ANDERS ROMBERG

Effects of Exercise Training on Functioning in Persons with Multiple Sclerosis

ACADEMIC DISSERTATION
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University of Tampere, School of Health Sciences
Masku Neurological Rehabilitation Centre
Research Department of the Social Insurance Institution
Finland

Supervised by
Professor Clas-Håkan Nygård
University of Tampere
Finland
Docent Juhani Ruutiainen
University of Turku
Finland

Reviewed by
Docent Juha-Pekka Erälinna
University of Helsinki
Finland
Docent Katriina Kukkonen-Harjula
University of Tampere
Finland

Cover design by
Mikko Reinikka

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To Rosa and Rasmus

Contents

List of original communications

This thesis is based on the following original communications, referred to in the text by the Roman numerals I-IV:

I Romberg A, Virtanen A, Aunola S, Karppi S-L, Karanko H and Ruutiainen J (2004). Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. Mult Scler 10:212-18.

II Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi S-L, Vaara M, Surakka J, Pohjolainen T and Seppänen A (2004). Effects of 6-month exercise program on patients with multiple sclerosis. A randomized study. Neurology 63:2034-38.

III Surakka J, Romberg A, Ruutiainen J, Aunola S, Virtanen A, Karppi S-L and Mäentaka K (2004). The effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis. A randomized controlled trial. Clin Rehabil 18:737-46.

IV Romberg A, Virtanen A and Ruutiainen J (2005). Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. J Neurol 252:839-45.

Abbreviations

CES-D	Centre for Epidemiologic Studies Depression Rating Scale
CNS	Central nervous system
EDSS	Expanded Disability Status Scale
FIM	Functional Independence Measure
500MWT	500-meter Walk Test
FI	Fatigue index
FS	Functional Systems
FSS	Fatigue Severity Scale
HRQoL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
MS	Multiple sclerosis
MRI	Magnetic resonance imaging
MSFC	Multiple Sclerosis Functional Composite
MSQOL-54	Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument
9HPT	Nine-Hole Peg Test
95% CI	Ninety-five percent confidence interval
PASAT	Paced Auditory Serial Addition Test
PPMS	Primary progressive multiple sclerosis
RCT	Randomized controlled trial
RM	Repetition maximum
RRMS	Relapsing-remitting multiple sclerosis
SD	Standard deviation
SEM	Standard error of the mean
SF-36	36-item Short Form Health Survey
SPMS	Secondary progressive multiple sclerosis
25FTW	Timed 25-foot Walk Test
VO_2max	Maximal oxygen consumption
VO_2peak	Peak oxygen uptake
WHO	World Health Organization

Abstract

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system causing progressive disability and a wide range of neurological symptoms. There exists no cure for MS, hence interventions are called for to ameliorate symptoms, maintain functioning, and improve quality of life in persons with the disease. Within the last decade, exercise training has been recognised as an effective tool in the rehabilitation of MS. Yet, evidence in the area is insufficient to guide detailed exercise prescriptions.

The present study was designed to examine the effects of long-term combined training on functioning in persons with MS in a randomized controlled trial. The secondary aim was, in a cross-sectional design, to explore the associations between exercise capacity, disability, and leisure-time physical activity (before the training intervention). The training intervention emphasized resistance exercises, but was complemented by endurance training. Subjects in the training group (n = 47) first attended supervised training for three weeks during an inpatient rehabilitation period, and thereafter continued training for 23 weeks at home. Subjects in the control group (n = 48) received no physical activity intervention. Assessments took place at baseline and at six months. The primary outcome was walking speed, measured by the timed 25-foot (7.62 m) Walk Test and 500-meter Walk Test. Secondary outcomes included measures of physical and mental functioning, disability, and health-related quality of life.

The drop-out rate over the intervention period was low (4%). The training group showed significant improvements, as compared with the control group, in primary outcome measures, upper extremity endurance, disability, and partly in motor fatigue. Training caused not serious adverse effects, but the adherence to the home training programme varied considerably. MS relapses were evenly distributed between the two groups (5/6 subjects). For the cross-sectional study, the results indicate that persons with MS present with poor cardiorespiratory fitness. Moreover, a main finding was that neurological disability was shown to be a predictor of endurance exercise capacity in MS.

This study provides rigorous evidence for the beneficial effects of long-term exercise training mainly on physical functioning in persons with MS. The results confirm that exercise training is safe for persons with the disease and should be recommended for those with mild to moderate disability. The findings underscore the importance of encouraging people with MS to take part in regular physical activity and exercise training already from the early stages of the disease.

Tiivistelmä

Multippeliskleroosi (MS) on keskushermoston krooninen tulehduksellinen ja degeneratiivinen sairaus, joka etenee monimuotoisesti aikaansaaden lisääntyvää haittaa ja vaihtelevia neurologisia oireita. MS-taudin syy on tuntematon, eikä siihen ole parantavaa hoitoa. Siksi keinot oireiden lievittämiseksi, toimintakyvyn ylläpitämiseksi ja elämänlaadun parantamiseksi ovat tärkeitä MS-tautia sairastaville. Liikuntaharjoittelu on osoittautunut tehokkaaksi menetelmäksi MS-taudin kuntoutuksessa viime vuosikymmenen aikana. Tutkimusnäyttö täsmällisten ja kattavien liikuntasuositusten pohjaksi on kuitenkin edelleen riittämätöntä.

Tämän tutkimuksen päätarkoituksena oli selvittää satunnaistetussa kontrolloidussa tutkimusasetelmassa pitkäkestoisen, voima- ja kestävyysharjoittelusta koostuvan, liikuntaharjoittelun vaikutuksia MS-tautia sairastavien toimintakykyyn. Toissijaisena tarkoituksena oli, poikkileikkausasetelmassa, selvittää hapenottokyvyn, MS-taudin aikaansaaman haitan ja vapaa-ajan fyysisen aktiivisuuden välisiä yhteyksiä (ennen harjoittelua). Tutkimuksen interventioryhmän jäsenet (n = 47) osallistuivat ensiksi kolmen viikon ajan ohjattuun harjoitteluun laitoskuntoutusjaksolla. Tämän jälkeen he jatkoivat harjoittelua 23 viikon ajan kotioloissa. Verrokkiryhmä (n = 48) ei saanut minkäänlaista liikuntaneuvontaa tai -ohjausta. Tutkimusmittaukset tehtiin molemmille ryhmille alkutilanteessa ja kuuden kuukauden jälkeen. Päävastemuuttujana oli kävelynopeus, jota arvioitiin 25 jalan (7.62 m) ja 500 metrin kävelytesteillä. Muina vastemuuttujina olivat useat fyysisen ja henkisen toimintakyvyn osa-alueet, MS-taudin aikaansaama haitta sekä terveyteen liittyvä elämänlaatu.

Tutkittavien kato tutkimuksen aikana oli pieni (4%). Harjoittelu paransi merkitsevästi kävelynopeutta, kohensi yläraajojen lihaskestävyyttä, lievitti MS-taudin aikaansaamaa haittaa ja vähensi osittain motorista uupumusta. Harjoittelulla ei ollut merkittäviä haittavaikutuksia, mutta siihen sitoutumisessa oli suuria vaihteluita. MS-taudin pahenemisvaiheet jakautuivat tasaisesti ryhmien kesken (5/6 henkilöä). Poikkileikkaustutkimuksen tulokset osoittivat MS-tautia sairastavien maksimaalisen hapenottokyvyn alhaiseksi ja MS-taudin aikaansaaman haitan ennustavan heikentynyttä maksimaalista hapenottokykyä.

Tutkimus antaa vankkaa näyttöä pitkäkestoisen liikuntaharjoittelun suotuisista vaikutuksista MS-tautia sairastavien fyysiseen toimintakykyyn. Liikuntaharjoittelu on turvallista, eikä sillä ole haittavaikutuksia sairauden luonnolliseen kulkuun tai oireisiin. Liikuntaharjoittelua voidaan perustellusti suositella henkilöille, joilla on lievä tai keskivaikea MS-taudin aiheuttama haitta. Tulokset korostavat, että on tärkeää kannustaa MS-tautia sairastavia liikunnallisesti aktiivisiksi jo sairauden varhaisvaiheista lähtien.

1. INTRODUCTION

MS is a chronic, progressive autoimmune disease of the central nervous system (CNS) (Compston & Coles, 2002; Lassman, 2013). Disease onset is typically in early adulthood (Noseworthy et al., 2000), and predominantly women are more often affected (Sadovnick, 2009). MS is characterized by lesions in all parts of the CNS, which cause a wide variety of debilitating neurological symptoms and – often unpredictable – progressive disability (Noseworthy et al., 2000). Ultimately, these can have a profound impact on daily functioning, family relationships, and social and leisure activities, which, in turn, may lead to reduced heath-related quality of life (HRQoL) (Kuspinar et al., 2012).

The exact aetiology of MS remains unknown, and the cure for it is yet to be found (Dutta & Trapp, 2011). Disease-modifying immunomodulatory drugs are effective in slowing down the disease process in relapsing forms of MS, but the evidence for delaying long-term disability is less convincing, incomplete, and controversial (Shirani et al., 2012). As the current MS disease-modifying medication also causes side effects (Miller & Allen, 2010), it is important, in addition to developing new disease-modifying drugs, to establish non-pharmaceutical interventions that aim to enhance optimization of functioning and symptom control, as well as to target the improvement of HRQoL in persons with the disease (Mitchell et al., 2005; Stevenson & Playford, 2007).

Physical activity and exercise are cornerstones of a healthy lifestyle. Nevertheless, previously, persons with MS were advised to avoid exercise because of fear of excessive fatigue and thermosensitivity (Petajan & White, 1999). Today, physical activity and exercise are recommended in MS (Dalgas & Stenager, 2012); a guideline based on a growing amount of research within the last decade focusing on exercise intervention responses. It has been ascertained, however, that the evidence needed to guide exercise prescription in MS is still insufficient (Asano et al., 2009). In the light of the chronic nature of MS, there is a particular lack of understanding about the long-term exercise training responses in the disease. Hence, the primary purpose of this study was to evaluate the effects of a six-month combined resistance and endurance training intervention on functioning in persons with MS. In addition, the associations between exercise capacity, neurological disability, and leisure-time physical activity were examined.

2. REVIEW OF THE LITERATURE

2.1 Physical activity, exercise, training and fitness: concepts and definitions

Regular physical activity is essential for health, as well as for longevity (Hellénius & Sundberg, 2011). It protects from premature death due to chronic diseases (e.g. cardiovascular diseases, diabetes mellitus, cancer) (Paffenbarger et al., 1993; Barengo et al., 2004; Warburton et al., 2006), enhances and protects brain function (Cotman & Engesser-Cesar, 2002; Ahlskog et al., 2011), improves independency in activities of daily living (Schroll, 2003), and has a positive impact on the quality of life (Cress et al., 2006; Pucci et al., 2012). It is well established that physical activity in adults also contributes to the primary and secondary prevention of several chronic conditions such as cardiovascular disease, diabetes mellitus, cancer, and osteoporosis (Warburton et al., 2006). This has led to the recommendation that to promote and maintain health, all adults should aim to take part in at least 150 min of moderate-intensity aerobic (endurance) activity each week, or at least 75 min of vigorous-intensity aerobic activity per week, or equivalent combinations of moderate- and vigorous-intensity activities. In addition, taking part in 8-10 different resistance exercises on two or more non-consecutive days each week is recommended (O'Donovan et al., 2010).

Physical inactivity is one of the most important public health problems of the 21st century (Blair, 2009). Inactivity may lead to deconditioning of multiple physiological systems including reductions in cardiopulmonary function, changes in body composition, and decreases in muscle strength and endurance (McDonald, 2002). Deconditioning may be particularly pronounced in people with disabilities and chronic diseases leading, in turn, to physical deterioration and a subsequent further reduction in physical activity. Specific consequences of an inactive lifestyle for a person with a chronic disease/disability can include diminished self-concept, greater dependence upon others for daily living, and reduced ability for normal societal interactions (Durstine et al., 2000).

By definition, physical activity means "any bodily movement produced by skeletal muscles resulting in energy expenditure" (Caspersen et al., 1985). Components of daily energy expenditure include resting (basal) metabolism (approximately 50%–75%), physical activity (15%–40%), and the thermic effects of food (≤ 10%) (Albanes et al., 1990). Of these, physical activity is the most varying component because it comprises numerous tasks and activities in daily life. Hence, the s hare of total energy expenditure accounted for by physical activity is greater for active individuals than for those with sedentary lifestyle(Kriska & Caspersen, 1997). Albeit closely related, physical activity and energy expenditure are

divergent concepts. Physical activity is behaviour that results in increased energy expenditure and is typically quantified in terms of its frequency (number of bouts) and its duration (e.g. minutes per bout), whereas energy expenditure reflects the energy cost or intensity associated with a given physical activity (Lamonte & Ainsworth, 2001).

A number of physical activity categories have been put forth. A commonly used approach is to segment it on the basis of identifiable portions of daily life during which the activity occurs (Caspersen et al., 1985). Accordingly, physical activity has been divided into work-related and leisure-time activity, where the latter is physical activity "that a person or a group chooses to undertake during their discretionary time" (Bouchard et al., 1990). If activity occurs outside work and leisure, a third category including activity while sleeping and lifestyle activity has been added (Caspersen et al., 1985).

The term "exercise" has been used interchangeably with physical activity, probably as a consequence of the number of common elements which they share. Both involve any bodily movement produced by skeletal muscles resulting in energy expenditure, and both are positively correlated with physical fitness (Caspersen et al., 1985). Exercise is, however, not synonymous with physical activity. It is limited to leisure-time, and can be seen 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 (Caspersen et al., 1985; Bouchard et al., 1990).

"Exercise therapy" aims to improve individuals' overall function and help them meet the demands of daily living. It is a general concept, which, for instance, can differ in content (e.g., muscle strengthening exercises, functional task-oriented exercises), dosage (e.g., frequency, intensity, duration), and delivery mode (e.g., individualized, group based, home based). It can be defined "as a range of activities involving the prescription of muscular contraction and bodily movement" (Pisters et al., 2007).

Training indicates "repetitive bouts of exercise conducted over periods of weeks or months" (Bouchard et al., 1990). Like exercise, training is intended for improvement of physical fitness. Commonly, the two terms are used in parallel as "exercise training" (Howley, 2001; Snowling & Hopkins, 2006; Snook et al., 2009). Another, somewhat overlapping, term in this context is "physical exercise" (Heesen et al., 2006; Ahlskog et al., 2011).

The two components of basic physical exercise training constitute endurance (aerobic) training and resistance training (Dalgas et al., 2008). Endurance training involves repetitive motions, uses large muscle groups, increases heart rate for an extended period, and raises core body temperature (McDermott &

Mernitz, 2006). It can help maintain and improve cardiovascular function, such as peak oxygen uptake (VO_2peak), as well as enhance submaximal cardiovascular performance. Examples of endurance training are walking, running, swimming, and cycling. Resistance training, in turn, is designed specifically to improve muscle strength, power and endurance by varying the resistance, the number of times the resistance is moved, the number of sets done, the rest interval between sets, and the frequency of training (Howley, 2001). Resistance can be created using elastic bands, weight cuffs, free weights, weight machines, or the person's body weight (McDermott & Mernitz, 2006).

Both endurance and resistance components are included in combined training (Dalgas et al., 2008). Combined training programmes may be additionally complemented by balance and/or flexibility exercises (McDermott & Mernitz, 2006; Learmonth et al., 2011). Evidence-based position-stand recommendations of physical activity for adults advocate a comprehensive programme of exercise with aerobic and resistance training as cornerstones (O'Donovan et al., 2010; Garber et al., 2011). Neuromotor training (or functional fitness training) incorporates motor skills such as balance, coordination, gait, and agility, and proprioceptive training. Examples of multifaceted neuromotor training modes are tai chi and yoga (Garber et al., 2011).

Physical fitness is a broad concept with several definitions. Howley (2001) defines it "as a set of attributes (i.e. cardiorespiratory endurance, muscle endurance, muscle strength, muscle power, flexibility, agility, balance, reaction time, and body composition) that people have or achieve related to the ability to perform physical activity". Health-related physical fitness includes components of fitness that are particularly related to health, and which can be improved by appropriate training (Warburton et al., 2006). Its components are body composition, cardiorespiratory fitness, muscular strength and endurance, flexibility, and metabolic fitness (Howley, 2001).

Valid and appropriate assessment of physical activity is challenging owing to its complexity as a multidimensional exposure variable, and to the marked variation in physical activity patterns (frequency, duration, intensity) both within and between individuals and populations (Kriska & Caspersen, 1997; Lamonte & Ainsworth, 2001). Physical activity can be assessed using either subjective or objective methods. Subjective methods include questionnaires, interviews, activity diaries (logs), and direct observation (Corder et al., 2008). A self-report questionnaire is the most frequently used subjective method owing to its practicality, applicability, and accuracy (Kriska & Caspersen, 1997; Lamonte & Ainsworth, 2001; Corder et al., 2008). Accelerometers and pedometers are examples of commonly used objective methods (Corder et al., 2008; Bassett Jr. et al., 2010; Cheung et al., 2011).

2.2 Multiple sclerosis

2.2.1 Characteristics and epidemiology

MS is a chronic inflammatory and neurodegenerative disease of the CNS (Lassmann et al., 2007). Inflammation of CNS is the primary cause of damage in the disease, but the specific elements that initiate this inflammation are thus far unknown (Noseworthy et al., 2000; Lassman, 2013). Probably, genetic and environmental factors such as infectious agents trigger a pathological chain of events, involving engagement of the immune system, acute inflammatory injury of axons and glia, recovery of function and structural repair, post-inflammatory gliosis, and neurodegeneration (Compston & Coles, 2002; Lassman, 2013).

The white matter areas of the CNS are predominantly involved in MS, manifesting as focal inflammatory demyelination and axonal loss with limited remyelination (Compston & Coles, 2002; Lassman, 2013). The pathological hallmark of MS is the demyelinated plaque consisting of mononuclear cell infiltrates composed of T cells, B lymphocytes, plasma cells, and macrophages (Noseworthy et al., 2000; Lassman et al., 2007). For a long time, it was assumed that the acquisition of progressive disability in MS resulted from the cumulative effect of plaques (DeLuca et al., 2006). However, the plaque-centred view of disease progression has been challenged as, apparently, white matter lesions along with cortical white matter lesions contribute substantially to disease progression (Seewann et al., 2009). Besides focal white matter lesions, extensive demyelination in grey matter areas, such as the cerebral and cerebellar cortex of the CNS, have been recognized as additional and major sites of MS pathogenesis (Lassmann, 2013). Grey and white matter changes in MS seem to occur, at least in part, independently; however, grey matter lesions are more strongly associated with physical and cognitive deterioration as compared to that induced by white matter lesions (Calabrese et al., 2012).

The symptoms and signs of MS appear depending upon the site of the lesions and may be linked to any part of the CNS. Most often the cerebrum, cerebellum, optic nerve, brain stem, and spinal cord are affected (Compston & Coles, 2002). Typical early symptoms include sensory disturbances, optic neuritis, limb weakness, clumsiness and/or fatigue. In more advanced stages of the disease, cognitive impairment, depression, pain, sensory loss, and spasticity, for example, may become troublesome (Noseworthy et al., 2000).

MS diagnosis is based on clinical and paraclinical laboratory assessments. The precise diagnostic criteria have evolved over 50 years; all successive versions have emphasized the need to demonstrate

dissemination of lesions in space and time, and to exclude alternative diagnoses (Miller et al., 2008; Polman, 2011). These principles were first established by the Schumacker panel in 1965 (Hurwitz, 2009). The Schumacker criteria were replaced in 1983 by those of Poser criteria, which introduced a new term, "laboratory-supported definite MS" (Poset et al., 1983). Current diagnostic criteria for MS, the McDonald criteria, are based on the International Panel on Diagnosis of MS 2001 recommendations (McDonald et al., 2001). The McDonald criteria allow an earlier and often more accurate diagnosis of MS to be made by utilising magnetic resonance imaging (MRI), evoked potentials, and cerebrospinal fluid immunological changes (Hurwitz, 2009). Since 2001, the original McDonald criteria have been revised twice (Polman et al., 2005; Polman et al., 2011).

Relapses and progression are the basic clinical features of MS (Confavreux et al., 2000). A relapse presents clinically as a focal or multi-focal CNS dysfunction usually developing over days and resolving either completely or partially over a few weeks (Bennetto et al., 2011). In around 80 – 90% of the subjects, relapses are the exclusive clinical expression of MS during the early years, which defines the relapsing-remitting disease form (RRMS) (Confavreux & Vukusic, 2006). In the subsequent phase, relapses become less prominent in the majority of patients, and the course of MS converts to a secondary progressive phase (i.e. secondary progressive MS; SPMS) (Tremlett et al., 2010). In 15 – 20% of subjects, no preceding relapsing-remitting phase occurs and the disease is progressive from the onset. This is termed primary-progressive MS (PPMS) (Confavreux et al., 2000, Compston & Coles, 2002). Based on the rate of progression and relapses, additional terms used to describe particular subtypes of MS have been introduced. The 10% subgroup of subjects who show little or no disease progression and minimal disability over 15 to 20 years after initial symptoms are referred to as having benign MS (Correale et al., 2012; Hutchinson, 2012). In contrast, a noteworthy proportion of subjects experience a more malignant course of MS; for these the use of assistance for ambulation may be required within five years from symptom onset (Gholipour et al., 2011).

MS onset is usually in the third or fourth decade (Compston & Coles, 2002), while the peak age is aproximately 30 years (Hirtz et al., 2007). An estimated 2% to 5% of all people with MS have onset before age 16, while few cases are diagnosed after the age of 50 (Ness et al., 2007; Hirtz et al. 2007). MS affects twice as many women as it does men (Alonso & Hernán, 2008). The unexplained bias of the female-to-male MS ratio resembles that seen in other putative autoimmune diseases (Compston & Coles, 2002). Factors related to MS prognosis have been extensively studied. An initial progressive course has been found as the strongest independent predictor of poor outcome, whereas neither onset symptoms nor number of relapses have a discernible long-term influence on disease progression (Myhr et al., 2001; Tremlett et al., 2010; Bennetto et al., 2011). There is good evidence that the prognosis is linked with age, i.e., current age

together with duration of disease, and older age at onset are among the key predictors of more rapid disease progression (Trojano et al., 2002). Furthermore, magnetic resonance imaging (MRI) markers, such as magnetization transfer ratio, have been shown to be worthy predictors of the long-term evolution of MS (Agosta et al., 2006)

The geographical distribution of MS indicates that it is more prevalent in latitudes north or south of the equator (Ascherio & Munger, 2007). However, the latitude effect seems to diminish when estimates are age- and sex-adjusted to a general population (Zivadinov et al., 2003). Since 1980, the latitude gradient has been attenuating, apparently owing to increased incidence of MS in regions closer to the equator (Alonso & Hernán, 2008), and an increase in the female-to-male ratio of MS over time (Koch-Henrikssen & Soelberg Sørensen, 201). Figures from 2008 reveal an overall world-wide (38 countries) incidence of 3.6 cases per 100,000 person-years in women, and 2.0 in men (Alonso & Hernán, 2008). Regarding MS prevalence, a systematic review by Hirtz et al. (2007) reported median figures of 90/100,000 in the USA, 60/100,000 in Mediterranean countries and 120/100,000 in other European countries (2007). Finland belongs to a high-risk zone of MS, but the disease is unevenly distributed across the country (Krokki et al., 2011). Epidemiological studies have reported incidence rates of 9.4, 6.3, 6.0 and 5.1 per 100,000 persons in four separate areas (Sumelahti et al., 2000; Krokki et al., 2011). The prevalence of 202/100,000 in the Southern Osthrobothnia region is exceptionally high, while the prevalence is lower in southern (108/100,000) and northern (103/100,000) Finland (Sumelahti et al., 2001; Krökki et al., 2011).

MS is not a lethal disease, yet the disease-related mortality is nearly three times higher, and the average life expectancy about 6 to 10 years shorter than in the general population (Brønnum-Hansen et al., 2004; 2008; Sumelahti et al., 2010; Kingwell et al., 2012). Premature death in MS is most likely to be due to disease complications such as infections and respiratory diseases (Smestad et al., 2009; Sumelahti et al., 2010). It has markedly declined since the 1950s (Brønnum-Hansen et al., 2004), an improvement connected with better treatment of complications, better general health care, and improved rehabilitation and management (Brønnum-Hansen et al., 2006).

There is no cure for MS (Loma & Heyman, 2011), consequently, the aims of drug treatment are to reduce the frequency, and limit the permanent effects of relapses, relieve symptoms, prevent disability arising from disease progression, promote residual tissue repair, ensure independence, and improve quality of life (Compston & Coles, 2002; Thompson et al. 2010). Disease-modifying agents are considered effective in RRMS by delaying disability progression, probably by decreasing immune-mediated inflammation (Brown et al., 2007). However, the efficacy of interferon beta, the most widely prescribed disease-modifying drug to reduce progression of MS disability, has been questionned (Shirani et al., 2012). Notwithstanding, in

combination with pharmaceutical therapy, and also alone, multidisciplinary rehabilitation is an important component of symptomatic and supportive treatment in that it reduces disability and improves overall ability to participate in society (Khan et al., 2011).

