Exercise Adherence Trial). *Prev Med* 2003; 36: 17–29.
 95. Takemasa S. Factors affecting QOL of the home-bound elderly disabled. *Kobe J Med Sci* 1998; 44: 99–114.
 96. Jones DA, Rutherford OM, Parker DF. Physiological changes in skeletal muscle as a result of strength training. *Q J Exp Physiol* 1989; 74: 233–56.
 97. Sharts-Hopko NC, Sullivan MP. Beliefs, perceptions, and practices related to osteoporosis risk reduction among women with multiple sclerosis. *Rehabil Nurs* 2002; 27: 232–36.
 98. Fujita K, Nagatomi R, Hozawa A, Ohkubo T, Sato K, Anzai Y *et al*. Effects of exercise training on physical activity in older people: a randomized controlled trial. *J Epidemiol* 2003; 13: 120–26.
 99. Hunter GR, Wetzstein CJ, Fields DA, Brown A, Bamman MM. Resistance training increases total energy expenditure and free-living physical activity in older adults. *J Appl Physiol* 2000; 89: 977–84.
 100. Kelley GA, Sharpe KK. Aerobic exercise and resting blood pressure in older adults: a meta-analytic review of randomized controlled trials. *J Gerontol A Biol Sci Med Sci* 2001; 56: M298–M303.
 101. Yamamoto K, Miyachi M, Saitoh T, Yoshioka A, Onodera S. Effects of endurance training on resting and post-exercise cardiac autonomic control. *Med Sci Sports Exerc* 2001; 33: 1496–502.
 102. Fleck SJ. Cardiovascular response to strength training. *Strength and power in sport*. 1996; 3: 305–18.
 103. Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure: A meta-analysis of randomized controlled trials. *Hypertension* 2000; 35: 838–43.
 104. McCarthy JP, Pozniak MA, Agre JC. Neuromuscular adaptations to concurrent strength and endurance training. *Med Sci Sports Exerc* 2002; 34: 511–19.
 105. Aagaard P, Simonsen EB, Andersen JL, Magnusson P, Dyhre-Poulsen P. Increased rate of force development and neural drive of human skeletal muscle following resistance training. *J Appl Physiol* 2002; 93: 1318–26.
 106. Kraemer WJ, Deschenes MR, Fleck SJ. Physiological adaptations to resistance exercise. Implications for athletic conditioning. *Sports Med* 1988; 6: 246–56.
 107. Andersen LB. Physical activity and physical fitness as protection against premature disease or death. *Scand J Med Sci Sports* 1995; 5: 318–28.
 108. Erikssen G. Physical fitness and changes in mortality: the survival of the fittest. *Sports Med* 2001; 31: 571–76.
 109. Kelley G. Aerobic exercise and lumbar spine bone mineral density in postmenopausal women: a meta-analysis. *J Am Geriatr Soc* 1998; 46: 143–52.
 110. Kraemer WJ, Ratamess NA, French DN. Resistance training for health and performance. *Curr Sports Med Rep* 2002; 1: 165–71.
 111. Osteoporosis prevention, diagnosis, and therapy. *NIH Consensus Statement* 2000; 17: 1–45.
 112. Paluska SA, Schwenk TL. Physical activity and mental health: current concepts. *Sports Med* 2000; 29: 167–80.

Copyright of *Multiple Sclerosis* (13524585) is the property of Sage Publications, Ltd. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.