Owing to its relatively early onset and progressive nature, the economic consequences of MS are considerable. The costs caused by MS consist, above all, of productivity losses (sick leave and early retirement due to MS), non-medical costs (devices and investments to adapt living conditions), and informal care by family and friends (Kobelt et al., 2006a). The total mean annual costs per patient in nine European countries in 2005 were estimated at 18,000 € for mild disease and 62,000 € for severe disease (Kobelt et al., 2006b). Another prediction covering the whole of Europe revealed that the overall economic burden of MS was 13 billion € per year, corresponding to a cost of 27 € per European inhabitant (Sobocki et al., 2007).

2.2.2 Disability and functioning in MS

MS is associated with a wide range of functional deficits and progressive disability (Compston & Coles, 2002; Holper et al., 2010). It can follow very different patterns of evolution and variable rates of disability accumulation (Confavreux & Vukusic, 2006). Ultimately, disease progression in MS results in impairments and disabilities that affect a variety of outcomes related to maintaining independence (Dunn, 2010). Characteristically, disability and functioning have been claimed to be the "core experiences of persons with MS" (Holper et al., 2010).

Disability milestones are clinically detectable thresholds in the disease process (Wynia et al., 2012) identified by long-term natural history studies of MS (Tremlett et al., 2010). They are usually defined using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983), a 20-grade disability rating scale, in which a score of 0 denotes normal neurological status, a score of 10 death due to MS (Sharrack & Hughes, 1996). Earlier, disability accumulation in MS was considered fairly unfavourable as is well shown by a classic Canadian work by Weinshenker and associates (1989), in which the median time from the onset of MS to reach the EDSS 6.0 milestone (a cane required for walking) was 15 years. The current conception of changes in MS disability profile over time is indisputably more positive. The median time from MS onset to sustained EDSS 6.0 may be as long as 28 years as shown by Tremlett et al. (2006) in another Canadian regional population-based cohort. Moreover, in a 30-year follow-up in Lyon, France, the median time from the onset of MS to EDSS 6.0 was somewhat shorter, i.e., 20 years (Confavreux et al., 2003). In a smaller sample with a 10-year follow-up in the USA, the corresponding figure was 24 years (Pittock et al., 2004). A

Norwegian population-based long-term follow-up estimated that after 15 years the probability of walking without assistance (EDSS <6.0) was 60.3%, and managing without a wheelchair (EDSS < 7.0) 75.8% (Myhr et al., 2001).

The International Classification of Functioning, Disability and Health (ICF) launched by the World Health Organization (WHO) provides a comprehensive framework for the assessment and modelling of the determinants of functioning in MS (Paltamaa et al., 2006). In the ICF, functioning is the umbrella term encompassing body functions and structures, activities and participation, whereas disability is the umbrella term for impairments, activity limitations, and participation restrictions (figure 1). ICF also lists environmental and personal factors that interact with all of these (De Klein-De Vrankrijker, 2003).

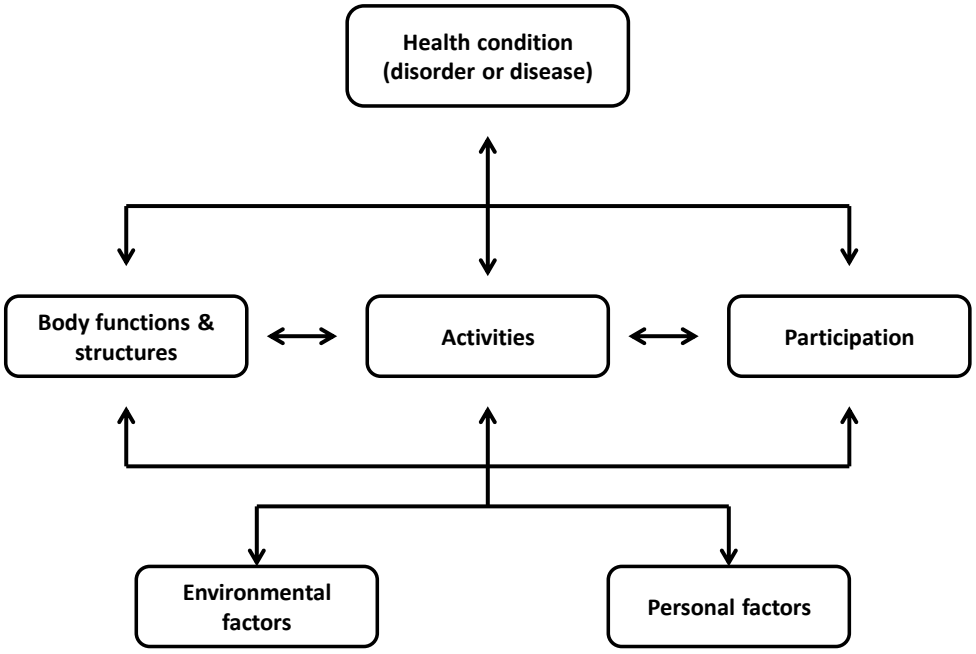

Figure 1. The ICF model (WHO 2001)

In the ICF, body functions are defined as "the physiological functions of body systems", and body structures as "anatomical parts of the body". Alterations in body structures and functions are called impairments (WHO, 2001), which characterize very much MS. Fatigue is one of the most frequent symptoms in MS (Bakshi, 2003) persisting over time (Téllez et al., 2006) and leading to impairments in both physical and psychological functioning (Mills & Young, 2010). Cognitive impairment in MS is often a hidden condition, but may affect 37-78% of the subjects, depending on the definition of cognitive impairment (Haussleiter et al., 2009; Baumstarck-Barrau et al., 2011). Psychological distress is present in MS already in early disease

(Kern et al. 2009), and clinically significant depression can affect up to 50% of subjects, a rate three times higher than that in the general population (Feinstein, 2011). Problems in urinary and sexual functions also affect high number of subjects, an over 50% prevalence of these impairments in MS have been reported (Nordtvedt et al., 2007; Holper et al., 2010).

Deviations in gait pattern functions are typical of MS. These include slower walking speed, decreased step length, decreased cadence, and reduced joint motion in lower limbs during gait (Thoumie et al., 2005; Cameron & Lord, 2010). Altered gait patterns in MS may be observed already in the absence of clinical disability (Martin et al., 2006). Impaired gait is strongly determined by lower limb strength (Thoumie et al., 2005), which has been consistently shown to be reduced across different studies (Dalgas et al., 2008). Compared to lower limb strength, upper limb strength may be relatively well preserved (Schwid et al., 1999). Along with reduced muscle strength, subjects with MS present a number of other deficits in muscle function (Dalgas et al., 2008). It has been proposed that reduced oxygen extraction ability by muscles has an influence on MS subjects' capability to tolerate exercise-induced physical strain (Chetta et al., 2004). This argument is supported by the fact that aerobic capacity, in terms of maximal oxygen consumption (VO_2max), has been shown to be reduced among persons with MS already in the early stages of the disease, suggesting inadequate aerobic training participation (Tantucci et al., 1996).

Activities, outlined in the ICF as "the execution of a task or action by an individual" (WHO, 2001), are frequently affected by MS. Mobility is particularly highly valued by MS subjects (Vazirinejad et al., 2003), obviously arising from the fact that deteriorations in it frequently restrict the person's ability to participate in family, social, vocational, and leisure activities (Freeman, 2001). The specific problems in mobility are also associated with increased odds of becoming unemployed (Julian et al., 2008). The primary factor contributing to loss of mobility in MS is difficulty in walking (Dunn, 2010). In a large (n = 3157) German MS cohort, 48% of the subjects were able to walk 1000 metres without assistance, and 21% at least 100 meters (Twork et al., 2010). Restricted walking distance is associated with limitations in the activities of daily living (ADL) (Savci et al., 2005), which may be present in up to approximately two-thirds of people with MS (McDonnell & Hawkins, 2001; Einarsson et al., 2006). In contrast, ADL independence may be well preserved as shown by a Finnish study, in which 69% of the MS subjects reported no difficulties in self care (Paltamaa et al., 2007).

Other activity limitations, such as balance problems and upper extremity dysfunction, are also common in MS (Goodkin et al., 1988; Frzovic et al., 2000; Paltamaa et al., 2006; Yozbatiran et al., 2006). Worsened balance contributes to increased risk of falls, which are prevalent in roughly about 50% of MS subjects (Finlayson et al., 2006; Sosnoff et al., 2011). Upper extremity function is acknowledged to be of great

importance for the ability to carry out many ADLs (Kierkegaard et al., 2012). Like walking, performances both in balance and upper extremity function tests have been found to significantly predict ADL performance (Paltamaa et al., 2007).

Participation refers to “involvement in a life situation”. This domain covers diverse aspects of interpersonal interactions and relationships, major life areas, and community, social, and civic life (WHO 2001). In a study characterizing functioning in MS from the ICF perspective, items of “recreation and leisure”, “community life”, “renumerative employment”, and “intimate relationships” were frequently reported to be restricted (Holper et al., 2010). Such restrictions may well explain the wide use of health, social, and informal care services among people with MS (Gottberg et al., 2008). As MS occurs during the peak years of employment, the disease significantly affects the ability to remain in the workforce (Patti et al., 2007). Unemployment rates vary considerably from 8% to up to 80% across different studies (Amato et al., 2001; Riazi et al., 2003; Patti et al., 2007; Turpin et al., 2007; Julian et al., 2008; Fernández et al., 2011; Pluta-Fuerst et al., 2011). This, however, depends, at least partly, on the differences in social security between countries (Patti et al., 2007). Early work cessation can cause substantial difficulties for persons with MS across economic, health insurance status, and psychosocial domains (Julian et al., 2008). The overall participation restrictions in MS are well depicted in an Irish study, in which only 6% of subjects with the disease were able to maintain their usual standard of living, despite receiving all the financial support available (McDonnell & Hawkins, 2001).

2.2.3 Health-related quality of life in MS

There is no single agreed definition of HRQoL. According to Testa and Simonson (1996) it refers to “the physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person’s experiences, beliefs, and perceptions”. ”Health status” and HRQoL are distinct entities, while health status influences and predicts HRQoL (Rejeski & Mihalko, 2001). Regardless of the variation in terminology, several features of HRQoL have been identified to further define the construct. HRQoL is subjective, individual, multifactorial, self-administrative, and of a fluctuative nature as a response to alterations in illness (Carr & Higginson, 2001; Miller, 2002).

A plethora of measures have been developed to evaluate overall quality of life, HRQoL, and health status in various populations and disease groups, including MS (Sanders et al., 1998; Fischer et al., 1999b; Nordvedt & Riise, 2003). HRQoL measures may be classified as generic or disease-specific (Meyers at al., 2000). Generic measures can be used across different diseases and enable comparisons to general populations (Garratt et al., 2002; Mitchell et al., 2005). Disease-specific measures address problems particularly related

to a single condition or disease. This is important in order to increase the sensitivity and specificity of measurement (Rejeski & Mihalko, 2001; Nordvedt & Riise, 2003; Mitchell et al., 2005).

MS has a considerable impact on HRQoL (Canadian Burden of Illness Study Group, 1998; Ford et al., 2001; Riazi et al., 2003; Beiske et al., 2007; Kern et al., 2009). Quality of life decreases most prominently in early MS, but may well remain on a remarkably stabile level in later stages of the disease (Wynia et al., 2012). Compared with the general population, persons with MS show lower scores on all, or at least most, HRQoL dimensions (Canadian Burden of Illness Study Group, 1998; Nordvedt et al., 1999; Patti et al., 2003a; Riazi et al., 2003; Allyson Jones et al., 2008). As a consequence of cultural or other country-specific factors, differences in HRQoL across different countries are apparent (Pluta-Fuerst et al., 2011). Comparisons with inflammatory bowel disease, rheumatoid arthritis, spinal cord injury, diabetes, epilepsy, or stroke, indicate that HRQoL is perceived more poorly in subjects with MS than in other long-term medical conditions (Rudick et al., 1992; Nicholl et al., 2001; Benito-León et al., 2003; Allyson Jones et al., 2008). A number of disease-specific features may particularly contribute to poor HRQoL in MS, including: 1) possible deficits in a broad range of neurological, neuropsychiatric and physiological functioning, 2) onset primarily in early adulthood, 3) unpredictable disease course, 4) lack of possibility for cure, 5) imperfect treatments, which carry some risk, and are sometimes inaccessible because of inequities in health care provision (Benito-León et al., 2003; Miller & Allen, 2010).

A substantial body of evidence supports an association between HRQoL and disability (Canadian Burden of Illness Study Group, 1998; Nordvedt et al., 1999; Patti et al., 2003a; Beiske et al., 2007; Montel & Bungener, 2007; Casetta et al., 2009; Kern et al., 2009; Fernández et al., 2011). As shown by a large German cohort study (n = 3157), this relationship seems to be complex and non-linear (Twork et al., 2010). Among other disease-related characteristics, progressive disease course, long disease duration, and shorter time since the last relapse have been found to be significant risk factors for reduced HRQoL (Pfennings et al., 1999; Benito-León et al., 2003; Pluta-Fuerst et al., 2011; Fernández et al., 2011).

Along with disease-related characteristics, several other determinants – with varying strengths of association – of HRQoL in MS have been identified. With regard to demographic variables, there is controversy whether increasing age and/or sex are associated with poorer HRQoL. Several studies indicate older individuals score worse on HRQoL dimensions (Solari et al., 1999b; Pfaffenberger et al., 2006; Turpin et al., 2007; Fernández et al., 2011; Pluta-Fuerst et al., 2011), whereas others have found no such association (Rudick et al., 1992; Beiske et al., 2007). However, a single study showed improved HRQoL along with higher age (Ford et al., 2001). A similar contradiction exists concerning the effect of sex on HRQoL. Research results predominantly support a relationship between female sex and reduced HRQoL (Rudick et

al., 1992; Pfennings et al., 1999; Hopman et al., 2009; Pfaffenberger et al., 2006; Aymerich et al., 2009; Fernández et al., 2011), while the findings of Casetta et al. (2009) showed reduced HRQoL particularly in men. Notwithstanding, negligible associations between sex and HRQoL have also been commonly reported (Solari et al., 1999b; Beiske et al., 2007; Pluta-Fuerst et al., 2011).

Depression has repeatedly been shown to be one of the strongest independent predictors of HRQoL (Solari et al., 1999b; Nicholl et al., 2001; Amato et al., 2001; Patti et al., 2003a; Benedict et al., 2005; Montel and Bungener, 2007). Other emotional state factors such as anxiety and psychological distress have also been linked with worsened HRQoL (Benito-León et al., 2003; Janssens et al., 2003; Montel & Bungener, 2007; Aymerich et al., 2009; Kern et al., 2009). Cognitive deterioration has been frequently reported to have a major impact on HRQoL (Benito-León et al., 2003; Gold et al., 2003; Wynia et al., 2008; Fernández et al., 2011). According to Baumstarck-Barrau et al. (2011), the association may be only weak depending on the neurocognitive assessments used. Fatigue and pain are among the key symptoms contributing independently to reduced HRQoL (Amato et al., 2001; Benedict et al., 2005; Beiske et al., 2007; Miller & Allen, 2010). Finally, as shown by Nordtvedt et al. (2007), bladder, bowel, and sexual problems have an unfavourable effect on HRQoL already in relatively early stages of MS.

Given the disabling nature of MS, it is not surprising that socioeconomic factors may have a considerable influence on HRQoL. Education level, employment status, marital status, and social contacts may all determine HRQoL (Patti et al., 2007; Turpin et al., 2007; Casetta et al., 2009; Fernández et al., 2011; Pluta-Fuerst et al., 2011). Notably, MS affects not only those who suffer from it directly. As shown by Aymerich et al. (2009), patients' caregivers' HRQoL may also be lower than that of the general population, being especially true for mental HRQoL.

HRQoL scales have gradually been incorporated into randomised controlled drug trials in MS (Mitchell et al., 2005). A number of studies suggest that the use of disease-modifying drug therapies including interferons, glatiramer acetate or natalizumab improve HRQoL (Lily et al., 2006; Rudick et al., 2007; Jongen et al., 2010), and the increase can be well sustained for at least one year (Jongen et al., 2010). Along with drug therapies diverse non-pharmacological treatment approaches to improve HRQoL have been tested. There is strong evidence on behalf of positive effects of multidisciplinary rehabilitation on HRQoL (Khan et al., 2007). Further, various behavioural intervention trials, e.g. wellness intervention, mindfulness training, and teleconference-delivered fatigue management programmes have successfully improved HRQoL (Stuifbergen et al., 2003; Grossman et al., 2010; Finlayson et al., 2011). The importance of clinical interventions as a constant viable means to enhance HRQoL in subjects with MS has been affirmed by meta-analytic procedures (Kuspinar et al., 2012).

2.3 Physical activity, exercise and training in MS

2.3.1 Physical activity in MS

Physical inactivity may have a profound effect on health, fitness, and functioning in persons with MS (Slawta et al., 2002; Snook et al., 2009; Stroud et al., 2009; Turner et al., 2009; Prakash et al., 2010a; Ranadive et al., 2012). Therefore, increasing physical activity and decreasing inactivity may serve as a powerful strategy for forestalling the worsening of symptoms, functional limitations, disability, and quality of life (Stuifbergen, 1997; Stuifbergen, 2006; Motl et al., 2007b; Motl et al., 2008b; Motl et al., 2009c). In addition, the observed link between physical activity and neuroprotection serves as an additional promising rationale to back up physical activity recommendations for persons with MS (Heesen et al., 2006; White & Castellano, 2008).

According to an early meta-analysis, physical activity is reduced in persons with MS as compared to the healthy, but not as compared to persons with other chronic diseases (e.g. Parkinson's disease). The analysis consisted of 13 studies between 1997 and 2004 with altogether 2360 MS participants (Motl et al., 2005a). More recent research suggests that the degree of physical activity in MS is higher than previously reported. A large case-control study with 77 MS cases and 77 healthy controls yielded an average effect size of –0.59 indicating that persons with MS were moderately less physically active than the matched controls (Sandroff et al., 2012). The magnitude of this overall difference in physical activity is substantially smaller than the effect size of –0.96 in the earlier meta-analysis (Motl et al., 2005a).

There is great variation in physical activity levels among MS subjects within and between different studies. In a Canadian survey study 94% of respondents engaged in some form of moderate-intensity physical activity at least once per week (Currie et al., 2009), whereas in another, larger survey, fewer than 25% of participants reported moderate or strenuous leisure-time physical activity (Marrie et al., 2009). In a large number of US veterans with MS (n = 2995, mean age 55 years), consisting mainly of men, 29% of the sample endorsed some form of activities ≥ 1 time/week, but only 10% exercised regularly ≥ 3 times a week (Turner et al., 2009).

The use of pedometer steps counts as an activity criterion shows that the average number of daily steps taken (5900, SD 3239) by MS subjects in one study (Motl et al., 2007c) may be twice as high as in another study (2985, SD not reported; range 689 – 5340) (Busse et al., 2004). Within a single study, the mean number of steps taken across seven days in mostly ambulatory subjects without an assistive device (n = 196) can range as much as from 1230 up to 19,473 steps (Motl et al., 2007a). It has been established that

7000-8000 steps/day is a reasonable lower threshold of free-living physical activity associated with current public health guidelines on minimal amounts of time spent in moderate-to-vigorous physical activity (Tudor-Locke et al., 2011). In the light of this, a sample of 30 individuals with MS (median EDSS 2.5) took on average 7097 (SD 3931) steps/day (Motl et al., 2006a), whereas in another US sample (n = 151; all ambulatory without a cane), the mean number of steps/day was 6488 (SD 3315) (Motl et al., 2007a). These figures are clearly higher than reported in a representative sample (n = 1136) of US adults averaging only 5117 steps/day (Bassett Jr. et al., 2010).

The comparison of physical activity levels in MS with existing public health norms also reveals some contradictory results. Slawta and co-workers (2003) found that 68% of women with MS met the Behavioral Risk Factor Surveillance System (BRFSS) recommendations for regular physical activity (at least 30 minutes of moderate-intensity physical activity on most days of the week). In a Dutch study (Beckerman et al., 2010), the amount of participants insufficiently physically active was 64% according to the criterion of the international guidelines for regular physical activity, i.e., they were not engaged in physical activities of moderate intensity for at least 30 minutes on five days per week or in vigorous aerobic activities for a minimum of 20 minutes on three days per week (Haskell et al., 2007).

Different findings in the physical activity levels may be related to measurement methodology (Romberg et al., 2013). One early study showed lower activity in persons with MS compared with healthy control subjects as measured using an objective method (accelerometer), but not when applying a questionnaire (Ng & Kent-Braun, 1997). More recently, in 21 subjects with MS (mean EDSS 3.3) and 20 mostlyinactive sex- and age-matched healthy controls, physical activity was reduced in the former group as compared to the latter only as assessed by a pedometer, but not by an accelerometer or a questionnaire (Romberg et al., 2013).

Typically, self-report questionnaires offer a subjective indication of activity level, are prone to recall bias, and correlate only moderately with objective methods (Gosney et al., 2007). In the physical activity studies between 1997 and 2004, a questionnaire was the most often used assessment method (Motl et al., 2005a). Ever since, objective methods including pedometers (Motl et al., 2006a; Gosney et al., 2007; Motl et al., 2007a; Motl et al., 2007c; Romberg et al. 2013) and/or accelerometers (Motl et al., 2006a; Kos et al., 2007; Motl et al., 2007c; Klassen et al., 2008; Motl et al., 2008c; Morris et al., 2008; Elsworth et al., 2009; Motl et al., 2009b; Prakash et al., 2010a; Merkelbach et al., 2011; Motl & McAuley, 2011b; Sandroff et al., 2012; Weikert et al., 2012; Romberg et al. 2013) have been increasingly used to measure free-living physical activity in MS.

In spite of their feasibility and wide-spread use, accelerometers and pedometers are, however, prone to certain limitations. Pedometers may underestimate when used for people with neurological diseases including MS (Elsworth et al., 2009). This may be evident particularly in subjects using a walking aid with deviations from normal gait patterns (Motl et al., 2005b). In the case of accelerometers, the optimal placement has been a matter of debate (Kayes et al., 2009). Ankle placement yields significant differences in activity counts between MS subjects and healthy controls, which is not the case when the accelerometer is placed on the wrist (Kos et al., 2007). Recent findings support the possibility that accelerometers primarily and specifically measure walking mobility, not physical activity, in persons with MS, and that the pattern of these findings is different from that in healthy controls (Weikert et al., 2011). This observation is supported by the fact that the energy cost of walking is increased in MS already in early stages of the disease (Franceschini et al., 2010). Hence, MS subjects are likely to expend more energy when carrying out their ADL, and this increase in energy expenditure may reduce the level of daily activity (Motl et al., 2012c). Such a rationale provides support for the argument that the degree of inactivity in MS is not so alarming as previously thought (Sandroff et al., 2012).

Consistent with its multifaceted behavioural nature, a wide spectrum of disease-related, psychosocial, and environmental factors have been found to determine physical activity in MS. The wide variations in physical activity patterns in MS are, apparently, attributable to the level of disability, i.e. physical activity decreases with increasing disability (Currie et al., 2009; Marrie et al., 2009; Beckerman et al., 2010; Merkelbach et al., 2011; Motl & Goldman, 2011a). In line with this, persons with RRMS are more physically active than those with PPMS or SPMS (Motl et al., 2005a; Motl et al., 2007a; Motl et al., 2007b), probably owing to the more pronounced accumulation of disability in the two latter forms (Confavreaux & Vukusic, 2006).

Symptoms overall as well as specifically (e.g., pain or cognitive deficits) have been found to be independently associated with reduced physical activity (Motl et al., 2006b; Motl et al., 2008d; Motl et al., 2009c; Plow et al., 2009; Turner et al., 2009; Kayes et al., 2010; Prakash et al., 2010a). This is not the case with perceived fatigue, which, at best, has only a weak adverse association with physical activity, much depending on the fatigue questionnaire used (Rietberg et al., 2011). Such a scale-dependent relation cannot be found between HRQoL and physical activity; both generic and disease-specific HRQoL measures show similar patterns of relationships with objectively and subjectively measured physical activity (Motl et al., 2008c).

Self-efficacy, reflecting the individual's beliefs in his/her personal capabilities, has been consistently found to be a correlate and/or an independent predictor of physical activity in MS (Motl et al., 2006b; Morris et al., 2007; Motl et al., 2007b; Kayes et al., 2010; McAuley et al., 2010). It may also play an important role in

the initiation, maintenance, and change of physical activity (Motl & McAuley, 2009a). Such an argument was, however, partly questioned by Kosma et al. (2012) who found that self-efficacy only at baseline predicted physical activity, while changes in it had no effect on changes in physical activity levels over a one-year period in persons with MS and other physical disabilities (spinal cord injury and cerebral palsy).

Restrictions in the social environment have been cited as common barriers to physical activity participation. These include caring for family members, fulfilling social role obligations, and persuasive arguments by family members and friends to convince participants not to exercise (Plow et al., 2009). In addition, social support, receiving a disability pension, and having children to care for all independently predict physical activity in MS (Plow et al., 2008; Beckerman et al., 2010). Moreover, regular exercise participation, compared to a non-exercising lifestyle, is associated with better social functioning and more active participation in life despite physical and emotional difficulties (Turner et al., 2009). So far, evidence regarding the influence of physical environment on activity levels is scarce. Difficulties in the accessibility of recreational facilities may be an important activity barrier for persons with MS (Plow et al., 2009). Accessibility of public transportation within a 10–15-min walk from one's home is another environmental issue shown to have some effect on physical activity in MS as measured by a pedometer (Doerksen et al., 2007).

Most of the studies examining physical activity patterns and behaviour in MS are based on cross-sectional designs. In the light of the progressive nature of MS, longitudinal studies are needed to allow exploration of the changing relationship between physical activity and symptoms/disability as the disease progresses (Klassen et al., 2008; Motl et al., 2008e). Such studies are few in number. Levy et al. reported that stable physical activity participation over one year had positive effects on fatigue and pain perception in 82 MS subjects with varying levels of disability (Levy et al., 2009). In a follow-up ranging from three to five years, deterioration of symptoms was related to lower physical activity in 51 moderately disabled (mean EDSS 4.1) subjects (Motl et al., 2008a). In another five-year follow-up study (n = 611 at entry, n = 560 at study termination) higher reported exercise levels at baseline were related to slower accumulation of functional limitations over time (Stuifbergen et al., 2006).

A series of studies from Motl and colleagues addressed the relationship of physical activity to symptoms, walking impairment, functional limitations and disability in nearly 300 MS subjects. Disability was evaluated using the Patient Determined Disease Steps, a surrogate measure strongly associated with the EDSS (Motl & McAuley, 2009a; Motl & McAuley, 2011b; Motl et al., 2011c). The Motl group concluded that a) a change in physical activity is associated with a change in disability occurring through an association with function (Motl & McAuley, 2009a), b) a reduction in physical activity is a behavioural correlate (but not necessarily a

cause) of short-term disability progression in MS (Motl & McAuley, 2011b), and c) physical activity is possibly important for preventing walking impairments (Motl et al., 2011c). In these studies, with regard to accumulation of impairments and disability, the follow-up of six months was relatively short.

2.3.2 Exercise training in MS

There is considerable heterogeneity in exercise intervention studies in MS in terms of study design, length of the intervention, sample size, training modality, and outcome measures. Nonetheless, exercise training seems to produce numerous benefits regarding physical fitness, functioning, and quality of life in persons with the disease (Rietberg et al., 2005; Dalgas et al., 2008; Motl & Gosney, 2008b; Motl & Pilutti, 2012b). The results can, however, be generalized only to ambulatory MS subjects (EDSS score 0 to 6.5); only one study also included non-ambulatory participants (Filipi et al., 2011).

In the following review, the effects of exercise training interventions in MS were determined on the basis of the following eligibility criteria: (1) the intervention applied repetitive bouts of exercise training over at least a three-week period, (2) the intervention clearly consisted of either endurance, resistance, or combined training, (3) the training programme could be implemented in a community-based exercise setting (e.g., public swimming pool or fitness centre). Studies evaluating the effects of neuromotor exercise training (tai chi, yoga), respiratory training, and specific clinical rehabilitation interventions (e.g., physiotherapy, vibration therapy, body-weight-supported treadmill training) were excluded. Case studies and studies published only in abstract form were not included because of the limited amount of information included. These criteria are in line with those in systematic reviews analysing exercise responses in people with MS, as well as with other disabilities (Dalgas et al., 2008; Snook & Motl, 2009; Rimmer et al., 2010). The review was based on a series of regularly updated literature searches between the years 2000 and 2013 (March) using PubMed and CINAHL databases. Searches were conducted using the terms “exercise”, “training”, “exercise therapy”, and “physical activity” in combination with “multiple sclerosis”.

The first exercise intervention trial in MS dates back to 1984. The study advocated a single-group design, and evaluated the effects of a 10-week aquatic exercise programme in 10 MS subjects (Gehlsen et al., 1984). The first RCT of exercise responses in MS was published in 1988, when Schapiro and co-workers reported on the effects of a 16-week aerobic training programme. The publication of the first major review in this field in 1993 can be also regarded as an important milestone (Ponichtera-Mulcare, 1993).

Within the past decade, the number of exercise intervention studies in MS has steadily increased. Former beliefs in the adverse effects of exercise on the disease progression and symptomology (Heesen et al., 2006) have been dissipated, and a substantial body of knowledge supports the use of exercise training as a therapeutic option in MS (Rietberg et al., 2009; Heesen et al., 2006; Dalgas et al., 2008; Motl & Gosney, 2008b). Nonetheless, a rigorous systematic analysis of the effectiveness of exercise interventions in MS concluded in 2009 that there is insufficient evidence to guide regular exercise prescription in persons with MS, particularly to guide implementation of a comprehensive exercise intervention (Asano et al. 2009). On the other hand, the findings of Asano et al. (2009) of the modest short-term effects of exercise training on activities and participation are very much in line with those produced by multidisciplinary rehabilitation for people with MS as evidenced by a Cochrane review (Khan et al., 2011).

The Cochrane review on exercise therapy for MS included nine RCTs (altogether 260 participants) examining the effects of exercise therapy interventions in MS (Rietberg et al., 2009). The best evidence synthesis in this review showed strong evidence in favour of exercise therapy compared to no exercise therapy in outcomes related to muscle power function, exercise tolerance functions, and mobility-related activities. The criteria for the studies included in the Cochrane review, however, differ markedly from those in the current overview. For example, two studies published only in abstract form were accepted in the analysis, and, at least two of the included studies more closely fullfil the criteria for “neurotherapeutic approaches” (Paltamaa et al., 2012) rather than exercise training. Hence, only four of the RCTs evaluated in the Cochrane review were considered in this overview. In another systematic review assessing the effects of physiotherapy interventions on balance in MS (Paltamaa et al., 2012), four studies (of which three are included in the present review) dealing with resistance and aerobic training were included. The results showed a low level of evidence for the efficacy of resistance and aerobic exercises on improving balance among ambulatory persons with MS.

2.3.2.1 Endurance training

The effects of endurance training have been extensively studied in MS as compared to resistance or combined training. Currently, at least 15 RCTs (Table 1) on the issue have been published. These data are complemented by several controlled trials and studies applying a single-group design. Overall, it is evident that endurance training in persons with MS induces multiple benefits concerning body functions and structures, activities, and participation (Dalgas et al., 2008; Asano et al., 2009; Motl & Pilutti, 2012b). However, in a number of studied outcomes, such as those related to mental functions (fatigue, depresssion, cognition) the findings are as yet inconclusive (Andreasen et al., 2011; Motl & Pilutti, 2012b).

The duration of the endurance training interventions has ranged from three weeks (two studies: Dettmers et al., 2009; Bansi et al., 2013) up to 26 weeks (one study: Oken et al., 2004). Training frequency has most commonly been either two or three times /week. One study applied a protocol of once weekly training session accompanied by encouragement to exercise at home (Oken et al., 2004). At the other end of the scale, two studies with short interventions (4 and 3 weeks), applied a programme including five weekly training sessions (Mostert & Kesselring, 2002; Bansi et al., 2013).

Training intensity, with few exceptions, has been defined as either "low" or "moderate" in all of the studies. "Moderate" corresponds to 60% of VO_2peak (or VO_2max), a common target intensity in endurance training studies in MS (Petajan et al., 1996; Ponichtera-Mulcare et al., 1997; Heesen et al., 2003; Schulz et al., 2004; Davis et al., 2005; Castellano et al., 2008a; Castellano & White, 2008b; Bansi et al., 2013). In one study (van den Berg et al., 2006), the upper limit of prescribed training intensity was set as high as at 85% of age-predicted maximum heart rate (lower limit 55%). However, the training groups (using portable heart rate monitors) spent on average 55% of the treadmill training time on intensities of 60% or less of age-predicted maximum heart rate. The effects of high-intensity vigorous training remain practically unexplored. Nonetheless, the question was addressed in a randomized comparator study of three cycling exercise protocols (Collett et al., 2011). In two (combined or intermittent leg cycling) of the three study groups, training intensity was set as high as at 90% of peak workload, whereas in the third (continuous) group it was set at 45% of peak workload. As a result, all three groups showed statistically significant effects on mobility and leg power after a six-week training period. The effects were maintained at least during a further six weeks of training for all programmes with no differences between groups. The authors concluded that greater benefit may be associated with higher intensity exercise, but this may be less well tolerated (Collett et al., 2011).

Most of the endurance training interventions have been carried out applying supervised cycle ergometry. At least 11 publications have reported the use of such a protocol in persons with MS (Table 1). Cycle ergometry training has repeatedly been shown to improve cardiorespiratory fitness (Schapiro et al., 1988; Petajan et al., 1996; Ponichtera-Mulcare et al., 1997; Mostert & Kesselring, 2002; Schulz et al., 2004; Rasova et al., 2006; Rampello et al., 2007; Bansi et al., 2013), walking capacity (Rampello et al., 2004; Kileff & Ashburn, 2005; Collett et al., 2011), and quality of life (Petajan et al., 1996; Mostert & Kesselring, 2002; Schulz et al., 2004; Rasova et al., 2006; Rampello et al., 2007).

To reduce localized fatigue, combined arm-leg ergometry has been recommended as a training tool for persons with MS (Ponichtera-Mulcare, 1995). Hence, three studies conducted endurance training using this training modality (Petajan et al., 1996; Oken et al., 2004; Davis et al., 2005). The RCT by Petajan et al. (1996)

led to results very similar to those of the studies applying conventional leg ergometry, i.e. improved cardiorespiratory fitness and positive effects on quality of life. Oken et al. (2004) found some improvements, similar to those after yoga classes, in fatigue and vitality after 26 weeks of endurance training. Davis et al. (2005) examined the effects of a 15-week arm-leg ergometry on cholinergic sweat function in individuals with MS (n = 7), but observed no changes in these variables, while peak aerobic capacity significantly increased.

Conventional cycle ergometry has also been used as a method to potentially promote neuro- and immunoprotective effects of repeated exercise in MS (Heesen et al., 2003; Schulz et al., 2004; Castellano et al., 2008a; Castellano & White, 2008b). Of these controlled trials, the German group failed to show any significant effects on immune-endocrine parameters or on neurotrophic factors (Heesen et al., 2003; Schulz et al., 2004). An American group found that brain-derived neurotrophic factor concentrations increased at week four but returned to baseline at week eight (Castellano & White, 2008b), and that MS and healthy control subjects showed similar cytokine responses to both acute and chronic exercise (Castellano et al., 2008a). More recently, a RCT (n = 60) comparing three-week endurance training conducted on a cycle ergometer or an aquatic bike indicated that exercise when immersed can activate the brain-derived neurotrophic factor regulation of persons with MS compared to overland training (Bansi et al., 2013).

Surprisingly few, i.e. two, studies have assessed the effects of systematically designed walking programmes in MS. In the pilot study by Geddes et al. (2009) walking distance and Physiologic Cost Index improved after a 12-week home walking program, but the improvements in the exercise group were not statistically significant, probably due to the small sample size (exercise group, n = 8; control group, n = 4). The pilot randomized trial by van den Berg et al. (2006) showed that treadmill training in persons with MS (16 completed the training programme) was feasible, well tolerated, increased gait speed and endurance, and did not worsen fatigue. In another report of the same study, Newman et al. (2007) relied on a single group design and concluded that treadmill training addressed cardiovascular de-conditioning and, thereby, reduced the effort of walking and fatigue.

Three studies, of which two are RCTs, have consistently found that aquatic exercise improves particularly HRQoL and fatigue (Sutherland et al., 2001; Roehrs & Karst, 2004; Kargarfard et al., 2012). Other benefits of aquatic exercise include improved muscle strength, mobility, and balance (Gehlsen et al., 1984; Salem et al., 2011). In addition, increased walking speed on the 10-meter timed walk has been reported (Salem et al., 2011). However, in another study, ten weeks of aquatic exercise had no effect on gait parameters including stride length, speed, or cadence (Gehlsen et al., 1986). The observations in the three last-mentioned studies should be interpreted with caution owing to the limited sample sizes (n = 10 or n = 11).

Contrary to aquatic exercise, regular elliptical training (providing “walking-like” movement patterns) alters joint kinetics in the hip and the ankle during walking, indicating that after training, persons with MS employ a walking strategy that is more similar to that of healthy young adults (Huisinga et al., 2012a). Moreover, elliptical training may also be beneficial to reduce fatigue and improve quality of life (Huisinga et al., 2011).

Only two RCTs examining endurance training responses have been based on group interventions (McCullagh et al., 2008; Dettmers et al., 2009). McCullagh et al. (2008) conducted a three-month trial with two weekly exercise classes supported by independent once-weekly training. The results showed improved exercise capacity, quality of life, and fatigue, with the improvements in the latter two lasting for three months beyond the intervention termination. Dettmers et al. (2009) investigated the effects of a three-week group training in 30 MS subjects with motor fatigue during inpatient rehabilitation, and found improved walking distance (on a treadmill) of 66% in the exercise group vs. 12% in the control group. No improvements in perceived fatigue, depression, or HRQoL were observed. Group exercise was also utilized in a cross-over trial comparing eight-week endurance and resistance training programmes (Sabapathy et al., 2011). A reasonably small proportion (76%) of the original 21 participants completed the study, which found no significant differences in any of the outcomes (including physical functioning, disease impact, depression, fatigue, and quality of life) at any of the study time points between the two training modalities.

Based on models from the field of gerontology (Kramer et al., 2006), it has been hypothesized that physical activity, endurance training in particular, could activate brain repair mechanisms and ameliorate cognitive dysfunction, as well as reduce long-term disability (White & Castellano, 2008; Motl et al., 2011d). For the present, only preliminary experimental data to support such associations exist. Two cross-sectional studies have suggested a positive relationship between cardiorespiratory fitness, cerebrovascular functioning, and cognition in subjects with RRMS (Prakash et al., 2007; Prakash et al., 2010b). More recently, Waschbisch et al. (2012), also in a cross-sectional design, found no relationship between cardiorespiratory fitness and brain-derived neurotrophic factors or cognitive function either in physically active (n = 21) or inactive (n = 21) MS subjects. The inconsistency in the findings may well be related to differences in the study samples; in the latter study the disability level of the participants was exceptionally mild with a mean EDSS of 1.4 (Waschbisch et al., 2012). To date, the study by Oken et al. (2004) is the only longitudinal endurance training study to include cognitive function as an outcome. In it, the low-dose endurance training group, similarly as in the yoga intervention and the wait-list control conditions, showed no changes in any of the several cognitive measures. To overcome the limitations in earlier studies, a model RCT in MS consisting of six-month endurance training has been proposed, based on exercise training parameters shown to maximize cognitive benefits in older adults (Motl et al., 2011d).

Table 1. RCTs evaluating the effects of endurance training in persons with MS

Study	Sample size	EDSS	Duration Frequency	Training regime Duration/session *	Main findings
Schapiro et al. (1988)	n = 50	1.0 – 6.0	16 weeks 4-5x/week	Cycle ergometry 15 – 30 min	Work load ↑; Graded exercise test time↑
Petajan et al. (1996)	n = 46	< 6.0	15 weeks 3x/week	Arm & leg ergometry 30 min	VO_2max ↑; Upper and lower limb strength ↑; QoL ↑
Sutherland et al. (2001)	n = 22	NR	10 weeks 3x/week	Water aerobics Duration: NR	HRQoL: energy, vigour, fatigue, pain ↑
Mostert & Kesselring (2002)	n = 26	1.0 – 6.5	3 weeks 4-5x/week	Cycle ergometry 30 min	VO_2max →; Aerobic threshold ↑; QoL: vitality and social functioning ↑; Sport-related physical activity ↑
"Hamburg group" Heesen et al. (2003) Schulz et al. (2004)	n = 28 n = 39 healthy controls: n = 20	< 5.0	8 weeks 2x/week	Interval training on a cycle ergometer 30 min	VO_2max →; Lactate response ↑; epinephrine, norepinephrine, ACTH, β-endorphin ↑; Coordination ↑; HRQoL ↑; Cytokine sIL-6R, a trend ↑; Cytokine IL-6 →; BDNF →; Nerve growth factor, a trend ↑
Oken et al. (2004)	n = 69	< 6.0	26 weeks 1x/week, + encouraged to training at home	Cycle ergometry + periodical Swiss ball training. Duration: until fatigue or personal goal reached	Fatigue ↑; QoL: vitality and mental health ↑; Mood →; Depression →; Cognitive functioning →
Van den Berg (2006)	n = 19	NR	4 weeks 3x/week	Treadmill walking Duration: max 30 min with max 3 rest periods	10-m walk time ↑; 2-min walk distance →; Fatigue →; **Follow-up week 12:** 10-m walk time →; 2-min walk distance →
Rampello et al. (2007)	n = 19	≤ 6.0	8 weeks 3x/week	Cycle ergometry 30 min	6-min walk distance ↑; VO_2peak ↑; Maximum work rate↑; VO_2peak / heart rate↑; HRQoL: emotional well-being, energy, health distress ↑; Fatigue →

Table 1. (Continued)

Study	Sample size	EDSS	Duration Frequency	Training regime Duration/session *	Main findings
McCullagh et al. (2008)	n = 30	NR	12 weeks 3x/week	Exercise classes, 40 min & home-training 40 – 60 min	Perceived exertion ↑; Heart rate ↑; QoL ↑; Fatigue ↑ **Follow-up week 26:** QoL ↑; Fatigue ↑
Dettmers et al. (2009)	n = 30	< 4.5	3 weeks 3x/week	Endurance exercises in groups 45 min	Walking distance & Walking time on a treadmill ↑; HRQoL →; Fatigue →; Depression →
Geddes et al. (2009)	n = 12	≤ 6.0	12 weeks 3x/week	Home walking program 15 – 30 min	6-min walk distance, Physiologic Cost Index ↑(NS); Fatigue→
Collett et al. (2011)	n = 61	NR	12 weeks 2x/week	Continuous, intermittent or combined cycle ergometry 20 min (each)	In all 3 groups: 2-min walk distance↑; Timed Up and Go ↑; Leg power ↑; Fatigue →; QoL ↓; **Follow-up week 24:** All outcomes →
Sabapathy et al. (2011)	n = 16	NR	8 weeks 2x/week	Circuit training with 8 exercise stations 40 min (2 min rest every 10 minutes)	Measures of physical functioning ↑; Fatigue ↑; MSIS-29 physical component ↑; MSIS-29 psychological component →; Depression →; QoL →
Kargarfard et al. (2012)	n = 32	≤ 3.5	8 weeks 3x/week	Aquatic exercise 40 min	Fatigue ↑; HRQoL ↑ (physical and mental composites + several subscales)
Bansi et al. (2013)	n = 60	1.0 – 6.5	3 weeks 5x/week	Cycle ergometry or cycling immersed in water 30 min	BDNF at rest and during exercise test ↑in the water training group.; Cytokines IL-6, sIL-6R, TNF-α →; VO_2peak in both groups ↑; Fatigue →

* Only actual training time expressed, warm-up or cooling periods not considered.
↑ indicates improvement, → indicates no change, ↓ indicates worsening.
BDNF = brain-derived neurotrophic factor, EDSS = Expanded Disability Status Scale, HRQoL = health-related quality of life, MSIS-29 = Multiple Sclerosis Impact Scale, NR = not reported, NS = changes not statistically significant, QoL = quality of life, VO_2max = maximal oxygen uptake, VO_2peak = peak oxygen uptake.

2.3.2.2 Resistance training

The effects of resistance training in MS have been examined in eight RCTs (Table 2) and four non-controlled trials. Parallel reports from the same study have been published from one RCT and all but two of the other trials. The quality of evidence regarding progressive resistance training in MS has been quantified in a systematic review using the Physiotherapy Evidence Database (PEDro) Scale (Kjølhede et al., 2012). Regarding the RCTs, the PEDro scores ranged from 4 to 8 out of a total 10 points, while the non-randomized studies were all rated with a score of either 3 or 4. A study with a PEDro score above 5 is considered level-1 evidence with scores of 6 to 8 indicating good, and scores of 9 or 10 excellent methodological quality. A score of 5 or less is considered level-2 evidence (4 or 5 fair, 1 to 3 poor methodological quality) (Asano et al., 2009).

The duration of resistance training interventions has ranged from three weeks (Fimland et al., 2010) up to 26 weeks (Filipi et al., 2010; Filipi et al., 2011), and the training frequency from 2 to 5 times /week, with 2 times /week being the most common frequency rate. With respect to training protocol, there is considerable variation between the studies in the number of exercises (range 1 to 10), number of repetitions carried out (range 4 to 15), and number of sets (range 1 to 5). The differences in the training protocols are, at least partly, dependent on the progression and intensity of training. The latter has been expressed either as a percentage of 1 RM, as the resistance for a given number of repetitions, i.e. 10 RM (Kjølhede et al., 2012), or using the Borg rating of the perceived exertion (Hayes et al., 2011). Respectively, the training intensity has been set at between 40 to 90% of 1RM (White et al., 2004; Gutierrez et al., 2005; Taylor et al., 2006; White et al., 2006a; White et al., 2006b; de Souza-Teixeira et al., 2009; Fimland et al., 2010), at 8 to 15RM (DeBolt & McCubbin, 2004; Dalgas et al., 2009; Dalgas et al., 2010a; Dalgas et al., 2010b; Broekmans et al., 2011; Filipi et al., 2010; Filipi et al., 2011), or at 11 (“fairly light”) to 13 (“somewhat hard”) in the Borg 6–20 scale (Hayes et al., 2011).

Except for two studies conducted in a home setting (Harvey et al., 1999; DeBolt & McCubbin, 2004), all other studies have applied supervised resistance training. Most of the studies have utilized a programme solely for the lower extremities (Harvey et al., 1999; DeBolt & McCubbin, 2004; Dalgas et al., 2009; Broekmans et al., 2010; Fimland et al., 2010; Dodd et al., 2011; Hayes et al., 2011; Huisinga et al. 2012a), whilst a clear minority have also included upper-body exercises (White et al., 2004; Ayán Pérez et al., 2007; Taylor et al., 2006; Filipi et al., 2011; Sabapathy et al., 2011).

There is incontrovertible evidence that muscle strength of the trained skeletal muscle groups increases following resistance training in MS. Typically, studies have focused on the strength of the lower limbs and

report relative increases in maximal voluntary contractions between ~ 7% and 47% for knee extensor, knee flexor, and wrist plantar flexor muscles (Harvey et al., 1999; White et al., 2004; Gutierrez et al., 2005; Dalgas et al., 2009; de Souza-Teixeira et al., 2009; Fimland et al., 2010; Broekmans et al., 2011). Dynamic strength, measured as the maximum amount of weight moved during one complete contraction (1 RM), has shown improvements in different leg exercises ranging from 17% to 51% (Taylor et al., 2006; Dalgas et al., 2009; Broekmans et al., 2011; Dodd et al., 2011), while one study reported a 14% increase in the arm press (Taylor et al., 2006). DeBolt and McCubbin (2004) detected a 37% increase in leg extensor power during a single-leg extension. Moreover, some improvements (10 - 22%) in the lower limb dynamic strength, as measured by isokinetic testing procedures, have been observed (Dalgas et al., 2010b), but statistically insignificant findings, depending on the movement velocity and measured joint angle, have also been found (Dalgas et al., 2010a; Broekmans et al., 2011). The positive effects of resistance training on muscle strength are accompanied by improved lower limb and trunk muscular endurance (Taylor et al., 2006; Ayán Pérez et al., 2007; de Souza-Teixeira et al., 2009; Dodd et al., 2011), as well as preliminary findings on the benefits for muscle hypertrophy (de Souza-Teixeira et al., 2009; Dalgas et al., 2010b) and neural adaptations (Harvey et al., 1999; Fimland et al., 2010).

Results of resistance training effects on balance and mobility are somewhat conflicting. Balance, as measured using the Berg Balance scale, remained stable when applying a high-intensity training protocol focusing on eccentric lower limb training for 12 weeks (Hayes et al., 2011), but improved, and included decreased fear of falling, in a study with longer (6 months) duration (Filipi et al., 2010). Employing another common measure of balance, the Functional Reach test, both Broekmans et al. (2010) and Sabapathy et al. (2011) showed significant increases in the outcome following lower limb or whole body resistance training, respectively. DeBolt and McCubbin (2004) reported no changes in postural sway measures after an 8-week home-based training; instead, Huisinga et al. (2012b) found some improvements in corresponding measures after a three-month supervised intervention.

Studies evaluating the effects of resistance training have commonly used short and long tests of walking capacity and/or the Timed Up and Go test to provide measures of functional mobility. In the RCT with the highest quality of evidence (PEDro score 8/11), participants in the resistance training group did not significantly increase the distance they walked over 2 min (Dodd et al., 2011). This was the case also in another RCT (Broekmans et al., 2010) and a non-controlled trial (Taylor et al., 2006). On the contrary, two RCTs found significantly longer walking distances measured by the 6-Minute Walk Test (Dalgas et al., 2009; Sabapathy et al., 2011), a finding which could not be replicated in the, probably underpowered (n = 19), RCT by Hayes et al. (2011). In the short walking tests (timed 10-m walk and 25-ft walk test) mostly no changes seemed to occur (White et al., 2004; Broekmans et al., 2010; Filipi et al., 2010; Hayes et al., 2011),

but there were exceptions to this tendency with some studies reporting significant improvements in walking speed (Taylor et al., 2006; Dalgas et al., 2009). Results on the Timed Up and Go test were evenly distributed between positive findings as implicated by faster performance (de Souza-Teixeira et al., 2009; Filipi et al., 2010; Sabapathy et al., 2011) and no intervention effects (DeBolt & McCubbin, 2004; Broekmans et al., 2010; Hayes et al., 2011).

A number of mobility-related measures have been sporadically used to evaluate resistance training effects. Dalgas et al. (2009) reported improvements both in a chair stand and a stair-climbing test. Harvey et al. (1999) found a positive training effect on chair transfer time by means of weighted leg raising exercises at home, while White et al. (2004) showed a significant increase in the number of steps taken during a 3-min test following twice-weekly (for 8 weeks) supervised resistance training. No effects in a timed stairs test were observed by Taylor et al. (2006) as a result of twice-weekly (for 10 weeks) supervised progressive training for the upper and lower body major muscle groups. Hayes et al. (2011) found in their RCT that the ability to ascend and descend stairs improved more when using standard exercise alone (consisting of aerobic training, lower extremity stretching, upper extremity strength training, and balance exercises) in comparison to the same programme with the addition of a high-intensity lower extremity eccentric resistance exercise. Conversely, two non-controlled studies suggest that parameters related to gait kinematics may be improved by means of resistance training (Gutierrez et al., 2005; Filipi et al., 2010). Finally, Broekmans et al. (2010) found no effects in the self-report Rivermead Mobility Index either after long-term (20 weeks) leg resistance training or after the same training with the addition of simultaneous electro-stimulation, whereas using another self-report measure, the Multiple Sclerosis Impact Scale (MSIS-29), improvement has been seen in the pre-post single group study by Taylor et al. (2006), and in the RCT by Sabapathy et al. (2011).

There is good evidence to support the use of resistance training as a means to alleviate fatigue in persons with MS. Four RCTs, two single-group trials, and one qualitative study have all consistently found reductions in the symptom as measured by self-report questionnaires (White et al., 2004; Dodd et al., 2006; Dalgas et al., 2010a; Filipi et al., 2010; Dodd et al., 2011; Hayes et al., 2011; Sabapathy et al., 2011). Results on mood and quality of life are not similarly uniform. Data based merely on RCTs indicate a positive training effect particularly on the physical component of quality of life (Dalgas et al., 2010a; Dodd et al., 2011), as well as on mood scores (Dalgas et al., 2010b). Such findings were not replicated in an Australian RCT, in which no post-training changes in either of the two outcomes were noted (Sabapathy et al., 2011). Nonetheless, the most consistent benefits gained from resistance training may be the changes in psychological well-being as suggested by a qualitative analysis of a progressive resistance training programme for people with MS (Dodd et al., 2006).

A small (n = 12) non-controlled study suggests that MS subjects can derive some coronary artery disease risk reduction benefits, i.e., decreases in blood triglyceride and glucose levels, from short-term (8 weeks) resistance training (White et al., 2006b). Another small single-group study (n = 10), also undertaking training protocol of 2 times/week for 8 weeks, reported statistically significantly reduced serum concentrations of cytokines IL-4, IL-10, CRP and IFN-gamma, suggesting that resistance training could have an impact on overall immune function and disease course in MS (White et al., 2006a). However, when evaluating disease progression using the EDSS, resistance training shows no effects (DeBolt & McCubbin, 2004; White et al., 2004; Dalgas et al., 2009). Finally, one non-controlled study (n = 33) found significant benefits in cognitive skills as measured by the Paced Auditory Serial Addition Test (PASAT) and in fine manual dexterity as measured by the Nine-Hole Peg Test (9HPT) (Filipi et al., 2010).

The adherence to resistance training interventions has been mostly high, with adherence percentages ranging between 69 and 100%, and drop-out rates between 0 and 13% (Harvey et al., 1999; Hayes et al., 2011; Kjølhede et al., 2012). Resistance training is well tolerated among MS subjects, and there are only few, rather anecdotal, notes about training-related adverse effects such as transiently increased dizziness (Filipi et al., 2010) or short-term muscle soreness (Dodd et al., 2011).

Table 2. RCTs evaluating the effects of resistance training in persons with MS

Study	Sample size	EDSS	Duration Frequency	Training regime	Main findings
Harvey et al. (1999)	n = 20	NR	8 weeks Daily	1 lower limb exercise 10 reps x 5 sets 2x/day	Lower limb strength →; Lower limb EMG →; Walking speed →; Chair transfer ↑
DeBolt and McCubbin (2004)	n = 37	1.0 – 6.5	8 weeks 3x/week	5 lower limb exercises 2-3 sets x 8-12 reps	Leg extensor power ↑; Balance →; Timed Up and Go →
Dalgas et al. (2009) Dalgas et al. (2010a) Dalgas et al. (2010b)	n = 38	3.0 – 5.5	12 weeks 2x/week	5 lower limb exercises 3-4 sets x 8-12 reps	Lower limb strength ↑; Several functional mobility measures ↑; Muscle fiber size ↑; Fatigue ↑; Mood ↑; QoL: mental health ↑
Broekmans et al. (2010)	n = 36	2.0 – 6.5	20 weeks 5x/2 weeks	3 lower limb exercises 1-2 sets x 10-15 reps	Lower limb strength ↑; Several functional mobility measures → Functional reach ↑;
Fimland et al. (2010)	n = 14	2.0 – 6.5	3 weeks 5x/week	2 lower limb exercises 4 sets x 4 reps	Lower limb strength ↑; Lower limb EMG-activity ↑; Voluntary motor output↑
Dodd et al. (2011)	n = 76	NR	10 weeks 2x/week	5 lower limb exercises 2 sets x 10-12 reps	6-min walk distance →; Lower limb strength and endurance ↑; Fatigue ↑; QoL: physical health ↑
Hayes et al. (2011)	n = 20	3.5 – 6.5	12 weeks 3x/week	CT (45-60 min) + high intensity lower extremity eccentric RT (on average 10 min/session)	Lower limb strength →; Several functional mobility measures →; Balance →; Fatigue →
Sabapathy et al. (2011)	n = 16	NR	8 weeks 2x/week	3 lower limb, 3 upper body exercises + 1 core and 1 stability exercise 2-3 sets x 6-10 reps	Measures of physical functioning ↑; Fatigue ↑; MSIS-29 physical component ↑; MSIS-29 psychological component →; Depression →; QoL →

↑ indicates improvement, → indicates no change, ↓ indicates worsening.
CT = combined training, EMG = Electromyography, EDSS = Expanded Disability Status Scale, MSIS-29 = Multiple Sclerosis Impact Scale, NR = not reported, QoL = quality of life, reps = number of repetitions, RT = resistance training.

2.3.2.3 Combined training

The effects of combined training have been sparsely investigated in MS; so far five RCTs (Table 3) and two small non-controlled trials have been published (Charlton et al., 2010; Motl et al., 2012d). In addition, Learmonth et al. (2013) carried out a parallel qualitative analysis of their RCT, and Garrett et al. (2013b) published a follow-up report of their trial. One large (n = 99) RCT with a range of long-term neurological conditions included 24 persons with MS (Elsworth et al., 2011), but the results of this trial are not presented here.

All but one study (Cakt et al., 2010) applying combined training have included components of both endurance and resistance training in the intervention protocol (Bjarnadottir et al., 2007; Charlton et al., 2010; Golzari et al., 2010; Learmonth et al., 2012; Motl et al., 2012d; Garrett et al., 2013a). Two studies have solely relied on these two training modes (Bjarnadottir et al., 2007; Charlton et al., 2010), two studies have added balance exercises as a third component (Learmonth et al., 2012; Motl et al., 2012d), whereas in one study the third core part consisted of flexibility exercises (Golzari et al., 2010). A Turkish group (Cakt et al., 2010) included in their trial two active exercise groups (vs. third non-exercising group), of which the first underwent supervised resistance training on a cycle ergometer complemented by balance exercises, and the other received a home-based programme consisting of lower limb strength training and balance exercises.

The duration of combined training interventions has ranged from five weeks (Bjarnadottir et al., 2007) to 16 weeks (Charlton et al., 2010). Training frequency has varied from 1 to 3 times/week in all studies (not mentioned by Charlton et al., 2010). Training intensity has been infrequently reported; only two studies have implemented programmes with a moderate level of intensity (Bjarnadottir et al., 2007; Motl et al., 2012d).

Based on the available evidence, solid overall conclusions on the effects of combined training are difficult to draw. Balance and strength have most commonly been used as target outcomes in these interventions. Combined training seems to consistently improve muscle strength (Charlton et al., 2010; Golzari et al., 2010; Learmonth et al., 2012), and balance outcomes (Cakt et al., 2010; Charlton et al., 2010; Golzari et al., 2010; Learmonth et al., 2012). Besides, it has the potential to reduce the fear of falling (Cakt et al., 2010).

Walking and functional mobility may be enhanced by combined training (Cakt et al., 2010; Motl et al., 2012d; Garrett et al., 2013a). The evidence is, however, not explicit. Learmonth et al. (2012) found in their RCT no significant effects in the 25-foot walk time, 6-min walk distance or the Timed Up and Go test,

whereas Garrett et al. (2013a) demonstrated significant improvements in the two training groups in the 6-min walk distance. Equally, findings in disease progression and aerobic capacity are diverse. Golzari et al. (2010) detected a significant reduction in the mean EDSS score, but no change in VO_2max, while Bjarnadottir et al. (2007) found no effect in the EDSS, but observed a 15% increase in VO_2peak in the exercise group compared to a slight decrease in the control group.

Fatigue has been an outcome in three of the combined training studies. Cakt et al. (2010) observed symptom alleviation following supervised, but not home-based training. Learmonth et al. (2012) noted a moderate positive clinical effect on fatigue but no statistical significance after a leisure-centre-based group intervention in persons with moderate disability (EDSS range 5.0 – 6.5). Garrett et al. (2013a) found significant fatigue reduction in the two combined training groups (n = 80 and n = 86), and the benefits were maintained for 12 weeks after the interventions (Garrett et al. 2013b). Corresponding long-lasting improvements were also observed in the psychological impact of MS (Garrett et al., 2013a; Garrett et al., 2013b). Improvements in psychosocial elements (confidence, mood, and energy) have been reported after a single-group (n = 11) Jazzercise programme (Charlton et al., 2010). Studies applying a more rigorous design have been partly able to reproduce these findings with significantly reduced depression scores (Cakt et al., 2010), but partly not, with unchanged levels of anxiety and depression (Learmonth et al., 2012). Regarding quality of life, the Cakt group (2010) reported improvements in the physical functioning dimension after both training interventions. Much in the same way, Bjarnadottir et al. (2007) detected a tendency towards improved quality of life in five of the eight dimensions, suggesting a clinically important finding. Notwithstanding, positive training effects on quality of life were not observed by Learmonth et al. (2012).

Two RCTs have reported novel results on outcomes rarely included in exercise intervention studies in MS. Learmonth et al. (2012) considered as a key finding the observed increase in overall physical activity levels (as measured using a questionnaire) in the exercise group (n = 20) vs. the non-exercising control group (n = 12). Golzari et al. (2010), in turn, explored the effects of combined training on the levels of cytokines IFN-gamma, IL-4 and IL-17 in the plasma and the supernatant of peripheral blood lymphocytes in women with MS. Apart from the IL-4, these parameters significantly decreased, leading to a conclusion concerning the possibly beneficial anti-inflammatory effects of combined training.

Precise percentages on training adherence have been reported in five studies, both the highest (93%; supervised training) and the lowest (60%; home-based training) average rates were found by Cakt et al. (2010). The mean attendance rate in exercise classes in the study by Garrett et al. (2013a) was 8 (out of 10) in the physiotherapist-led classes, 7 (out of 11) in the fitness instructor-led classes, and 8 (out of 9) in the

yoga classes. Combined training seems a feasible option for persons with MS; no injuries or other complications in connection with these interventions have occurred. Furthermore, taking part in such a training programme may be a positive experience offering social support and leading to symptom improvement (Learmonth et al., 2013).

Table 3. RCTs evaluating the effects of combined training in persons with MS

Study	Sample size	EDSS	Duration Frequency	Training regime Duration/session	Main findings
Bjarnadottir et al. (2007)	n = 16	< 4.0	5 weeks 3x/week	Bicycle ergometry + resistance training 60 min	VO_2peak ↑; anaerobic threshold ↑; QoL: vitality ↑; EDSS →
Cakt et al. (2010)	n = 45	≤ 6.0	8 weeks 2x/week	1) Bicycle ergometry + balance exercises + walking and stretching 2) Balance exercises + walking and stretching 30 – 70 min	10-m walk time ↑; Functional Reach ↑; Falls Efficacy Scale↑; Fatigue ↑; Depression ↑; QoL: physical functioning ↑
Golzari et al. (2010)	n = 20	0 – 4.0	8 weeks 3x/week	Endurance, resistance and stretch training 55 – 65 min	EDSS ↑; Muscle strength ↑; Balance ↑; Cytokines IL-17 and INF-γ ↑; Cytokine IL-4 →; Supernatant INF-γ and IL-17 production ↑; Supernatant IL-4 production →
Learmonth et al. (2012)	n = 32	5.0 – 6.5	12 weeks 2x/week	Mobility, resistance and balance training 60 min	Balance confidence ↑; Physical activity levels ↑; Leg strength ↑; Timed Up and Go →; Fatigue →; 25-foot walk time →; HRQoL →
Garrett et al. (2013a) Garrett et al. (2013b)	n = 314 (a) n = 121 (b)	NR	10 weeks 1-3x/week	a) resistance training classes + home-based endurance training b) endurance + resistance training classes	MSIS-29 physical and psychological components↑; 6-min walk distance ↑; Fatigue ↑ **Week 22:** Benefits on MS psychological impact and fatigue were maintained.

↑ indicates improvement, → indicates no change, ↓ indicates worsening.
EDSS = Expanded Disability Status Scale, HRQoL = health-related quality of life, MSIS-29 = Multiple Sclerosis Impact Scale, NR = not reported, QoL = quality of life, VO_2peak = peak oxygen uptake.

3. AIMS OF THE STUDY

The overall aim of this study was to examine the effects of combined resistance and endurance exercise training on functioning in persons with multiple sclerosis.

The detailed study objectives were as follows:

1. to examine exercise capacity, disability, and leisure-time physical activity and their associations in men and women with MS (study I)
2. to evaluate the effects of a combined six-month training programme on walking speed and other aspects of physical functioning (study II)
3. to investigate whether combined training for six months has an influence on perceived fatigue and on the motor fatigue of knee extensor and flexor muscles in men and women with MS (study III)
4. to explore how long-term combined training affects disability and HRQoL (study IV).

4. SUBJECTS AND METHODS

4.1 Subjects

Study subjects were screened from a waiting list for an inpatient rehabilitation course at the Masku Neurological Rehabilitation Centre, Masku, Finland over an eight-month period in 2001. The initial screening, including 276 subjects, was based on admission records. Eligibility was confirmed if the subject had a diagnosis of clinically or laboratory supported MS (Poser et al., 1983), scored 1.0 to 5.5 on the EDSS (inclusive), and was aged between 30 and 55 years. The exclusion criteria were a relapse during the preceding month, a disease other than MS preventing participation in the training programme, engagement in regular exercise ≥ 5 times/week for at least 30 minutes/session during the three months before admission, or signs of any other medical or mental condition precluding participation.

Following the initial screening, potential participants were interviewed by phone. The purpose of the study was explained to them, and they gave preliminary approval for participation. The eligibility criteria were met by 114 subjects. After the phone interview, the potentially eligible subjects were stratified by sex and randomly assigned either to the training intervention group (n = 56) or to the control group (n = 58). Following post-randomization withdrawals and exclusions, 95 subjects were considered for statistical analyses. Altogether 91 subjects completed the study. The recruitment procedure with the number of subjects excluded/included in the study is depicted in a flow diagram in Figure 2.

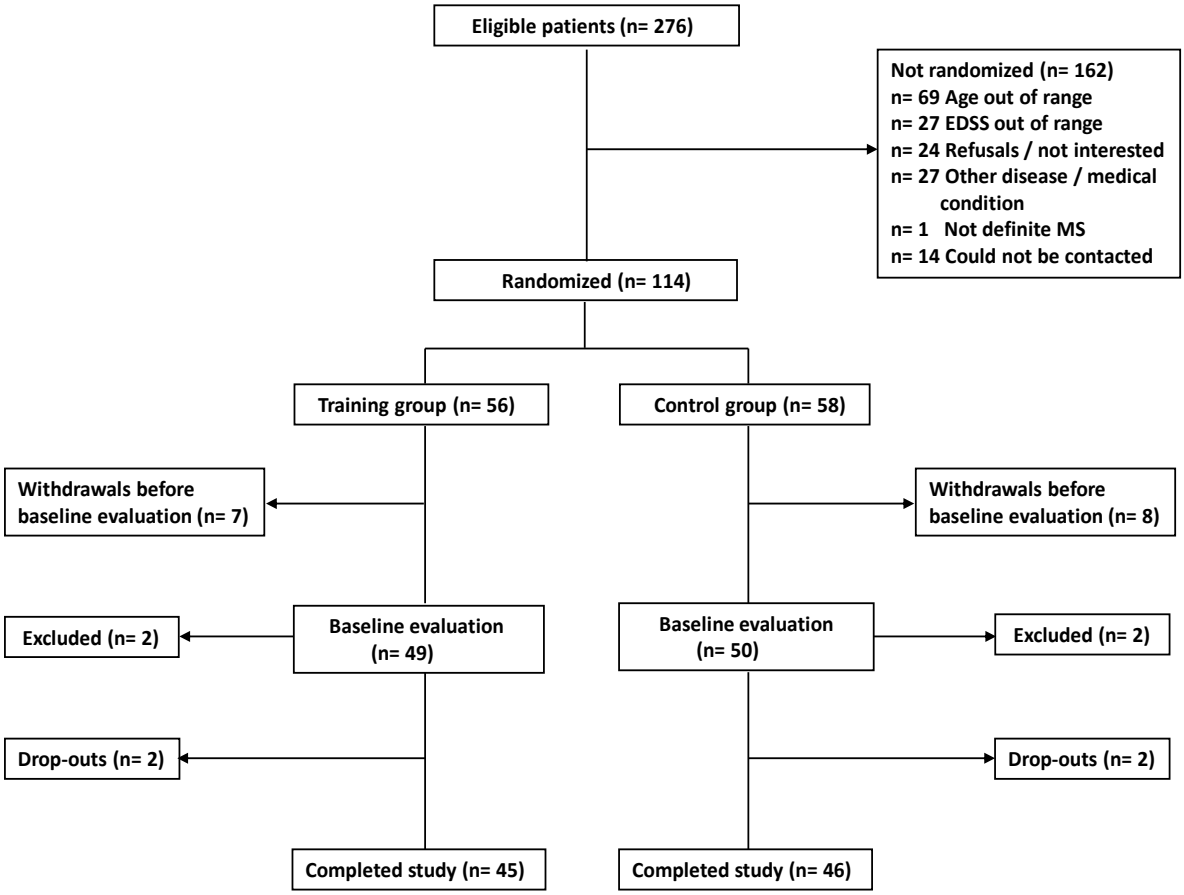

Figure 2. Flow chart of the study.

4.2 Study design

4.2.1 Study I

Study I applied a cross-sectional descriptive design, in which the baseline data of the VO_2peak, neurological disability, and leisure-time physical activity of the participants in the randomized training study were analysed.

4.2.2 Studies II, III, IV

Studies II, II and IV utilized a randomized controlled trial design. The subjects in the intervention group completed a combined training programme lasting for 26 weeks. The results were compared to those of a wait-list control group receiving no intervention. The assignment into the two groups was implemented by the study statistician in computer-generated random sequence using the SAS software (version 8.2, SAS

Institute, Inc, Cary, NC, USA). The statistician had no access to study participants' medical records, nor was she involved in any personal contacts with them during the trial.

4.3 Assessments

4.3.1 Procedure

Participants in both study groups were assessed at baseline (studies I – IV) and at 26 weeks (Studies II – IV). Subjects in the training group underwent a neurological examination on entry to a three-week rehabilitation course. Thereafter, study assessments were conducted on days two and three of the rehabilitation course. Some of the clinical tests for the training group were also conducted at three weeks (at the end of the rehabilitation course). For the control group, all the baseline assessments, including the neurological examination, were carried out during two-day baseline study visits. To reduce measurement variability all study subjects were assessed at baseline and at 26 weeks at approximately the same time of the day, that is, either in the morning (8:15 to 12:30) or in the afternoon (12:30 to 16:00).

Information on subjects' disease and physical characteristics, medication, other diseases than MS, marital status, employment, and education length was obtained from medical records, questionnaires and interviews (by A. Romberg). In the course of the study, the number of relapses treated with steroids was recorded based on subjects' self-reports and confirmed with information from medical records.

Neurological examinations and clinical tests of physical functioning were carried out at the Masku Neurological Rehabilitation Centre. Study subjects underwent the neurological examination by the same experienced neurologist at baseline and at 26 weeks to ensure intra-rater reliability. Clinical tests of physical functioning were carried out by an independent trained assessor (physiotherapist) not otherwise involved in the study. Blinding the assessor to the group allocation was not possible. However, a number of precautions to limit her awareness of the trial progression were taken into account according to the practical guidelines for independent assessment in randomized controlled trials of rehabilitation (Siemonsma & Walker, 1997). The Functional Independence Measure (FIM) assessments were done by nurses specially trained and certified to use the instrument.

An incremental maximal exercise test and measurements of knee flexor and extensor torque and strength were conducted in the laboratory of the Research Department of the Social Insurance Institution (Turku, Finland).

4.3.2 Primary and secondary outcome measures

Walking speed was selected as the primary outcome because walking limitations are highly prevalent in MS, and impaired walking stands as a marker of both disability and MS progression. Walking speed was measured over short (25 ft, that is 7.62 m) and long (500 m) distances. All other outcome measures were secondary. An overview of study outcome measures is presented in Table 4.

Table 4. Overview of the study outcome measures

Outcome	Measure	Study	Reference(s)
Primary outcome			
Walking speed	25FTW	II, IV	Cutter et al. (1999) Romberg et al. (2001)
Walking speed (and endurance)	500MWT	II	Schwid et al. (1997) Schwid et al. (1999)
Secondary outcomes			
VO_2peak	Incremental maximal spiroergometry on a cycle ergometer	I	Wasserman et al. (1994)
Perceived exertion in spiroergometry	RPE Scale (6 – 20)	I	Borg (1982)
Balance	Equiscale	II	Tesio et al. (1997)
Knee flexor and extensor maximal strength	Knee muscle dynamometer	II	Surakka et al. (2004)
Upper extremity endurance	Weight lifting test	II	Rytökoski et al. (1997) Paltamaa et al. (2005)
Gross manual dexterity	Box and Block test	II	Goodkin et al. (1988)
Motor fatigue of knee flexor and extensor muscles	Motor fatigue index	III	Surakka et al. (2004)
Perceived fatigue	Fatigue Severity Scale	III	Krupp et al. (1989)
Fine manual dexterity	Nine-Hole Peg Test	IV	Goodkin et al. (1988)
Cognitive functioning	PASAT	IV	Gronwall (1977)
Disability	EDSS	I - IV	Kurtzke (1983)
Disability	MSFC	IV	Cutter et al. (1999)
Disability	FIM	IV	Granger et al. (1990)
Health-related quality of life	MSQOL - 54	IV	Vickrey et al. (1995)
Depressive symptoms	CES-D	IV	Radloff (1977)

CES-D = Centre for Epidemiologic Studies Depression Rating Scale, EDSS = Expanded Disability Status Scale, 500MWT = 500-meter Walk Test, MSQOL-54 = Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument, PASAT = Paced Auditory Serial Addition Test, RPE = Rating of perceived exertion, 25FTW = Timed 25-foot Walk Test, VO_2peak = Peak oxygen uptake

4.3.3 Tests of physical functioning

4.3.3.1 Measurement of peak oxygen uptake (I)

Peak oxygen uptake (VO_2peak) was measured to evaluate the subject's exercise capacity. This was done using a 2-min incremental exercise test on an electromagnetically controlled cycle ergometer (Rodby Ergometer RE 820®, Rodby Innovation AB, Södertälje, Sweden) until volitional exhaustion or fatigue of the lower limbs interrupted the test.

During the exercise test the subjects pedalled at a constant frequency of 60 rpm. The test was preceded by a 4-min warm-up at 30 W. Thereafter, the work rate was increased every 2nd min with equal steps throughout the test. The increments were individually determined to at least 10 W, but to no more than 25 W, on the basis of the subject's estimated aerobic fitness, to reach the maximum work rate in about 12–15 min. The test continued until the subject was unable to maintain the pedalling frequency above 45 rpm. Respiratory gas exchange parameters were continuously determined with a breath-by-breath method (SensorMedicsVmax 229™, SensorMedics Corp., Yorba Linda, CA, USA). The VO_2 values were averaged over the breath-by-breath values of the 30-s intervals. Because of uncertainty about how close to their maximum the subjects would cycle, the term VO_2peak was used instead of VO_2max. VO_2peak was recorded as the highest averaged value at the maximum work rate. The corresponding heart rate from continuous ECG and work rate were recorded and used to represent their maximums. Subjects rated their perceived exertion using the Borg 6–20 RPE scale (Borg 1982), and the amount of their lower limb fatigue on a 1–5 scale every 4th min, and every 2nd min at the final stages of the test. Data for VO_2peak were expressed as absolute ($l \cdot min^{-1}$) and relative ($ml \cdot kg^{-1} \cdot min^{-1}$) values.

4.3.3.2 Tests of walking capacity (II, IV)

The 25FTW is a well-established part of the Multiple Sclerosis Functional Composite (MSFC) measure, has very good psychometric properties, and has been proposed as a preferred short test for documenting overall walking capacity in MS (Cohen et al., 2000; Phan-Ba et al., 2011; Gijbels et al., 2012; Kieseier & Pozzilli, 2012). The subjects were asked to walk as fast as possible over a 25-ft expanse of floor as follows: A) twice according to test instructions for the MSFC (Fischer et al., 1999a): this included a static start just behind the start line. A stopwatch was used for timing. B) After about 1 min rest, the test was repeated twice. This protocol included a 2-m acceleration and deceleration path before and after the actual 25-ft test distance. The time to walk was this time recorded using photocell sensors (Newtest Powertimer System,

Newtest Oy, Oulu, Finland). In pilot tests, both methods have shown excellent reliability (Romberg et al., 2001). The results of protocol A were used for study IV, those of protocol B for study II. In all cases, the mean time of two consecutive trials was included in the analyses.

The 500-m Walk Test (500MWT), was applied to measure ambulatory endurance (Schwid et al., 1997; Schwid et al., 1999). The subjects walked, at their maximum speed, back and forth in a 25-m hallway turning around cones at each end. A stopwatch was used for timing. The total walking time and the time for the first and the final 50-m laps were recorded.

4.3.3.3 Tests of balance, muscle strength, upper extremity endurance and function (II)

Static balance was assessed by the Equiscale, which is a Rasch-validated short clinical measure of balance disorders in ambulatory MS subjects (Tesio et al., 1997). The eight items of the Equiscale were derived from the frequently used Tinetti Performance-Oriented Balance Scale and the Berg Balance Scale. Each item reproduces real-life performances (e.g. picking up a pen from the floor or turning around), and is rated by a score of 0, 1, or 2. The overall top score of 16 points indicates excellent balance.

Maximal isometric torque of knee extensor and flexor muscles was measured in a seated position using a knee muscle dynamometer (HUR®, Kokkola, Finland). This is a reliable method of measuring lower extremity strength in persons with MS (Surakka et al., 2004). The subject was instructed to perform maximal extension and flexion contractions, and to maintain them for 5 s. Two attempts with 2-min intervals were measured for each leg, the one with the highest torque was used for analysis.

To assess upper extremity endurance, a weight-lifting test was carried out (Rytökoski et al., 1997). The subjects alternately raised their right and left arm upwards holding a 7 kg (women) or 10 kg (men) dumbbell in each hand. The number of maximal repetitions for both arms was recorded. Repetitive dumbbell raises have shown good test-retest and inter-rater reliability in MS subjects (Paltamaa et al., 2005).

Upper extremity function (gross manual dexterity) was quantified using the Box and Block test, which is a reliable measure both in the healthy and in persons with MS (Mathiowetz et al., 1985; Goodkin et al., 1988; Paltamaa et al., 2005). The score was the number of blocks carried from one box compartment to the other in one minute by both dominant and non-dominant hand.

4.3.3.4 Motor fatigue evaluation (III)

Motor fatigue of knee extensor and flexor muscles was measured using a knee muscle dynamometer (HUR®, Kokkola, Finland). The measurement was performed once for each leg, with an at least two minutes rest between the attempts. In a seated position, the subject was instructed to exert maximal extension and flexion torques and to sustain them for 30 s. The decline in force (Nm) during the 30 s was recorded, and based on this, a motor fatigue index (FI) was calculated. The FI used in the current study has been shown to be a reliable and highly reproducible model in persons with MS. Its detailed development and calculation have been described elsewhere (Surakka et al., 2004). The analyses were based on the torque measured from the right leg owing to the lack of differences in the performances of right and left leg. Training intervention effects on FI were also analysed for men and women separately owing to general sex differences in muscular fatigability (Semmler et al., 1999) and to differences in exercise adherence between the sexes in the present study. Moreover, to establish possible learning effects related to the measurement, the results after the three-week supervised training period were analyzed (for the training group only).

4.3.4 Disability rating scales (I, II, IV)

The EDSS (Expanded Disability Status Scale) is a 20-step ordinal scale, which ranges between 0 (normal neurological status) and 10 (death due to MS) (Kurtzke, 1983). In spite of criticisms of its measurement properties (Hobart, 2003), it has been considered a gold standard for measuring disability in MS (Kragt et al., 2006). The EDSS score is determined according to the history and the findings of a standard neurological examination in the appropriate grades of eight Functional Systems (FS). The FSs are pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral and “others”. An overall score describing disability is obtained by combining the different FS grades and the ability to walk (assessed separately), use of upper limbs, ability to communicate or to swallow. The lower points, up to 3.5, are largely dependent on the FS, disability in the higher grades is mainly determined by walking ability (Sharrack & Hughes, 1996).

The MSFC (Multiple Sclerosis Functional Composite) was developed in the late 1990s and is a multidimensional quantitative measure of neurological disability in MS (Cutter et al., 1999; Rudick et al., 2002; Polman & Ruddick, 2010). It is made up of three components that measure lower extremity function/ambulation, upper extremity function, and cognition (Cutter et al., 1999). Accordingly, the three component composites are the 25FTW, the Nine-Hole Peg Test (9HPT) and the Paced Auditory Serial Addition Test (PASAT). In the present study, the MSFC was administered according to standardized

instructions (Fischer et al., 1999a). First, the subjects performed the 25FTW twice. Thereafter, the 9HPT was carried out twice with each hand with the mean time (s) for each hand being statistically analyzed. Finally, the PASAT (3-s version) was done once; the final score was the number of correct additions in the series. To obtain the MSFC score, Z-scores for each measure were calculated, and the composite score was then calculated as recommended by the Administration and Scoring Manual for the MSFC (Fischer et al., 1999a). To create an internal reference population, the means and standard deviations of the baseline visits for the entire study sample (n = 95) were used.

The Functional Independence Measure (FIM) is an 18-item, interviewer-rated, summed rating scale to evaluate disability in terms of dependency (Granger et al., 1990). The FIM uses a seven-level scoring system based on whether or not assistance of another person is required. Consequently, independent (no helper; gradations 6 – 7) and dependent (helper needed; gradations 1 – 5) are the gross classifications. The total score ranges from 126 (normal status) to 18 (totally dependent). The FIM has high internal consistency, high sum score inter-rater reliability, variable item-score inter- and intra-rater reliabilities, and correlates well with the EDSS (Sharrack et al., 1999).

4.3.5 Self-report questionnaires (I, III, IV)

In the brief leisure-time physical activity questionnaire (I), the first item included a single, slightly adapted, question from Lamb (1992), in which the subjects were asked to indicate their present self-perceived physical fitness on a 1–5 scale. In the second item, the subjects were asked about the type, frequency and duration of exercise for the past four weeks. In the third item the subjects were asked to denote whether they had become breathless or not, and their degree of sweating. Items 2 and 3 were slightly adapted from a questionnaire used previously as a part of the Mini-Finland Health Survey (Mälkiä et al., 1988). The purpose of the questionnaire was primarily to classify subjects into activity categories rather than to assess physical activity comprehensively. For the analyses, physical activity was grouped according to the types of structured exercise as follows: no exercise, walking (including Nordic walking), other aerobic endurance exercise, strength/resistance training, and other exercises (including balance/co-ordination exercises and outdoor activities). The time spent on each activity (per week) was then calculated.

Perceived fatigue (III) was measured using the nine-item Fatigue Severity Scale (FSS), which quantifies the severity, frequency, and impact of fatigue in daily living. The FSS shows sensitivity, reliability, and internal consistency in the assessment of fatigue in persons with MS (Krupp et al., 1989). The mean of the items is taken as the FSS score (range 1–7) with higher scores indicating more severe fatigue. To produce a Finnish

version of the FSS, a translation procedure similar to the development of a Norwegian FSS was adapted (Lerdal et al. 2003). The translation procedure was carried out during spring 2001, and involved two researchers (A. Romberg and J. Ruutiainen) and an authorized translator with Finnish as her mother tongue. The back-translation from Finnish to English was commented on and approved by Dr. L Krupp, who developed the original English version.

Depressive symptoms (IV) were evaluated with the Center for Epidemiologic Studies Depression Rating Scale (CES-D) (Radloff, 1977). The CES-D has 20 items, each of which is rated on a 4-point scale, with a score range from 0 to 60. It has been shown to be a highly reliable screening tool for depression in MS, and has good prediction accuracy of clinically significant depressive disorders among persons with the disease (Verdier-Taillefer et al., 2001; Pandya et al., 2005). The cut-off point for a clinically significant level of clinical depression is 16 (Radloff, 1977).

To assess HRQoL (IV), the disease-specific Multiple Sclerosis Quality of Life-54 questionnaire (MSQOL-54) was used. It comprises questions from the Short Form 36-Item Health Survey as a generic measure of quality of life complemented by 18 additional MS-specific items. The 54 items are divided into 12 multi-item and two single-item scales. Evidence supports the reliability and validity of the MSQOL-54 (Vickrey et al., 1995; Vickrey et al., 1997; Solari, 2005). A Finnish version of the SF-36 has been available since 1996 (Hagman, 1996). The 18 MS-specific items of the MSQOL-54 were translated into Finnish according to the guidelines for the cross-cultural adaptation of HRQoL measures (Guillemin et al., 1993). The translation procedure was undertaken in spring 2000 and it involved a professional translator, two researchers (A. Romberg, J. Ruutiainen), an MS nurse expert on HRQoL, and an independent medical specialist. The back-translation from Finnish to English was commented on and approved by Dr. B Vickrey, who developed the 18 original English MS-specific items. For statistical analyses, the MSQOL-54 item results were transformed linearly to 0-100 scores and final scale scores were created by averaging items within the scales. A higher score in each scale indicates a better HRQoL. Physical health composite and mental health composite scores were calculated as a weighted sum of selected scale scores (Vickrey et al., 1995).

4.4 Training intervention (II, III, IV)

The intervention in the training group consisted of structured exercise, initiated at the time of inpatient rehabilitation (weeks 1–3) and followed by a progressive home-based programme (weeks 4–26) instructed by trained physiotherapists during inpatient rehabilitation. The subjects in the training group were contacted by phone by A. Romberg on weeks 5, 8, 14 and 20 to monitor progression, to provide feedback and encouragement, and to answer questions.

The control group received no intervention. At the time of the baseline study visits members of the control group were advised to avoid any greater changes in their physical activity habits during the following six months. To ensure the study compliance they were contacted three times by phone before the follow-up visit on week 26.

4.4.1 Supervised programme (weeks 1–3)

Five supervised resistance and five endurance group-training sessions, on separate days, were carried out during inpatient rehabilitation. In addition, the patients participated in a comprehensive rehabilitation programme consisting of individual and group therapies based on a multidisciplinary team approach.

The endurance training programme consisted of aquatic training for about 45 minutes with varying forms of calisthenic exercises done in shoulder-deep water (temperature approximately +28 °C). Apart from the cool-down phase at the end (consisting mainly of stretching), all the exercises were done in an upright position. While training in the water the subjects monitored their heart rate with a portable heart rate monitor (Polar A3™, Polar Electro, Kempele, Finland). The target training intensity was 65 - 70% of age-predicted maximal heart rate. In the target intensities, the effects of immersion on cardiac output responses were considered. Therefore, the actual target heart rates were prescribed 10 beats · min^{-1} lower in the water than they would have been on land (Svedenhag & Seger, 1992).

The resistance training programme was circuit-based. After standard warm-up, each participant completed two sets of 10 exercises with 10 to 15 repetitions. Rest periods of 1 min between the exercises and 4 min between the entire circuits were allowed. The programme included 10 exercises; four exercises for both lower and upper extremities, and two exercises for the trunk. Apart from one exercise (hip extension against gravity), pressurized air resistance or weight stack machines were used. The load throughout the training was 50 - 60% of 1RM. After the third session the loads were individually re-evaluated. Training sessions lasted for 45 to 50 minutes, and were completed by a cool-down mainly consisting of muscle stretching.

4.4.2 Home programme (weeks 4–26)

On weeks 4–20, the programme included resistance training three times/week and endurance training once/week. On weeks 21–26, one resistance training session was added to the programme. On weeks 4–26, the resistance exercises to be conducted at home mainly reproduced the exercises of weeks 1–3. Two

exercises (hip flexion and hip extension) were done in a standing position for imitation of walking patterns. The subjects were equipped with two elastic bands (Theraband®), one for the lower, one for the upper extremities. On weeks 4–8, the programme included two sets of 10–12 repetitions of each resistive exercise. On week 9, the number of repetitions was increased to 12–15. On week 15, if the training had been regular and no detrimental symptoms had occurred, new, stiffer elastic bands were delivered. Now, the repetitions were decreased to 10–12 for the rest of the exercise period.

The advice for endurance training over the entire home exercise period was to continue, if possible, with aquatic training, or to continue with other mode of moderate endurance training at least once a week for at least 20 min/bout.

The subjects kept a diary for each training session. They recorded the duration and perceived intensity (4-step scale) of exercise, as well as any MS-related or other symptoms occurring during or after training. Adherence was determined for all exercise and for strength training and aerobic training separately using the number of training sessions reported as a percentage of training sessions prescribed for the home exercise period.

4.5 Statistical analyses

The sample size calculation was based on the primary outcome. A 20% increase in the walking speed on the 25FTW was defined as a threshold to indicate a clinically meaningful improvement (Kaufman et al., 2000). To detect a difference of this magnitude between the groups, a minimum of 62 participants would be required to provide 80% power at two-sided $\alpha = 0.05$. Previous data on the 25FTW (Goodkin et al., 1998) were used as a reference in the power analysis. In the reference study, the EDSS ranged between 1.0 and 3.5. Because we also considered subjects with higher EDSS scores, and to allow for a reasonable dropout rate, the aim was to recruit a total of 100 persons for the study.

The SAS® for Windows package (SAS institute, Cary, NC, USA) was used for all statistical analyses.

4.5.1 Study I

Differences between men and women in continuous variables were calculated using the t-test or the Wilcoxon test, and in categorical variables using the chi-square test. The strength of associations between disease or physical characteristics and VO_2peak was determined using correlation analysis. Significant

independent variables ($p < 0.1$) were included in the multivariate regression models. Three regression models were fitted with VO_2peak as the dependent variable. The first model was used to examine the influence of age, height, weight, and sex. The second model included the EDSS, and the third model the current amount of aerobic endurance exercise. The final regression model included those independent variables from initial models that remained statistically significant ($p < 0.1$). Interaction terms were included in all models. The normality of residuals was checked by the Shapiro-Wilk statistic, and the graphic analysis of residuals was carried out to provide information about the constancy of residuals. Detection of outliers and influential data points were assessed using studentized residuals and other diagnostics measures. If any outliers or influential data points were observed, regression models were used both with and without them and the results were compared.

4.5.2 Studies II, III, IV

The baseline characteristics between groups were compared using the *t*-test, Wilcoxon's test, the Mantel-Haenszel test, or the χ^2–test, when appropriate. Primary, and most secondary outcome measures, were analyzed using mixed-models analysis of variance (Littell et al., 1998). In the models, sex and group were considered as between-group factors and time as the within-subject factor. The Tukey-Cramer method was used to adjust for individual α-level when multiple tests were done. In the Equiscale, differences between the groups were compared using the signed rank-test. All group comparisons were based on an intention-to-treat approach (Hollis & Campbell, 1999).

A series of covariate adjustments were applied if any imbalance was detected between groups, or if the covariate correlated with the outcome. This method has been recommended for the analysis of continuous data measured at baseline and follow-up in RCTs (Vickers & Altman, 2001; Vickers, 2005). Most of the covariates were considered fixed, because they were only collected at baseline or no change was seen at follow-up. For the primary outcome measures, the EDSS and established biological determinants of physical function were chosen as covariates (II). For the FI, the EDSS and FSS scores were used as fixed covariates. In addition, the duration of aerobic and resistance training in the training group, and the maximal and mean torque (Nm) values were used as variable covariates to find out the associations of these with the FI (III). For the MSFC score, age, education, employment status and disease duration served as covariates, and for the MSQOL-54 (physical and mental health composites), sex, employment status, EDSS, and depression were the covariates, correspondingly (IV).

To supplement the statistical testing and to give a more complete picture of the magnitude and clinical relevance of the change in various scores, the effect size statistic was calculated (Kazis, 1989). Cohen's (1977) classification was used to interpret the effect sizes, i.e., a value of < 0.20 denotes no effect, ≥ 0.20 a small, ≥ 0.50 a medium, and ≥ 0.80 a large treatment effect.

4.6 Ethical considerations

The study was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all study subjects at the inception of the study. The study protocol, documents, and progress were reviewed regularly by an independent adjudication committee.

5. RESULTS

5.1 Baseline subject characteristics

5.1.1 Study I

Data on physical and disease characteristics were sorted by sex (Table 5), because anatomical and physiological characteristics contribute more to lower exercise capacity in women compared to men (Harms, 2006). In the sample, 64% of the subjects were women and 36% men. As expected, men were taller and weighed more than the women. In addition, men had more severe MS, as indicated by a higher mean EDSS score and by higher rates of both primary and secondary progressive disease forms.

Table 5. Physical and disease characteristics (Study I)

Variable	Men (n = 34)	Women (n = 61)	p-value*
Age (years)	44.4 ± 6.8	43.5 ± 6.6	0.50
Height (cm)	176.5 ± 6.8	166.1 ± 5.6	<0.0001
Weight (kg)	80.1 ± 14.5	68.5 ± 12.4	<0.0001
BMI (kg/m^2)	25.7 ± 4.5	24.8 ± 4.0	0.28
Disease course (%)			0.04
Relapsing-remitting	65	87	-
Primary progressive	20	7	-
Secondary progressive	15	6	-
Disease duration (years)	5.7 ± 6.2	5.8 ± 6.6	0.99
EDSS [range]	3.0 ± 1.2 [1.0 – 5.5]	2.2 ± 0.9 [1.0 – 4.0]	0.004

Values are expressed as mean ± SD, or %.
BMI = Body Mass Index; EDSS = Expanded Disability Status Scale
* p-values denote differences between men and women.

5.1.2 Studies II, III, IV

Subject characteristics of the training group (n = 47) and the control group (n = 48) at baseline are presented in Table 6. The groups were well matched for background variables.

Table 6. Subject characteristics at baseline (Studies II, III, IV)

Variable	Training group n = 47	Control group n = 48
Age, y, mean ± SD	43.8 ± 6.3	43.9 ± 7.1
Female sex	30 (64%)	31 (65%)
Married / cohabiting	17 (36%)	12 (25%)
Employment		
Full- or part-time employed	29 (62%)	26 (54%)
Retired	18 (38%)	22 (46%)
Education		
6 – 9 years	8 (17%)	13 (27%)
9 – 12 years	25 (53%)	21 (44%)
12 – 16 years	8 (17%)	14 (29%)
≥ 16 years	6 (13%)	0
Disease duration, y, mean ± SD (min-max)	6.0 ± 6.5 (0 - 23)	5.5 ± 6.4 (0 - 28)
EDSS score, mean ± SD (min-max)	2.3 ± 1.0 (1.0 - 5.5)	2.7 ± 1.1 (1.0 - 5.5)
FIM score, mean ± SD (min-max)	123.4 ± 2.1 (116 - 126)	123.9 ± 2.3 (117 - 126)
Using disease-modifying drugs, n (%)	19 (40)	26 (54)

Differences between the groups were not statistically significant for any of the variables.
EDSS = Expanded Disability Status Scale; FIM = Functional Independency Measure

5.2 Exercise capacity and its association with disability and leisure-time physical activity (I)

Ninety-two subjects passed the incremental exercise test. The reasons for test failure (one man, two women) were knee joint contracture, dizziness and nausea, and inability to maintain pedalling frequency. The mean absolute VO_2peak in women was 1.5 (SD 0.4) $l \cdot min^{-1}$, the relative VO_2peak being 21.7 (SD 5.5) $ml \cdot kg^{-1} \cdot min^{-1}$. The corresponding figures for men were 2.2 (SD 0.5) $l \cdot min^{-1}$, and 27.0 (SD 5.2) $ml \cdot kg^{-1} \cdot min^{-1}$. Differences between the sexes were highly significant in both variables ($p < 0.001$). After adjusting for height and weight, both the absolute and relative VO_2peak values of men remained clearly higher than those of women ($p < 0.001$).

Half of the subjects (51%) perceived themselves as “moderately” physically fit. Walking was the most frequent exercise mode, followed by resistance training, aerobic endurance exercise, and other exercise. Six subjects (five men, one woman) had not taken part in any kind of exercise during the past four weeks. The subjects reported getting breathless in 49% of all exercise, sweating a little in 56%, and sweating a good deal in 9% of all exercise.

In women, the VO_2peak was weakly, inversely associated with disability assessed by the EDSS (Spearman’s correlations; $r = -0.31$, $p = 0.02$ for absolute VO_2peak; $r = -0.25$, $p = 0.05$ for relative VO_2peak). In men, the

association was, correspondingly, weak for absolute VO_2peak (r = -0.29, p = 0.09), but moderate for relative VO_2peak (r = -0.50, p = 0.004). Neither disease duration nor perceived fitness correlated with VO_2peak. In women, a weak correlation between absolute VO_2peak and perceived fitness was found (r = 0.27, p = 0.04).

In the multivariate regression analyses, sex, age, and weight explained 61% of the variability in absolute VO_2peak. The R^2 was 67% after adding the EDSS to the model. In relative VO_2peak, sex and age together attributed 30% of the variability; adding the EDSS to the model increased R^2 to 38%. Further, sex together with the EDSS (excluding age and weight) predicted the level of absolute VO_2peak for 42%, and of relative VO_2peak for 29%. There was no interaction between the EDSS and sex (p = 0.61); consequently, an increase of one point in the EDSS was associated with a decrease of about 2 ml · kg^{-1} · min^{-1} in relative VO_2peak in both sexes (Figure 3). Because of a significant sex difference (p < 0.001), the VO_2peak of men is 6.7 ml · kg^{-1} · min^{-1} higher than that of women, regardless of the EDSS score.

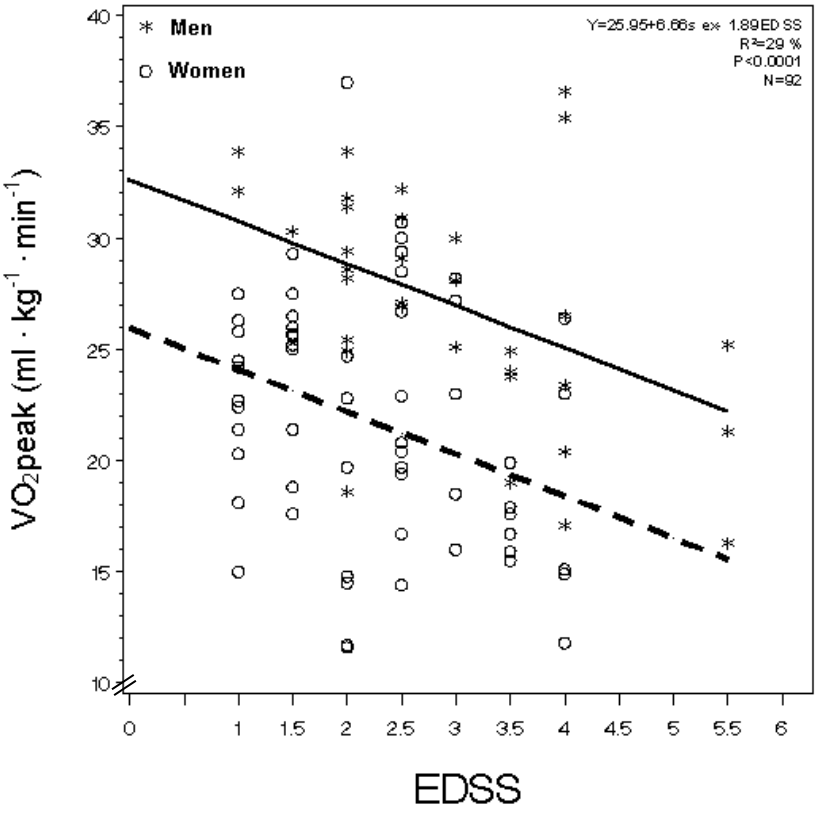

Figure 3. The association between VO_2peak and disability, as assessed by the EDSS, in 33 men (straight line) and 59 women (dashed line) with MS.

No association between endurance exercise capacity and leisure-time physical activity was found. When participation only in aerobic endurance exercise was examined, R^2 of the regression model in relative VO_2peak was 42%, but this was related to one statistical outlier. An additional subgroup analysis (n = 21)

showed that even high amount (≥ 1 hour/week) of aerobic endurance exercise (p = 0.10), sex (p = 0.30) and interaction between these two (p = 0.11) did not significantly predict VO_2peak in the sample.

5.3 Training effects on walking capacity (II)

The most obvious training effects were observed in the primary outcome measures; detailed values and changes in the 25FTW and the 500MWT are shown in Table 7. At six months, relative to baseline, participants in the training group walked on average 12% (95% CI 7% to 16%, p < 0.001) faster in the 25FTW. The control group also improved, by 6% (95% CI 2% to 11%, p = 0.002), in the 25FTW. There was a significant group-by-time interaction for change between groups. Ten (22%) subjects in the training group improved by at least 20% in the 25FTW, whereas only one (2%) in the control group (p = 0.01). In terms of the effect size, the training group showed a medium (0.50), and the control group a negligible (0.19) improvement in the 25FTW.

The total walking time in the 500MWT decreased by 6% (95% CI 10% to 2%, p < 0.001) in the training group, whereas in the control group, no change occurred (mean change 0%; 95% CI -3% to 4%, p = 0.99). The group-by-time effect for the change between the groups was significant in the total time, and in the first 50-m lap of the 500MWT (Table 7). The effect size indicated a small (0.26) improvement in the training group vs. no improvement (0.02) in the control group in the 500MWT.

According to the covariate analyses, height, weight, or body mass index had no effect on either the 25FTW or the 500MWT. By contrast, the EDSS was a significant covariate (p < 0.001) in both measures. Moreover, age was found to significantly affect the 25FTW time (p = 0.01), as well as that of the first 50-m lap in the 500MWT (p = 0.02).

Table 7. Results of 25-foot (25FTW) and 500-m (500MWT) walk tests at baseline, and 6-month changes (95% confidence intervals) in walking speed in the study groups.

	Training group, n = 47		Control group, n = 48		
	Baseline mean ± SD	Change mean (95% CI)	Baseline mean ± SD	Change mean (95% CI)	p*
25FWT (s)	3.8 ± 0.9	-0.44 (-0.62 to -0.27)	4.0 ± 1.1	-0.25 (-0.43 to -0.08)	0.04
500MWT					
Total time (min)	5.50 ± 1.2	-0.33 (-0.53 to -0.12)	5.63 ± 1.4	-0.02 (-0.23 to 0.19)	0.01
First 50-m lap (s)	30.4 ± 5.9	-2.31 (-3.23 to -1.39)	31.1 ± 6.3	-0.90 (-1.83 to 0.04)	0.01
Final 50-m lap (s)	32.6 ± 8.7	-1.78 (-3.99 to 0.42)	33.7 ± 11.0	0.12 (-2.12 to 2.36)	0.12

* p -values denote changes between groups with group-by-time interaction.

5.4 Training effects on balance, muscle strength, upper extremity endurance and function (II)

The mean Equiscale score at baseline was 14.7 (SD 2.3) in the training group, and 14.1 (SD 2.3) in the control group. Values at six months were 14.6 (SD 2.4) and 14.2 (SD 2.4); consequently, static balance over time remained unchanged in both groups.

No change was seen in knee extensor strength in either group. On the contrary, knee flexion strength of the right leg increased in the training group by a mean of 9.6 Nm (95% CI 3.7 to 15.5 Nm, $p < 0.001$), and of the left leg by 10.1 Nm (95% CI 3.6 to 16.6 Nm, $p < 0.001$). In the control group, knee flexion strength increased significantly in the left, but not in the right leg, with a mean change of 7.0 Nm (95% CI 1.2 to 12.8 Nm, $p = 0.01$). Despite the greater strength increases in the training subjects, the magnitude of change between the groups at six months did not differ statistically significantly (left leg, $p = 0.48$; right leg, $p = 0.28$).

Upper extremity endurance of the right side improved in the training group on average by 2.9 (95% CI 0.7 to 5.1) repetitions vs. 0.2 (95% CI -2.0 to 2.4) repetitions in the control group ($p = 0.02$ for change between groups). The corresponding figures for the left side were 3.1 (95% CI 1.1 to 5.0) vs. 0.3 (95% CI -1.7 to 2.3) repetitions ($p = 0.01$ for change between groups). Both groups showed a minor improvement in their upper extremity function, as measured by the Box and Block test. The difference in the change between the groups was, however, insignificant for the dominant ($p = 0.64$) as well as for the non-dominant ($p = 0.84$) hand.

5.5 Training effects on motor fatigue (III)

In knee extension FI, the group-by-gender-by-time interaction was not significant. At six months, the FI was reduced by -3.3% (SEM 2.5, 95% CI -8.2 to 1.6) in trained women (n = 30), but increased by 4.3% (SEM 2.5 95% CI -0.7 to 9.4) in the female control group (n = 31). A completely insignificant training effect was seen in trained men (n = 17) with a mean increase of 2.0% (SEM 3.6, 95% CI -5.1 to 9.1) in knee extension FI. The corresponding increase was 1.8% (SEM 3.3, 95% CI -4.8 to 8.4) in the male control group (n = 17). Significant covariates were EDSS ($p = 0.04$), maximal torque ($p = 0.001$), and mean torque ($p < 0.001$). After covariate adjustment, the mean change in knee extension FI was -3.0% (SEM 1.5, 95% CI -6.0 to 0.1) in trained women; in the female control group it was 1.8% (SEM 1.5, 95% CI -1.2 to 4.9), in trained men 3.7% (SEM 2.3, 95% CI -0.8 to 8.2), and in the male control group 1.5% (SEM 2.0, 95% CI -2.5 to 5.5).

In knee flexion FI, the group-by-gender-by-time interaction was significant ($p = 0.01$). Trained women decreased their knee flexor fatigue on average by -1.9% (SEM 1.8, 95% CI -5.4 to 1.6), whereas in non-

trained women there was a significant ($p < 0.05$) mean increase of 5.3% (SEM 1.8, 95% CI 1.7 to 8.8). No differences were found in the changes of knee flexion FI between trained and untrained men, the mean FI change in trained men was 2.8% (SEM 3.3, 95% CI -3.7 to 9.3), and in the non-trained men 2.4% (SEM 3.1, CI -3.9 to 8.8), correspondingly. In contrast to knee extension, none of the covariates showed an association with the FI of knee flexion. Similarly, analysis of covariance with the amount of aerobic or strength training as covariates showed no association between these and the FI of either muscle group.

In trained men, the training effects on motor fatigue over either the supervised three-week training, or the home-based 23-week training phase, were insignificant. By contrast, in trained women, the changes in fatigue resistance followed differing patterns depending on the muscle group. For them, the main improvement in knee flexion occurred already during the first three weeks, whereas in knee extension, the improvement was verified after the home exercise period. Other sex-related differences in motor fatigue included the capability to produce maximal torque more quickly in men vs. women, and a greater and faster torque decline in men than in women after the time point of maximum torque was reached.

5.6 Training effects on disability (II, IV)

The EDSS remained practically unchanged over the course of the six-month period (group-by-time interaction; $p = 0.16$). In the training group, the EDSS score increased on average by 0.1 points. Hence, at six months, the mean score of the group was 2.4 (SD 1.1). In the control group, there was a decrease of 0.1 points in the EDSS over time, making the final mean score 2.6 (SD 1.0). The effect sizes were -0.09 (training group) and 0.09 (control group).

Changes in the MSFC score and its component scores are presented in Table 8. The overall MSFC and the component scores all improved in the training group following the intervention, whereas they deteriorated over time in the control group. The group-by-time interaction for change scores was significant in all variables except for the PASAT. The observed changes remained unaltered after the inclusion of covariates (age, education, employment status, disease duration) in the linear mixed models of the MSFC. Altogether 44% of the participants in the training group, and 20% in the control group showed an improvement in the MSFC score. The effect sizes were 0.16 (training group) and -0.18 (control group).

In the FIM, no training-related effects was seen ($p = 0.84$ for group-by-time interaction). The mean increase over time in the FIM total score was 0.3 points in both groups. The effect sizes were 0.15 (training group) and 0.04 (control group). At baseline, 63% of all study participants had a FIM score of ≥ 124, indicating a considerable ceiling effect of the measure in the studied sample.

Table 8. Changes in the MSFC score and in its component Z-scores at 6 months.

	Training group (n = 47)		Control group (n = 48)		
Variable	Mean change (95% CI)	p-value*	Mean change (95% CI)	p-value*	p-value**
MSFC	0.114 (0.010 to 0.218)	0.031	-0.128 (-0.232 to -0.025)	0.015	0.001
TWT	0.185 (0.041 to 0.328)	0.012	-0.119 (-0.261 to 0.023)	0.101	0.004
9HPT	0.071 (-0.038 to 0.180)	0.200	-0.106 (-0.214 to 0.003)	0.056	0.025
PASAT	0.092 (-0.115 to 0.298)	0.379	-0.161 (-0.366 to 0.045)	0.124	0.088

* p-values denote statistical significance for changes within the groups. ** p-values denote statistical significance for changes between groups with group-by-time interaction. MSFC = Multiple Sclerosis Functional Composite; TWT = Timed 25-Foot Walk Test; 9HPT = Nine-Hole Peg Test; PASAT = Paced Auditory Serial Addition Test.

5.7 Training effects on health-related quality of life, depression and perceived fatigue (III, IV)

No differences were found between the groups on any single subscale, or the physical and mental health composites, of the MSQOL-54 at baseline ($p > 0.1$ in all) or at six months ($p > 0.2$ in all). When adjusted for covariates, sex ($p = 0.078$) and the EDSS ($p = 0.064$) had a slight effect over time on the MSQOL-54 physical health composite. Depression, in turn, had a major influence on the HRQoL, with the CES-D scores being highly significant covariates ($p < 0.001$) both for physical and mental health composites of the MSQOL-54. In terms of effect sizes, the training group showed a small improvement on four MSQOL-54 subscales: role limitation – emotional (0.20), health perception (0.21), sexual satisfaction (0.22), and change in health (0.35). Accordingly, the control group improved on one subscale (sexual function; effect size 0.33), but, worsened on the cognitive function subscale (effect size -0.21). All other effect sizes indicated negligible 6-month changes for both groups.

The intervention had no effect on depression or perceived fatigue. The mean CES-D score at baseline was 14.7 (SD 10.5) in the training group and 15.6 (SD 9.5) in the control group. The mean FSS score was 4.6 in both groups (SD 1.6 training group; SD 1.2 control group) at baseline. In the CES-D, a small decrease in the mean score over time in both groups was observed (training group, 0.4 points; control group 1.2 points). FSS scores, on the other hand, slightly increased by 0.1 point in the training group and 0.2 point in the control group. The minor changes in raw mean scores in both variables were accompanied by statistically non-significant group*time interaction and negligible effect sizes. However, the time effect for fatigue increase approached significance (95% CI -0.02 to 0.36, $p = 0.07$).

5.8 Training adherence and adverse effects (II)

The supervised training groups during weeks 1 – 3 were well attended; there were only a few occasional absences resulting in ~ 98% adherence. For the 23-week home training period, the members of the training group totalled altogether 4135 training sessions. The mean adherence was 93% for all training, 59% for resistance training, and 185% for endurance training. The proportion of participants doing less than one third of the prescribed resistance training was 24%, and of the prescribed endurance training 9%.

The women, overall, adhered better to the training than the men. The mean training adherence for all training was 98% in women and 85% in men ($p = 0.33$ for the difference). However, one woman showed exceptionally high frequency of endurance training (266% of the targeted amount). After omitting her data, the mean adherence dropped to 92%. Of the 75 pre-planned resistance training sessions, women completed 62% vs. 53% by the men ($p = 0.45$ for the difference). The figures for the 24 pre-planned endurance training sessions were 46% vs. 43% ($p = 0.31$ for the difference), correspondingly. The most frequent endurance training mode was walking, followed by cycling and swimming.

Over the course of the trial, 11 MS relapses were treated with steroids. Of these, five occurred in the training group and six in the control group. In both groups, two relapses were experienced by one participant. Analysis of the participants' diaries showed no training-related injuries, and only minor occurrence of MS-related, musculoskeletal or other symptoms (such as dyspnoea or dizziness). All the symptoms and sensations were reported as temporary and perceived as not severe enough to preclude the subjects from further training.

6. DISCUSSION

The present study examined, in a RCT design, the effects of combined resistance and aerobic training on functioning in ambulatory persons with MS (studies II, III, IV). The study showed that long-term exercise training is beneficial in individuals with MS to improve walking speed (both in short and long distances), upper extremity endurance, disability (as assessed by the MS Functional Composite), and, to some extent (in women only), motor fatigue. The trial had a low attrition rate and the training intervention was well tolerated. In addition, in a cross-sectional design the associations between exercise capacity, disability, and leisure-time physical activity were explored (study I). The results indicated that persons with MS show poor cardiorespiratory fitness. Moreover, a main finding was that neurological disability (as evaluated by EDSS) was shown as a predictor of exercise capacity in MS.

6.1 Exercise capacity and its association with disability and leisure-time physical activity (I)

This study examined exercise capacity and its association with neurological disability and leisure-time physical activity in subjects with MS at baseline of the RCT. The results imply that VO_2peak was low in the sample. Disability, as measured by the EDSS, was found to inversely correlate with VO_2peak. In a multivariate regression analysis, disability was confirmed as a predictor of VO_2peak, indicating a relationship between MS severity and aerobic capacity. The study was unable to detect an association between VO_2peak and leisure-time physical activity. Additionally, disease duration and perceived physical fitness were found to be unrelated to VO_2peak.

To date, this is the second largest study to perform a maximal bicycle test with spiroergometry parameters in subjects with MS. The largest study in the field (n = 112) was conducted by Rasova and colleagues (2005). Other studies applying a spiroergometric incremental cycle ergometer test with VO_2peak analyses have been based on clearly smaller samples. VO_2peak is a recognized indicator of endurance exercise capacity and cardiorespiratory fitness (Wasserman et al., 1994). We observed on average 5.3 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} higher relative VO_2peak values in men than in women. This figure is well in line with data from the healthy; for example, Ogawa et al. (1992) reported (after normalization of results to fat-free mass) VO_2max values approximately 15% (range 9 – 19%) higher in men than in women. Such a basic anatomically and physiologically based sex difference in physical performance (Harms, 2006) has often been neglected, and the results may be somewhat misleading in studies on spiroergometry in MS (Ponichtera-Mulcare, 1997; Rasova et al., 2005; Koseoglu et al., 2006; Rasova et al., 2006; Bjarnadottir et al., 2007). In our sample, 64% were women and 36% men. This corresponds well with the female:male ratio of about 2:1 in a MS

population (Noseworthy et al., 2000), and supports the generalisability of our results among ambulatory subjects with MS. Of other "biological markers", we found that age (together with sex), accounted for 30% of variability in relative VO_2peak. This may be an indication of age-related decline in maximal aerobic capacity, which is about 10 – 11% per decade in healthy women (Fitzgerald et al., 1997) and 7 – 9% in healthy men (Wilson & Tanaka, 2000).

Comparison of the VO_2peak results with the normative data of healthy persons indicates that, overall, endurance exercise capacity was markedly reduced in both sexes. Using a 7-point scale ranging from "very poor" to "excellent" (Shvartz & Reibold, 1990), both the male and female subjects' aerobic fitness was "poor". This is in agreement with Mostert and Kesselring (2002) who found up to 30% lower aerobic capacity in 26 MS subjects compared to healthy controls, and with Rasova and colleagues (2005) who observed a decrease in all spiroergometric values in MS subjects as compared to the age- and sex-matched values of an untrained, healthy population. Comparison with results of another autoimmune disease, rheumatoid arthritis, give further perspective to our findings. The mean relative VO_2peak in women in the present study was 21.7 ml · kg^{-1} · min^{-1}. Women with early rheumatoid arthritis (mean disease duration 2.9 years) obtained a value of 26.7 ml · kg^{-1} · min^{-1}, and those with long-term disease (mean disease duration 14.5. years) a value of 23.1 ml · kg^{-1} · min^{-1} (Häkkinen et al., 2002).

The finding of low endurance exercise capacity in MS is comparable to the findings of a number of other investigations. In three other samples including only women with MS, the VO_2peak was 21.1, 21.4 and 21.7 ml · kg^{-1} · min^{-1} (Prakash et al., 2007; Motl & Goldman 2011a). The relative VO_2peak in men and women together was 23.6 ml · kg^{-1} · min^{-1} in our study. Cohen et al. (1989) reported a mean value of 23.5 ml · kg^{-1} · min^{-1} in 16 ambulatory MS subjects (mean EDSS 2.7). Mostert and Kesselring (2002) included two MS groups (n = 13 in both) in their study scoring 4.6 and 4.5 on the EDSS. Their VO_2peak was 22.7 and 22.3 ml · kg^{-1} · min^{-1}, respectively. Morrison et al. (2008) tested sedentary MS subjects with a median EDSS of 2.8. They averaged a VO_2peak of 22.9 ml · kg^{-1} · min^{-1}. More recently, VO_2peak values as low as 17.1 and 18.1 ml · kg^{-1} · min^{-1} have been observed in two MS groups (mean EDSS 4.7 and 4.6) by Bansi et al. (2013).

Studies reporting clearly higher VO_2peak values than ours are few in number. A German study reported a mean VO_2peak of 27.3 ml · kg^{-1} · min^{-1} for an inactive (n = 21, mean age 36 years), and 34.7 ml · kg^{-1} · min^{-1} for an active (n = 21, mean age 39 years) MS group (Tallner et al., 2012). The disability level of both groups was particularly low with a mean EDSS of 1.4 in the active, and 1.2 in the inactive group (Waschbisch et al., 2012). Notwithstanding, also another German study (Schulz et al., 2004) found significantly higher VO_2peaks compared to ours with values of 33.1 and 28.9 ml · kg^{-1} · min^{-1} in two groups matching our cohort well with regard to disability (mean EDSS 2.0 and 2.5) and reasonably well with age (mean 39 and 42 years).

The question whether neurological disability determines exercise capacity in persons with MS has received long-standing attention. An EDSS score of > 2.5 has been found to predict markedly impaired exercise capacity (Cohen et al., 1989). Our findings, however, do not support such a clear-cut limit of reduced VO_2peak. As shown by our regression analyses, it rather follows a linear slope (Figure 3) so that a one point increase in the EDSS corresponds to a roughly 2 ml · kg^{-1} · min^{-1} decrease in relative VO_2peak. Other previous studies on the subject have been inconclusive. Foglio et al. (1994) tested endurance exercise capacity in 24 MS subjects using arm crank ergometry and reasoned that reduction in exercise capacity was related to respiratory muscle function, not to disability level. The average EDSS (5.3) was, however, relatively high in this study and only one third of the participants were able to perform the exercise test acceptably. Ponichtera-Mulcare et al. (1995) compared three types of ergometry in four men and six women with MS (mean EDSS 1.7; mean age 39 years) and found a significant correlation between the EDSS and VO_2peak only when using combined leg/arm, but not leg or arm ergometry. The same group later observed a moderate negative relationship between the two variables in a larger sample (n = 23) using leg/arm ergometry (Ponichtera-Mulcare et al., 1997). More recent findings, also based on a maximal spiroergometric exercise test, are consistent with ours. According to Koseoglu et al. (2006), VO_2peak, as measured using arm crank ergometry, correlated moderately, negatively (r = -0.45) with the EDSS in 25 mainly moderately disabled (mean EDSS 4.4) MS subjects. Using a multiple linear regression analysis, Motl and Goldman (2011a) found disability, measured by a self-reported version of the EDSS, to be an independent correlate of the VO_2peak in a sample of women with RRMS (n = 25).

Epidemiological studies in general populations have predominantly supported a positive association between exercise capacity and physical activity (Cheng et al., 2003; Jackson et al., 2009; Wang et al., 2010). Our data did not support such an association; even the highest amount of aerobic exercise during the previous four weeks did not predict a high fitness in persons with MS. Quite similarly, in the study by Talbot et al. (2000), leisure-time physical activity, across a wide age range of healthy men and women, was only a minor independent contributor to VO_2peak after accounting for the influences of age and body mass index.

Contrary to our observation, other MS studies have mainly supported an association between physical activity participation and exercise capacity. In 80 individuals with MS, 7-day accelerometer activity moderately, inversely correlated with the EDSS (Motl et al., 2008e). The authors, however, warned that a causal relationship could not be established due to the cross-sectional nature of the study. In markedly smaller samples (n = 24 and n = 25), moderate correlations between disability and physical activity as measured by either a questionnaire or an accelerometer have been found (Motl & Goldman, 2011a). Moreover, Motl and McAuley (2011b) showed that a change in physical activity (7-day accelerometry) was associated with a change in disability progression over a six-month period in 292 MS subjects. Thus, a

reduction in physical activity is a behavioural correlate, but not necessarily a cause of short-term disability progression. Finally, pre-morbid physical activity, i.e. physical activity before disease onset, measured by a questionnaire, has been found to be an independent contributor to disability progression in an extensive sample (n = 269) of persons with RRMS (Motl et al., 2012a).

Our results indicate that persons with MS have poor cardiorespiratory fitness already in early stages of the disease. Given that poor cardiorespiratory fitness constitutes the largest attributable fraction (about 16 %) of all causes of deaths worldwide (Blair, 2009), this is alarming since most of our study participants had a relatively recent onset MS (median disease duration 3.0 years), and 45% scored only 2.0 or less in the EDSS. There are several possible explanations for the low VO_2peak in our sample. Obviously, this is related to an inadequate amount of endurance training. The case-control study by Tantucci et al. (1996) concluded that in persons with low-grade disability (n = 10, EDSS 0 to 2.0) exercise capacity appeared limited first and foremost by poor training status. Moreover, a trace training amount may become apparent even in low intensity exertion, such as during the six-minute walk test (Chetta et al., 2004). Another possible explanation is the influence of autonomic nervous system dysfunction, which is frequently found in early MS (Flachenecker et al., 2001). Senaratne et al. (1984) and Cohen et al. (1989) suggested that attenuation of the heart rate and blood pressure responses during exercise may be a consequence of impaired sympathetic stimulation as a manifestation of autonomic innervation. Furthermore, our subjects' poor aerobic capacity may, at least in part, be a consequence of the reduced respiratory muscle function observed in the early phase of MS (Bosnak-Guclu et al., 2012).

Physiological deconditioning due to inactive lifestyle may manifest as limited aerobic capacity (Bogdanis, 2012). This would seem as a plausible explanation since only 22% of the participants in the present study did aerobic endurance training ≥ 1 hour/week. The current position stand for developing and maintaining cardiorespiratory fitness in healthy adults recommends a total of ≥ 150 min moderate intensity or ≥ 75 min vigorous intensity cardiorespiratory exercise training /week complemented by muscle-strengthening activities on two or more non-consecutive days each week (O'Donovan et al., 2010).

Our findings underscore the importance of encouraging people with MS to participate in regular endurance training. The results are well applicable to clinical practice where fitness testing is rarely possible. Our data can be used as indicative information when planning training programmes for persons with MS. For example, an individual with an EDSS score of 3.0 probably has a reduced VO_2peak, which should be considered when prescribing the duration and/or intensity of aerobic training (and other training modes). Published general training recommendations for persons with MS may be additionally helpful in this planning (Dalgas et al., 2008).

6.2 Training effects on walking capacity (II)

The six-month combined training programme was effective in improving walking capacity in persons with mild and moderate MS. Training led to statistically significant and clinically meaningful changes in the primary outcome, the walking speed, measured over both a short (25 ft) and a long (500 m) distance. The study contributes important information on training responses in MS. After the publication of our results, the effects of combined training in MS have been further examined mainly in small studies (Bjarnadottir et al., 2007; Cakt et al., 2010; Charlton et al., 2010; Golzari et al., 2010; Learmonth et al., 2012; Motl et al., 2012c). Only one Irish study (Garrett et al., 2013a) included a sample (baseline n = 314) clearly larger than ours. Moreover, our study is among the few RCTs to address the question of long-term exercise training effects in MS (Oken et al., 2004; McCullagh et al., 2008; Garrett et al., 2013b).

There are several arguments to justify our selection of walking speed as the primary outcome. Walking deficits are a major determinant of overall MS disability measured by EDSS, since the score in its mid-range (from 4.0 to 7.0) is mainly based on ambulatory ability (Kurtzke 1983). Difficulty in walking is a main factor contributing to loss of mobility in MS (Dunn, 2010). Walking speed is highly correlated with, and predicts, activity and participation, and thereby is an important factor of daily living (Kierkegaard et al., 2012). From a practical point, the maintenance of walking speed is crucial, for example, when crossing a signalled intersection (Gijbels et al., 2012).

We included two walking measures to complement each other. The 25FTW is a short, quick, and well-characterised objective measure of walking capacity in MS (Kieseier & Pozzilli, 2012), whereas the 500MWT is basicly a measure of ambulatory endurance (Schwid et al., 1997). Currently, the preferred long walk test would be the Six-minute Walk Test, which can be regarded as a “gold standard” to evaluate walking endurance and functional exercise capacity in MS (Bosnak-Guclu et al., 2012; Gijbels et al., 2012), as well as in a number of other medical conditions such as chronic obstructive pulmonary disease or heart failure (Rasekaba et al., 2009). Owing to its lack of validity/reliability data in MS in 2001, we opted for the 500MWT.

Other combined training studies in MS including a mixture of different types of training modalities have led to somewhat inconsistent results in walking capacity. Learmonth and co-workers (2012) conducted a randomized 12-week group-based combined training study and used the 25FTW as the primary outcome measure. The intervention consisted of mobility, balance and resistance exercises carried out twice weekly in 60-minute-long groups. The training group, with a mean EDSS of 6.2, improved on average by 24% (effect size 0.30), and the non-trained control group, with a mean EDSS of 5.8, by 19% (effect size 0.23) on the

25FTW. The difference between the groups was not significant, and large individual variability was present in both groups. The corresponding 25FTW figures in our study were 12% (effect size 0.50) and 6% (effect size 0.19). More homogenous 25FTW results together with the lower overall disability level in the current trial, probably explains the large differences in the 25FTW gain between the studies.

The results of walking endurance in the Learmonth et al. (2012) study also deviated from our positive findings on 500MWT. They found no training-related effect in the Six-minute Walk Test distance. In another well-designed RCT, both physiotherapist- and fitness-Instructor-led combined 10-week endurance and resistance training significantly improved walking distance (Garrett et al., 2013a), but the improvement was not maintained on re-assessment 12 weeks post-intervention (Garrett et al., 2013b). In a single-group combined training trial by Motl et al. (2012d), the mean 25FTW improvement was 16% (effect size 0.90). Increased post-trial walking speed was accompanied by improvements in spatiotemporal gait parameters (gait velocity, stride length, single support, swing phase). Apart from the training effect, the particularly high effect size was, apparently, a consequence of a small (n = 13) homogenous study group (EDSS range 4.0 – 6.0). Cakt et al. (2010) reported significant post-training improvement on a timed 10-m Walk Test in their eight-week trial in one of the two training groups. However, the training protocol for the group with significantly improved walking speed differed markedly from ours, theirs being based on supervised resistance training on a cycle ergometer complemented by balance exercises. The other active training group, without significant gains in walking speed, received a home-based programme combining lower limb strength training and balance exercises (Cakt et al, 2010).

Walking capacity measures have been widely included in studies evaluating the effects of endurance and resistance training programmes in MS (Harvey et al., 1999; White et al., 2004; Kileff & Ashburn, 2005; van den Berg et al., 2006; Rampello et al., 2007; Newman et al., 2007; Dalgas et al., 2009; Dettmers et al., 2009; Geddes et al., 2009; Broekmans et al., 2010; Filipi et al., 2010; Collett et al., 2011; Dodd et al., 2011). Findings from these studies predominantly corroborate our results on the positive effect of exercise training on walking speed and endurance. Very similar improvements to ours in the 25FTW have been frequently reported in the 10-m Walk Test. The walking speed over 10 m increased by 10% following home-based resistance training (Harvey et al., 1999), by 12% following aerobic treadmill training (Newman et al., 2007), and also by 12 % following supervised resistance training (Dalgas et al., 2009). Our observation of positive training-induced changes in walking endurance have been almost invariably replicated in subsequent aerobic training studies (Kileff & Ashburn, 2005; van den Berg et al., 2006; Rampello et al., 2007; Newman et al., 2007; Dettmers et al., 2009; Collett et al., 2011). Resistance training intervention studies have yielded more discordant results in long walking capacity tests (Two-minute or Six-minute Walk Tests). Dalgas et al. (2009) reported a 15% increment in walking distance, while several other investigations

ended in negligible changes in walking endurance (Taylor et al., 2006; Geddes et al., 2009; Broekmans et al., 2010; Dodd et al., 2011; Hayes et al., 2011).

Cumulative evidence based on meta-analytic procedures from 22 studies, including ours, indicates that exercise training is related to a small improvement (effect size 0.19) in walking mobility in persons with MS (Snook & Motl, 2009). In the meta-analysis, the mode of exercise (aerobic/nonaerobic/resistance/aerobic and resistance) was not a significant moderator of the overall effect of exercise training. Nonetheless, resistance training was associated with larger effects than the other modes of exercise. The possible superiority of either endurance or resistance training was specifically addressed by Sabapathy et al. (2011) in an eight-week cross-over pilot trial. In the Six-minute Walk Test they found an improvement in walking distance favouring resistance training (mean increase 38 m) as compared to endurance training (mean increase 19 m), but the difference was insignificant. This may be, at least in part, related to the low statistical power with only 16 (76%) of participants completing the study.

The intervention approach emphasized strengthening exercises, which may have played a key role in the improvement of walking speed. Particularly the resistive hip flexion and extension exercises done in a standing position may have facilitated movement patterns closely mimicing those of walking. Taylor et al. (2006) suggested that exercised muscles are able to generate force more efficiently than unexercised muscles to enable physical activities (such as walking) to be performed without the need to slow down or rest over a period of time. To further back up this argument, two uncontrolled studies have shown that resistance training induces positive changes in gait kinematics in subjects with MS (Gutierrez et al., 2005; Filipi et al., 2010), possibly resulting in more co-ordinated and less energy-demanding walking patterns (Motl et al., 2010). Similar findings were observed by Huisinga and co-workers (2012b) after an elliptical training intervention including 15 sessions over six weeks. Conversely, two small non-controlled studies with non-specific training of walking have reported negligible changes in gait parameters in persons with MS. Ten weeks of aquatic exercise did not significantly alter walking cadence, stride length, or lower limb joint kinematics (Gehlsen et al., 1986), and six months of cycle ergometer training had minimal or no effect on walking velocity, cadence, ground reaction forces, or three-dimensional walking kinematics (Rodgers et al., 1999).

6.3 Training effects on balance, muscle strength, upper extremity endurance and function (II)

The intervention had no effect on balance and gross manual dexterity. Regarding muscle function, it improved upper extremity endurance, but did not produce significant changes in maximal isometric knee extension and flexion strength.

The negative finding on balance differs from the results of most other combined training studies in MS (Cakt et al., 2010; Charlton et al., 2010; Golzari et al., 2010; Learmonth et al., 2012). In addition, a number of studies employing endurance (Schulz et al., 2004; Sabapathy et al., 2011; Salem et al., 2011) or resistance training (Broekmans et al., 2010; Filipi et al., 2010; Sabapathy et al., 2011; Huisinga et al., 2012a) have also shown improved balance in persons with MS. The negative result in the present trial may be related to training specificity, a concept according to which the best gains in measured performance are achieved when the training closely mimics the performance (Wilson et al., 1996). In a systematic literature review, Paltamaa and co-authors (2012) pointed out that the interventions to improve balance in MS should be based on specific balance exercises. In the present study, the home training programme, apart from two resistive exercises done in a standing position (hip flexion and extension), challenged only slightly, if at all, postural control, reflecting the non-specific nature of the intervention with regard to balance.

Another cause underlying unchanged balance scores may be linked to measurement methodology. Studies reporting positive training responses on balance have employed a wide variety of measures differing from the one used, the Equiscale, in our study. The Equiscale is an 8-item clinical balance measure specifically validated for persons with MS using the rigorous Rasch-analysis method (Tesio et al., 1997). However, the sensitivity of the Equiscale remains unexplored. It may well be prone to a ceiling effect in mildly impaired MS subjects similar to the widely used 14-item Berg Balance Scale (Karst et al., 2005; Cattaneo et al., 2006). The high baseline Equiscale scores in both study groups, 14.4 (training group) and 15.0 (control group) out of the maximum 16, supports such a phenomenon. In other studies the most commonly applied measure has been the Functional Reach (Broekmans et al., 2010; Cakt et al., 2010; Sabapathy et al., 2011), a test of self-generated perturbation (Frzovic et al., 2000). Other measures have included self-report or performance-based scales, subjective balance estimation, or force-platform devices (Cakt et al., 2010; Charlton et al., 2010; Filipi et al., 2010; Golzari et al., 2010; Salem et al., 2011; Huisinga et al., 2012a; Learmonth et al., 2012).

Two measures of upper extremity performance were included, weight lifting (with dumb-bells) and the Box and Block tests, in the assessment battery. Such a practice is rare in MS training studies. Consequently, our study, together with that of Petajan et al. (1996), is so far the only RCT in the field to show improvement in

upper extremity performance in MS. Two other RCTs utilizing grip strength as an outcome found no improvements following either strength or endurance training (Dalgas et al., 2009; Sabapathy et al., 2011). Instead, one non-controlled study found increased grip strength after a five-week aquatic exercise programme (Salem et al., 2011). In addition, two other resistance training studies employing single group design have reported improvements in upper limb strength (Taylor et al., 2006; Filipi et al., 2011), and one in gross upper limb function (Ayán Pérez et al., 2007). In the current study, gross manual dexterity was assessed using the Box and Block test. Our training programme was presumably too non-specific to match such a functional measure to produce improvements. Particularly, because upper limb function was relatively intact in our study subjects as evidenced by the average Box and Block test results, falling reasonably well within the range of normative data for healthy adults (Mathiowetz et al., 1985). By contrast, and supporting a range-of-motion type training specificity (Morrissey et al., 1995), one of the two strengthening exercises for the upper limbs closely resembled the weight lifting test to measure upper extremity endurance. This may well be the causal chain behind the positive results in upper extremity endurance.

No strength gains were seen in knee extensor muscles, whereas significant increases in knee flexion strength were observed within the training group. Such results are open to multiple interpretations. The discrepancy may be a consequence of the inadequate training load produced by the elastic bands on the knee extensors compared to the knee flexors, owing to the fact that, characteristically, the maximal strength of the extensor muscle group is approximately double that of the flexors in ambulatory persons with MS (Schwid et al., 1999; Thoumie et al., 2005). There are, however, data to support the effectiveness of resistive band training to improve isometric knee extension strength in persons with stroke (Duncan et al., 2003). Nevertheless, the control group also partly significantly improved lower limb strength (right knee flexors), and no between-group differences over time were observed in this outcome. This may possibly arise from high variability in the strength values, which could have precluded an interaction in the overall analysis model. Another explanation behind the scarce improvements may lie in the lower than expected training adherence, with as many as 24% of the participants in the training group engaging in less than 1/3 of the prescribed resistance training. This fact is supported by the wide 95% CIs in the strength measures which suggest there may have been a true training effect in part of the training group members.

6.4 Training effects on motor fatigue (III)

Overall, training responses on motor fatigue were modest; the FI was significantly reduced only in knee flexors, and only in women undergoing the training intervention. Despite training adherence being clearly

higher in women than in men, the different group responses found in FI could not be explained by the amount of training.

Motor fatigue (or muscle fatigue), defined as “a decline in motor performance during sustained muscle activity” (Schwid et al., 2002) is a distinct component of the multidimensional construct of fatigue in MS (Kos et al., 2008; Mills & Young, 2008). Long-standing efforts have been made to examine the pathophysiological mechanisms of motor fatigue in MS, including intramuscular factors and impaired central activation (Sharma et al., 1995; de Haan et al., 2000; de Ruiter et al., 2001; Garner et al., 2003; Thickbroom et al., 2006; Scheidegger et al., 2012). In the light of this, it is surprising that research on the effects of exercise therapy has almost exclusively focused on perceived aspects of fatigue (Andreasen et al., 2011). We are aware of only one previous study addressing the question of exercise responses on motor fatigue in MS as measured by a rigorously defined objective method. Gehlsen and colleagues (1984) were able to detect a significant 14% decline (of which 13% already at mid-trial) in lower extremity muscle fatigue after a 10-week aquatic training programme in 10 subjects with MS. No significant changes were observed in upper extremity fatigue. Our observation of the major improvement in knee flexor fatigue occurring already after three weeks of training is congruent with this early work, particularly bearing in mind that one half of the training in our trial consisted of aquatic training during its initial stages. The stimulus provided by aquatic training combined with training-induced neural adaptations to resistance training (Sale, 1988) possibly contributed to the improvement in knee flexor fatigue already after three weeks of training.

Our findings on the FI may accrue from sex-related differences in human skeletal muscle fatigue, that is, women may be less fatigable than men due to disparities within the neuromuscular system that influence physiological adjustments during a fatiguing task (Hunter, 2009). Accordingly, healthy women are usually able to sustain a muscle contraction on a higher level and for a longer duration than men (Wüst et al., 2008), a finding also discerned by our FI analyses in subjects with MS. Moreover, de Haan et al. (2000) reported that excessive motor fatigue in knee extensor muscles was present only in male, not in female subjects with mild to moderate MS (mean EDSS 3.8) as compared to age-matched, inactive or mildly physically active healthy controls. Because the men in our study (training and control groups taken together) tended to show more progressive and disabling MS than the women, one could assume that these differences might contribute to the mixed results concerning motor fatigue. However, our data showed that the EDSS was a significant covariate only in the analysis models of knee extension, and similarly in both sexes.

The training programme in the present study was not targeted to affect motor fatigue as the primary outcome. Probably greater physiological benefits could have been obtained via high-intensity intermittent training, compared with moderate-intensity continuous training, as ascertained by evidence from other conditions resulting in physiological deconditioning, such as pulmonary and coronary artery diseases (Bogdanis, 2012). The feasibility and effectiveness of such a training regimen remain practically unexplored in MS. However, Fimland and co-workers reported enhanced neural drive, a factor affecting motor fatigue (Albert et al., 2006), in their RCT following a three-week maximal strength training programme accompanied by conventional rehabilitation exercises in MS subjects.

6.5 Training effects on disability (II, IV)

Using three recognized disability measures, positive results were found in one, the MSFC, but unchanged scores in two, the EDSS and the FIM. Rather little evidence exists for physical training in slowing the progression of MS as measured by a clinical scale (Dalgas & Stenager, 2012). The present study is among the few trials to report such a benefit.

EDSS is the most widely used assessment scale for disability in epidemiological studies of MS. It is also the only measure for disease progression approved by the healthcare regulators in clinical drug trials of MS (Goldman et al., 2010; van Winsen et al., 2010). Accordingly, it has been the most commonly used disability measure also in MS training studies (Rodgers et al., 1999; White et al., 2004; Bjarnadottir et al., 2007; Dalgas et al., 2009; Fimland et al., 2010; Golzari et al. 2010). Only one RCT, by Golzari et al. (2010), has reported a mean improvement of 0.5 points on EDSS following an eight-week combined training programme in women with RRMS. However, due to intra/inter-rater inconsistencies of the scale, changes of ≤ 0.5 cannot be seen as evidence of true improvement in disability (Ebers et al., 2008).

The MSFC was developed to overcome the psychometric limitations (sensitivity, reliability, rater-to-rater variability, responsiveness) of the EDSS (Cutter et al., 1999). Hence, we chose it as a disability outcome measure. MSFC had not been applied in clinical rehabilitation trials previous to the current study and, to our knowledge, it has not been used since in other randomized MS training intervention studies either. The fact that MSFC showed improvement in the training group vs. deterioration in the control group is in line with Patzold et al. (2002) and Ozakbas et al. (2005) who concluded that the MSFC is a more sensitive measure than EDSS to catch a treatment effect in function.

The improvement in MSFC was primarily accounted for by the 25FTW, which is contrary to Uitdehaag et al.'s (2002) finding that MSFC outcomes were predominantly weighted by 9HPT changes. Fox and

colleagues (2007) have presented support for equal weighting of the three MSFC components in longitudinal studies, especially if the reference population is the study population at baseline. We agree with Goldman et al. (2010) that dependence on a reference population for Z-score calculation is a major disadvantage of the MSFC, severely affecting comparisons across studies.

Recognising that the training intervention mainly focused on gross motor function, the 25FTW-dominant MSFC Z-score change was perhaps not so unexpected. The improvement may be related to knee flexion strength, which significantly increased in both legs within the training group. Using the 25FTW and the Two-minute Walk Test, Broekmans et al. (2013) showed that maximal knee flexor strength, like knee extensor muscle endurance, is a main predictor for walking capacity in persons with MS. The 25FTW is not prone to the same practice effects, i.e. improved performance and decreased session-to-session variability (Cohen et al., 2001), as the other MSFC components, the PASAT and the 9HPT (Solari et al., 2005), thus supporting the reliability of the improved MSFC score in our study. For the PASAT and the 9HPT, three and four pre-baseline testing sessions, respectively, have been recommended (Solari et al., 2005). For logistic reasons, we were unable to organize these. If practice effects influenced the results, they were, however, probably similarly distributed in both groups.

Improvement in FIM has been shown in a number of clinical rehabilitation trials of multidisciplinary rehabilitation in MS (Freeman et al., 1997; Solari et al., 1999a; Patti et al., 2003b; Khan et al., 2008). Apart from the differences between the interventions, all these studies have included subjects with advanced disability levels (average FIM score < 120 in all). Acknowledging the fact that over half of the sample in the present study had a FIM score ≥ 124 (out of 126), it is evident there was a marked ceiling effect. Indeed, precautions regarding the usefulness of the FIM in clinical trials of MS have been suggested in relation to its insensitivity to change and its ceiling and floor effect vulnerability (Sharrack & Hughes, 1996; Sharrack et al., 1999).

6.6 Training effects on health-related quality of life, depression, and perceived fatigue (III, IV)

No statistically significant changes in HRQoL were seen. The effects sizes of several MSQOL-54 scale scores favouring the training group suggest, however, that regular training emphasizing resistive exercises might have had an impact on HRQoL. The effect size is a recognised distribution-based method to define clinically meaningful change in HRQoL (Crosby et al., 2003). Compared to other combined training RCTs, our results are much in line with Learmonth et al. (2012), reporting a clinical effect (calculated as percentage change from baseline to study termination) in HRQoL in 26% of the trained participants vs. 13% in the controls, without a statistically significant group difference. Very similarly, Bjarnadottir et al. (2007) found a

statistically significant change in only one of the eight subscales of the SF-36 quality of life measure, but considered the tendency towards a statistically significant change in five subscales as a clinically important finding. Further, also using the SF-36, Cakt et al. (2010) observed statistically significant improvements in two subscales in the supervised training group vs. in one subscale in the home-based group vs. no changes in the control group.

Accumulating evidence from three successive meta-analyses indicates a rising trend affirming exercise training as a viable means to improve HRQoL in MS. In 2005, Rietberg et al. found no evidence of exercise therapy vs. no exercise on HRQoL as an outcome; in 2008, Motl and Gosney reported a weighted mean effect size of 0.23 on HRQoL-associated training effects, and in 2012, Kuspinar et al. observed an effect size of 0.43 related to training interventions on HRQoL in MS. The magnitude of the effects in the two latter publications is comparable to those from disease-modifying or symptomatic medications (Motl & Gosney, 2008b; Kuspinar et al., 2012).

There are multiple potential reasons why our results differ from the overall positive trend of training responses on HRQoL in other studies. First, the type of training modality may have had a fundamental influence, a vast majority of the studies reporting positive changes in HRQoL have employed some form of endurance training (Petajan et al., 1996; Sutherland et al., 2001; Mostert & Kesselring, 2002; Schulz et al., 2004; Roehrs & Karst, 2004; Rasova et al., 2006; Rampello et al., 2007; McCullagh et al., 2008; Huisinga et al., 2011; Sabapathy et al., 2011; Kargarfard et al., 2012). Secondly, the length of intervention and the volume of weekly training may serve as moderators of the overall training effects on HRQoL. Consequently, interventions of < 3 months and exceeding 90 min/week may ensure the best training stimulus to ensure improvement in HRQoL in persons with MS (Motl & Gosney, 2008b). On the other hand, a large (n = 430) exercise trial on postmenopausal women clearly showed that higher doses of exercise over a six-month period were associated with larger improvements in both mental and physical aspects of quality of life (Martin et al., 2009). Moreover, data from a systematic review clearly support a positive association between more leisure-time physical activity and better quality of life in healthy elderly adults and individuals with different clinical conditions (Pucci et al., 2012). Thirdly, differences in training responses on HRQoL in MS may be attributable to the setting, in that motivational aspects of social support connected with supervised training are superior to non-controlled home-based training alone (Petajan et al., 1996; Rampello et al., 2007; Cakt et al., 2010). These should, however not be considered as mutually exclusive; home-based training in other chronic conditions such as chronic obstructive pulmonary disease and knee osteoarthritis has resulted in improved HRQoL (Behnke et al., 2000; Baker et al., 2001).

In good agreement with the existing literature (Solari et al., 1999b; Nicholl et al., 2001; Amato et al., 2001; Patti et al., 2003a; Benedict et al., 2005; Montel & Bungener, 2007), depression strongly affected participants' HRQoL. In the present study this aspect was not particularly accounted for. Nonetheless, research results addressing training responses on depression in MS are thus far utterly conflicting. Irrespective of training type, some of the studies have shown a reduction in depressive symptoms and/or improved mood (Petajan et al., 1996; Rasova et al., 2006; Cakt et al., 2010; Charlton et al., 2010; Dalgas et al., 2010a), others not (Oken et al., 2004; Schulz et al., 2004; Dettmers et al., 2009; Sabapathy et al., 2011; Learmonth et al., 2012). The divergent results may be, similarly to training responses on perceived fatigue in MS (Andreasen et al., 2011), due to study samples which have not comprised persons with clearly defined levels of clinical depression. Subsequently, many studies, like ours, have involved relatively non-depressed subjects.

In the light of the fact that the study participants were an unselected group regarding their depressive and fatigue symptoms, the negligible changes in these secondary outcomes were not entirely unexpected. Depression and perceived fatigue often co-occur in MS (Kos et al., 2008). This is one possible explanation for the scarce results of the two resembling each other. We agree with Fischer et al. (2011) that future behavioural interventions in MS, including exercise training, should aim to better differentiate between depression and fatigue.

In opposition to motor fatigue, training responses on perceived fatigue have been extensively evaluated in MS. Andreasen and co-workers (2011) addressed the question in a systematic review based on 21 trials (the current study included). Among other things, they concluded that all types of training have the potential to reduce MS fatigue, but the findings were heterogeneous, e.g. because only few studies evaluated fatigue as the primary endpoint, and because most of the subjects in the studies were non-fatigued patients. Furthermore, Andreasen et al. (2011) noted that selection of the assessment method may have an influence on the mixed results. In the present study the FSS was chosen as the fatigue measure owing to its wide use in MS research (Bakshi, 2003). However, Mills et al. (2009), using Rasch analysis, questioned the validity of the FSS. Instead, the Fatigue Scale for Motor and Cognitive Functions (FSMC) is currently recommended for the assessment of fatigue in MS (Elbers et al., 2012). Given that the FSMC accounts better than the FSS for the multidimensional nature of MS-related fatigue by differentiating between cognitive and physical aspects of the symptom, and that it presents clear cut-off values for fatigue severity (Penner et al., 2009), today it probably would have been our number one choice for the fatigue scale.

6.7 Training adherence (II)

Training adherence for the first three supervised weeks was excellent (~ 98%). As was also the adherence for the home training (93%), as derived from the exercise diaries. However, there was an imbalance between the planned and actually realized training mode. Endurance training with an adherence of 92% (with one outlier excluded) was preferred over resistance training (59%). Considering that the 23-week home training protocol emphasized resistance training (3–4 times/week vs. once weekly endurance training), the result was not as intended. Another aberrance from the training protocol was that participation in aquatic training was infrequently reported in spite of the fact that it was the recommended mode of endurance training for the home training period (based on the positive experiences during the in-patient training period). This shortcoming may have been related to the limited accessibility to aquatic training since the participants came from all over Finland, and often from small communities, where the availability of such a training mode was probably often limited.

There has been a marked variation in adherence rates across training intervention studies in MS. Usually such information has been neglected. For combined training, Cakt et al. (2010) reported an average adherence rate of 93% in the supervised, and 60% in the home-based group, whereas the corresponding figure was 77% in the study by Learmonth et al. (2012), and 81 % in the study by Motl et al. (2012d). Adherence rates for endurance training have ranged from 45% (Oken et al., 2004) to 97% (Petajan et al., 1996), and for resistance training from 69 % (Harvey et al., 1999) up to 100 % (White et al., 2004; Gutierrez et al., 2005).

Adherence to training prescription in persons with MS seems to be influenced by the extent of supervised or unsupervised activity, and individual or group support given. With one exception (DeBolt & McCubbin, 2004), studies utilizing supervised training, preferably in a group, have shown the highest adherence rates (≥ 88%). The appeal of supervised vs. unsupervised training was well depicted by McCullagh et al. (2008); in their pilot RCT all subjects (n = 17) completed at least 20 of the 24 supervised exercise classes, but none of them more than half of the 12 home sessions. Comparable figures were reported by Oken et al. (2004), in their six-month trial, the attendance rate in the exercise intervention arm for weekly supervised ergometer cycling classes being 65% but 20% less for weekly home exercise including first and foremost cycling, which was complemented by periodical Swiss ball exercises.

The 23-week home training programme in the present study comprised four to five weekly training sessions. Thus, it is possible that simply lack of time may have limited the prescribed activity, particularly in the 62% of the training group that was employed. Indeed, shortage of time represents a common barrier to

exercise participation. It is, however, not the only explanation for the poor adherence. Perri et al. (2002) have shown that a prescription for a higher frequency of training (5 – 7 days per week) resulted in similar adherence compared to a moderate frequency (3 – 4 days per week) of training in a large (n = 379) six-month trial in inactive healthy persons.

To ensure commitment and to facilitate training motivation, the members of the training group were regularly contacted by phone (by A. Romberg) four times over the home training period. In physically inactive, healthy middle-aged persons such a procedure has been described to result in equal adherence rates and increases in fitness following low-intensity home-based training when compared to the high-intensity supervised group-based training over a one-year period (King et al., 1991). In that study there were, however, as many as 16 phone contacts, which is more frequent than the number of calls in the present study. This implies that more frequent contacts might have ensured better commitment to the resistance training protocol. Another practical option to improve adherence could have been the use of videotaped instructions (Reo & Mercer, 2004). This method was used by DeBolt and McCubbin (2004) who prepared an instructional video of their home-based resistance training programme to be given to each of the training participants. As a result, the adherence to the eight-week programme was excellent (95%).

6.8 Adverse effects of training (II)

The relapses (exacerbations, bouts) of the disease were evenly distributed between the training and control groups, indicating that exercise training had no deleterious effects on MS disease progression. Earlier, Petajan et al. (1996) reported a similarly balanced distribution of relapse rates (training group, n = 4; control group n = 3) in 54 subjects over a 15-week endurance training intervention. Further, Bjarnadottir et al. (2007) recorded identical relapse rates in the training and the control group (n = 1 in both groups) over a combined training intervention. More recently, these observations were extensively replicated by Tallner et al. (2012), who showed that MS relapses were not associated with exercise, either in a retrospective (n = 632), or a cross-sectional examination (n = 42). In these analyses only the latter included a clinical validation of relapses, whereas the former was based on self-reports. In our study, only those demanding steroid treatment and confirmed by a physician were taken into account.

Apart from a few minor exceptions (Ponichtera-Mulcare et al., 1997; Rampello et al., 2007; Collett et al., 2011), exercise training has been well tolerated by persons with MS, and the reported adverse effects have been rare. Our observations match these overall implications well. Based on the data from the exercise diaries, we argue, similarly to Smith and associates (2006), that the augmentation of MS symptoms, such as fatigue or sensory disturbances, after training sessions is only a temporary phenomenon, and does not lead

to long-term detrimental effects. Theoretically, as outlined by Waxman (2006), physical activity can contribute to axonal energy depletion at various stages of MS, and thus to axonal injury resulting in deleterious changes in symptoms. Empirical findings from our, as well as those from other MS training studies, do not, however, support such reasoning.

6.9 Study strengths and limitations

The results of the present work should be evaluated in the light of certain methodological issues. The external validity of studies I – IV is high owing to the large sample size based on an antecedent statistical power calculation. Hence, the results are widely generalizable to MS subjects with mild and moderate disability. In studies II, III and IV, the RCT design, which represents the gold standard in evaluating clinical interventions (Schulz et al., 2010), was used. Another major strength of the study is the length of the follow-up, which is among the highest in the field.

In terms of external validity, we have reason to believe that the differences between the results for training and the control group were not a consequence of chance (studies II, III, IV). First, the drop-out rate from enrolment to final assessments was low and evenly distributed between the groups (n = 4/4). It has been suggested that a drop-out rate of less than 20 % for short-term and less than 30 % for long-term follow up ensures unbiased results (van Tulder et al., 2003). Secondly, our results were based on an intention-to-treat principle to ensure an unbiased group comparison provided by randomization. Thirdly, in the primary and in several of the secondary outcomes, the principal statistical tests were complemented by a series of covariate analyses to control for the confounding effect of, e.g., demographic variables. Fourthly, our results were not solely based on statistical significances, since we also calculated the effect sizes for most of the outcomes to assess the clinical significance of the findings.

In study I, a particular strength was the high number of participants able to complete the incremental exercise test satisfactorily (92 out of 95). Further, the average rating of perceived exertion (19.3 of 20) at the termination of the test indicates that the subjects reached more or less their maximum level of effort. This is quite opposite to the largest study in the field (n = 112), in which as many as 76% of the subjects quit the test prematurely because of sudden lower limb weakness, and the average rating of perceived exertion was as low as 14.2 (Rasova et al., 2005).

A certain limitation of our study was the lack of blinding (studies II, III, IV), an irresistible problem in exercise training trials in MS (Asano et al., 2009; Kjølhede et al., 2012). Unblinded assessments serve potentially as a source of observational bias, a shortcoming we aimed to eliminate by strictly following the

practical guidelines set for independent assessment in RCTs of rehabilitation (Siemonsma & Walker, 1997). Accordingly, the assessor of the clinical measurements was, e.g., not allowed to view other research data and, at the time of the follow-up measurements, to review the baseline data. Subject blinding could not be carried out for logistic reasons (i.e. all the participants took part in inpatient rehabilitation programme) making our trial vulnerable to the Hawthorne effect. In the clinical trial setting, this is defined as "altered study subjects' behaviour or study results by the subjects' awareness that they are being studied or if they received additional attention" (Fernald et al., 2012). At the time of the baseline study visit, the members of the control group were advised to avoid any greater changes in their physical activity habits during the following six months. Nonetheless, we cannot overrule the possibility that they behaved otherwise because of the lack of, e.g. exercise diary information. Consequently, the modestly improved performance seen in the control group in some of the clinical measures (e.g. the 25FTW and left knee flexion strength) may have been attributed to the Hawthorne effect. Another means to eliminate this effect in the control subjects was to offer them an opportunity at study termination to participate in inpatient rehabilitation courses for 3 weeks, which, with regard to physical training, were identical to those arranged for the training group members at the beginning of the study.

We were forced to complete the random allocation of the subjects to groups before fully confirming their eligibility. The reason for this is related to the fact that the from all over Finland were on the waiting list for inpatient rehabilitation courses and randomization had to be carried out before setting the dates for the inpatient courses. Because of the sometimes long travelling distances, the subjects could not be examined before final acceptance to the study. However, we believe that the post-randomization exclusions were legitimate because the subjects never received the intervention, and because an independent adjudication committee systematically reviewed all the included and excluded subjects, as recommended (Fergusson et al., 2002).

An obvious flaw in study I was the use of a non-validated physical activity questionnaire. This limitation has been also acknowledged by other researchers (Motl & Goldman, 2011a). Considering the large sample size, a questionnaire, owing to its practicality, was our chosen method to assess physical activity. Validity data of self-report physical activity questionnaires in MS have not been available until 2006 and 2007 (Motl et al., 2006a; Gosney et al., 2007). In the questionnaire we used, the amount of leisure time physical activity was determined on the basis of sports and recreational activities only. It might have been appropriate to also consider household, occupational and/or commuting activities, particularly because a majority of the sample was employed. We recognize that one possible option for the assessment of physical activity would have been the use of a broader questionnaire designed for population-based studies. A wide range of such

questionnaires, with reasonable validity and reliability in healthy persons, are available, of which many already before the 1990s (van Poppel et al., 2010).

Finally, irrespective of the questionnaire used, our subjects' levels of physical activity may have been influenced by seasonal factors. The physical activity data were collected over a six-month period from autumn to winter when outdoor activities in Finland may be limited compared with the spring and summertime.

7. CONCLUSIONS

Based on the findings, the following conclusions can be drawn from this study:

1. Persons with MS present with low cardiosrespiratory fitness already in relatively early stages of the disease. Considering the overall, mainly mild disability of the sample, inadequate aerobic endurance training was probably the cause behind the finding. Explicitly, the influence of neurological disability on the pathophysiological pathways affecting cardiorespiratory fitness cannot, however, be excluded. Exercise capacity, in terms of VO_2peak, and neurological disability, as measured by EDSS, were inter-related in such a way that MS subjects with more disability had lower VO_2peak. The study failed to show an association between VO_2peak and self-reported leisure-time physical activity.

2. Six-month combined physical training, initiated during inpatient rehabilitation and continued at home with three to four weekly resistance, and once weekly endurance training, led to both statistically and clinically significant improvements in walking speed over short (25 ft) and long (500 m) distances. These improvements were accompanied by significant increases in upper extremity endurance. MS clinical relapses were evenly distributed between the two study groups, indicating that training has no detrimental effect on MS activity. Taken together, long-term exercise training is safe in MS, benefits persons with the disease, and should be prescribed in clinical practice for those with mild or moderate disability.

3. The six-month training programme reduced motor fatigue in the lower limbs only in women, not in men. Perceived fatigue remained unaffected following the training. The results on motor fatigue may be a consequence of sex-related differences in skeletal muscle fatigue. Notwithstanding, the training programme may have not been specific enough to influence motor fatigue. Both resistance and endurance training are viable means to produce favourable effects on motor fatigue. However, training programmes, irrespective of their modalities, should clearly be more intensive than the programme in the current study to be able to significantly reduce motor fatigue in persons with MS.

4. The physical training intervention significantly reduced MS-related disability as assessed by MSFC, but not using other disability measures (EDSS and the FIM). Compared to EDSS and the FIM, MSFC may be more sensitive to show clinical treatment effects, i.e. changes over time. The intervention had no significant effect on HRQoL. However, the effect sizes favouring the training group suggest that the intervention may have had some clinical effect on some HRQoL composites. The modest finding on HRQoL may be related to the nature of the training, which predominantly consisted of exercises done alone at home over a relatively

long time period. The lack of peer support and socialization, as compared to group-based exercise, may have been the key elements behind the scarce results in terms of HRQoL.

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Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis

A Romberg[*,1], *A Virtanen*[2], *S Aunola*[2], *S-L Karppi*[2], *H Karanko*[2] *and J Ruutiainen*[1]
[1]*Masku Neurological Rehabilitation Centre, 21251 Masku, Finland;* [2]*Research Department, Social Insurance Institution, 20720 Turku, Finland*

The purpose of the present study was to examine exercise capacity and its relationship to neurological disability as measured using the Expanded Disability Status Scale (EDSS) and to leisure physical activity in subjects with multiple sclerosis (MS). Thirty-four men and 61 women (mean age 44 ± 6.7 years, mean disease duration 5.7 ± 6.4 years) with mild to moderate disability (EDSS range 1.0–5.5) participated. They underwent an incremental exercise test on a leg cycling ergometer. Leisure physical activity was measured using a questionnaire. Peak oxygen uptake (VO_2peak) in men was 27.0 ± 5.2 mL/kg/min, and in women 21.7 ± 5.5 mL/kg/min. The disability correlated inversely with the VO_2peak both in men ($r = -0.50$, $P = 0.004$) and in women ($r = -0.25$, $P = 0.05$). No correlation between disease duration and VO_2peak was found. In a multivariate regression analysis, neurological disability was confirmed as a predictor of VO_2peak. No evidence of a relationship between leisure physical activity and VO_2peak was found. A main finding was that disability and exercise capacity are inter-related, even in subjects who are not severely handicapped (84% had an EDSS of < 4.0). The level of disability should be taken into account in the planning of aerobic exercise programs for fully ambulatory MS subjects.
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Key words: *disability; exercise; exercise testing; multiple sclerosis; peak oxygen uptake; physical activity*

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that destroys myelin, oligodendrocytes and axons.[1] MS typically has its onset in early adulthood and has a variable prognosis.[2] Its clinical picture is characterized by a multitude of neurological symptoms, such as disturbances of bladder function, fatigue, motor weakness and sensory disturbances. Finland belongs to a high-risk Fennoscandian zone, with a disease prevalence of about 100/100 000. MS is estimated to affect approximately 6000 persons in the country.[3]

Exercise capacity can be evaluated by measuring maximal external work rate or maximal/peak oxygen uptake (VO_{2max}) achieved during a progressive ergometry test. VO_{2max} describes cardiovascular capacity of the body to transport oxygen and the capacity of exercising muscles to use it for external muscle work and body metabolism. VO_{2max} is dependent on alveolar ventilation, diffusion of oxygen in the lungs, total blood haemoglobin, cardiac output, blood volume, peripheral circulation in exercising muscles, oxygen extraction capacity from blood and fibre type composition.[4]

*Correspondence: Anders Romberg, Masku Neurological Rehabilitation Centre, PO Box 15, FIN-21251 Masku, Finland.
E-mail: anders.romberg@ms-liitto.fi
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In a chronic disease such as MS, it is important to maintain cardiovascular capacity as well as possible in order to ensure independence in daily life.[5] Studies evaluating exercise capacity of subjects with MS have not shown unambiguously whether VO_{2max} is related to neurological disability,[6–8] as measured using the Expanded Disability Status Scale (EDSS).[9] In one study, VO_{2max} in MS subjects with a wide EDSS range (2.0–8.5) was related to reduced respiratory muscle function rather than to disability.[6] Other investigations suggest that VO_{2max} may correlate inversely to EDSS in mild to moderate MS.[7,8] All these studies suffer from small sample size ($n \leq 24$ in each), and the results should, therefore, be interpreted with caution. The studies are also subject to criticism because men and women have been reported as one group, although men in all age groups have higher VO_{2max} values than women.[10,11]

A number of studies have investigated the effects of regular training on VO_{2max} in MS.[8,12–14] Persons with the disease are able to exercise efficiently enough to improve their aerobic fitness and the observed gains in fitness are independent of disease severity.[13,14] Less attention has been paid to the possible relationship between leisure physical activity and VO_{2max} in MS. Physical activity as a whole is reduced in subjects with MS.[15,16] This could, at least to some degree, explain these subjects' impaired exercise capacity.[14] In healthy people aged 25–55 years, it has been shown that leisure physical activity is related to VO_{2max}.[17] On the other hand, in a study population across a broader range of age (18–95 years) this was not the case.[18] A study of patients with Parkinson's disease suggests that regular physical activity helps to maintain

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normal exercise capacity.[19] This may also be true of other neurological diseases, such as MS.

The main purpose of the present descriptive cross-sectional study was to examine the relationship between exercise capacity and neurological disability in men and women with mild to moderate MS. In addition, we wanted to find out if leisure physical activity is related to exercise capacity.

Materials and methods

The subjects, 95 patients with mild to moderate MS, were selected from a waiting list of an inpatient rehabilitation programme at a neurological rehabilitation centre. Eligible subjects had a clinically supported or laboratory confirmed diagnosis of MS.[20] They were aged 31–54 years with an EDSS score of 1.0–5.5. The exclusion criteria were a relapse during a preceding month or any other disease likely to interfere with the prescribed exercise testing. Two of the subjects were using beta-adrenergic blockers at the time of the study. The study was approved by a local ethical committee. All subjects gave their written informed consent to participation in the study.

Neurological examination

All subjects underwent a complete neurological examination, and the neurological impairments and disability were scored by two experienced raters according to the Functional Systems and the EDSS.[9] Information was obtained of subjects' disease and physical characteristics, medication, other diseases than MS and smoking habits.

Exercise test and peak oxygen uptake (VO_2peak)

A two-minute incremental exercise test on an electromagnetically controlled cycle ergometer (Rodby Ergometer RE 820®, Södertälje, Sweden) until volitional exhaustion or fatigue of the lower limbs was used for measurement of the VO_2peak. Because of uncertainty about how close to their maximum the subjects would cycle, we used the term VO_2peak instead of VO_{2max}.

The subjects pedalled at a constant frequency of 60 rpm. The test was preceded by a four-minute warm-up at 30 W. Thereafter, work rate was increased every second minute with equal steps throughout the test, but it was individually determined (10–25 W) on the basis of the subject's physical fitness in such a way that the maximum work rate could be reached in about 12–15 minutes. The test continued until the subject was unable to maintain his or her pedalling frequency above 45 rpm. Respiratory gas exchange variables were continuously determined using a breath-by-breath method (SensorMedics® V_{max} 229). The VO_2 values obtained were averaged over the breath-by-breath values of the 30-s intervals. VO_2peak was recorded as the highest averaged value at the maximum work rate. The corresponding heart rate and work rate were recorded and used to represent their maximums. Subjects rated their perceived exertion using the Borg RPE scale 6–20.[21] The amount of fatigue in the lower limbs was rated by using a 1–5 scale every fourth minute, and every second minute at the end of the test. Data for VO_2peak were expressed as absolute (L/min) and relative (ml/kg/min) values.

Physical activity

To give information of their leisure physical activity, the subjects completed a self-report questionnaire. The purpose of our short questionnaire was to classify subjects into activity categories, rather than to measure physical activity levels comprehensively. The questionnaire included items of: 1) *Self-perceived fitness.* A single, slightly adapted question from a study by Lamb was used.[22] In this, the subjects were asked to indicate their present self-perceived fitness on an ordinal scale of 1–5 (with 1 indicating poor and 5 indicating good fitness). 2) *Leisure exercise during the previous four weeks*. The period of four weeks was deemed sufficiently long to represent the typical activity patterns, yet short enough to prevent the influence of disease fluctuation. The question was adapted from a questionnaire used previously as a part of Mini-Finland Health Survey in 8000 healthy adults aged 30 years and over.[23] We were primarily interested in the average time spent on each episode for sports or recreational activity. The subjects reported the type, frequency and duration of exercise (not more than five exercise modes). Physical activity was grouped according to the exercise modes as follows: no exercise, walking (including Nordic walking = walking with specially designed poles), aerobic endurance exercise, strength training and other exercise (including balance/co-ordination exercises and outdoor activities). For the analysis, we calculated the time spent in activity (per week). 3) *Estimates of breathlessness and sweating as indicators of exercise intensity.* The subjects reported if they had got breathless or not, and their degree of sweating (no sweating/sweating a little/sweating a good deal). The reliability of these questions, as estimated by Fleiss' kappa coefficients, has been reported as quite high.[23]

Statistical analysis

Differences between men and women in continuous variables were calculated using Student's t-test or the Wilcoxon test, and in categorical variables using the chi-square test. The strength of associations between disease or physical characteristics and VO_2peak was determined using correlation analysis. Those independent variables, which were significant at the 10% level, were included in the multivariate regression models. Different regression models were fitted with VO_2peak as dependent variable. The first model was used to examine the influence of age, height, weight (not with relative VO_2peak) and sex. The second model included the EDSS and the third model the amount of aerobic endurance exercise at present. The final regression model included those independent variables from initial models that remained significant at 10% level (i.e., $P < 0.1$). Interaction terms were included in all models.

The regression models are based on the assumptions that the distribution of residuals is normal and their variance constant. The normality of residuals was checked

by the Shapiro-Wilk statistic, and the graphic analysis of residuals was carried out to provide information about the constancy of residuals. The detection of outliers and influential data points were assessed using studentized residuals and other diagnostics measures. If any outliers or influential data points were observed, regression models were used both with and without them and the results were compared.

All statistical calculations were performed using SAS® for Windows 8.2 package (SAS institute).

Results

Table 1 shows the subjects' physical and disease characteristics. A rough 2:1 female:male preponderance occurred in the cohort.

Exercise test and peak oxygen uptake

Of the 95 subjects, 92 were able to complete the cycle ergometry test. The reasons for test failure were knee joint contracture (one subject), dizziness and nausea (one subject) and inability to maintain pedalling frequency (one subject). Table 2 shows the results of the exercise test. Maximal workload, absolute and relative VO_2peak were, as anticipated, significantly ($P < 0.0001$) higher in men than in women. No significant sex difference was seen in either maximal heart rate or perceived exertion. In two subjects who were on beta-adrenergic blocker medication, the maximal heart rates were 172 and 173 beats per minute, respectively. Because these values did not significantly differ from the maximal heart rate of the total sample, these two subjects were included in all analyses. In Spearman's correlations, VO_2peak showed a weak inverse relationship with EDSS in women ($r = -0.31$, $P = 0.02$ for absolute VO_2peak; $r = -0.25$, $P = 0.05$ for relative VO_2peak). In men, the corresponding correlation was weak ($r = -0.29$, $P = 0.09$) for absolute VO_2peak and moderate ($r = -0.50$, $P = 0.004$) for relative VO_2peak. Rather weak negative correlations emerged between the maximal workload and the pyramidal functions ratings of the Functional Systems in both sexes ($r = -0.35$, $P = 0.04$ in men; $r = -0.30$, $P = 0.02$ in women). The cerebellar function scores of the Functional Systems also correlated weakly with maximal workload ($r = -0.32$, $P = 0.07$ in men; $r = -0.26$, $P = 0.05$ in women).

Table 2 Exercise capacity of subjects (mean ± SD)

Variable	*Men (n = 33)*	*Women (n = 59)*	*P*
Maximal workload (W)	154 ± 43	113 ± 32	< 0.0001
Maximal heart rate (beats/min)	159 ± 22	152 ± 20	0.10
VO_2peak ($l \cdot min^{-1}$)	2.2 ± 0.5	1.5 ± 0.4	< 0.0001
VO_2peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	27.0 ± 5.2	21.7 ± 5.5	< 0.0001
Perceived exertion[a]	19.3 ± 1.0	19.5 ± 1.0	0.13

VO_2peak, peak oxygen uptake.
[a] Borg RPE scale value, score ranges 6–20.

Self-perceived fitness

Forty-eight of the subjects (51%) perceived themselves as moderately physically fit. Two subjects (2%) rated their fitness as good, 14 subjects (15%) as fairly good, 29 subjects (30%) as fairly poor and two subjects (2%) as poor. No correlation between perceived fitness and relative VO_2peak was seen in men or in women. Absolute VO_2peak was found to correlate weakly to perceived fitness only in women ($r = 0.27$; $P = 0.04$). When examining the relationship between EDSS and perceived fitness, a weak and inverse correlation ($r = -0.22$; $P = 0.03$) existed in the total sample.

Physical activity

Of all activities during the past four weeks, walking accounted for 36%, aerobic endurance exercise for 29% and strength training for 30%. Other exercise only accounted for a minor proportion (5%). The subjects reported of getting breathless during 49%, sweating a little during 56% and sweating a good deal during 9% of all activities. Aerobic endurance exercise specifically caused breathlessness in 53%, sweating a little in 54% and sweating a good deal in 11% of the subjects. The most frequent aerobic endurance exercise modes were cycling (including cycling with an ergometer) and swimming. Six subjects (five men, one woman) did not take any kind of

Table 1 Subject characteristics (mean ± SD, or %)

Variable	*Men (n = 34)*	*Women (n = 61)*	*P*
Age (years)	44.4 ± 6.8	43.5 ± 6.6	0.50
Height (cm)	176.5 ± 6.8	166.1 ± 5.6	< 0.0001
Weight (kg)	80.1 ± 14.5	68.5 ± 12.4	< 0.0001
BMI (kg/m^2)	25.7 ± 4.5	24.8 ± 4.0	0.28
Current smoker (%)	35.3	29.5	0.56
Disease course			0.04
Relapsing–remitting (%)	64.7	86.8	–
Primary progressive (%)	20.6	6.6	–
Secondary progressive (%)	14.7	6.6	–
Disease duration (years)	5.7 ± 6.2	5.8 ± 6.6	0.99
EDSS [range]	3.0 ± 1.2 [1.0–5.5]	2.2 ± 0.9 [1.0–4.0]	0.004

BMI, body mass index; EDSS, Expanded Disability Status Scale.

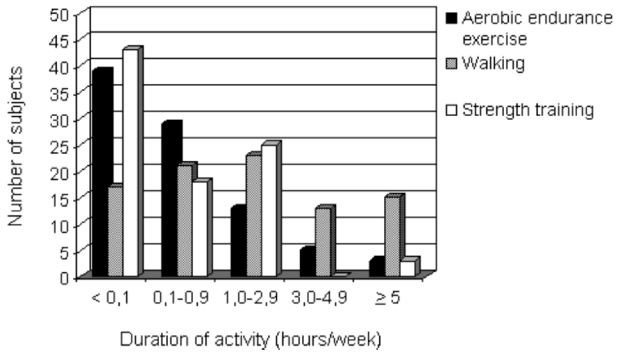

Figure 1 *Average weekly leisure physical activity according to its duration (n = 89). Sedentary subjects (n = 6) are not considered in the figure. Note that the same subject can be included in more than one activity category.*

exercise. Figure 1 shows the average weekly duration of various physical activities in the rest of the 89 subjects.

Multivariate predictors of VO_2peak

Men were taller ($P < 0.0001$) and heavier ($P < 0.0001$) than women, but even after covariate adjustment both the absolute and relative VO_2peak values of men were higher than those of women ($P < 0.0001$). Sex, age and weight explained 61% of the variability in absolute VO_2peak. When EDSS was added to this model, R^2 was 67%. Hence, the prediction accuracy of the model was quite high in absolute VO_2peak. Of variability in relative VO_2peak, 30% was directly attributable to variability in sex and age. When EDSS was added to the model, R^2 was 38%. EDSS together with sex (excluding age and weight) predicted the level of absolute VO_2peak for 42% and of relative VO_2peak for 29%. In Figure 2, regression lines for both men and women are fitted. As no interaction was seen between EDSS and sex ($P = 0.61$), the slope is equal for both sexes, i.e., each increase of one point on EDSS is associated with

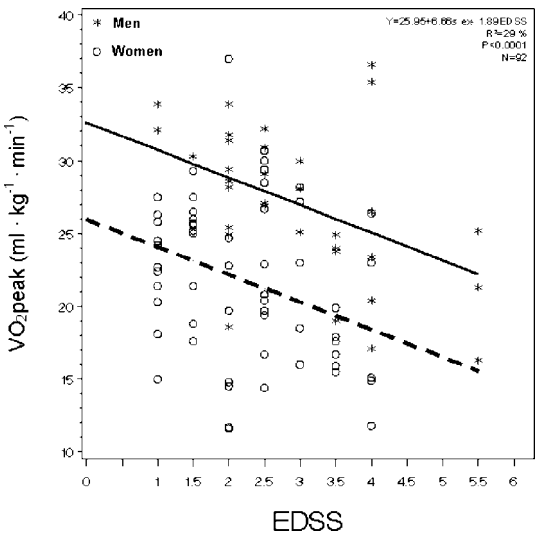

Figure 2 *The relationship of relative VO_2peak to neurological disability as measured by the EDSS in 34 men and 61 women with mild to moderate MS.*

a decrease in relative VO_2peak of about 2 mL/kg/min. Because of a significant sex difference ($P < 0.0001$), the VO_2peak of men is always 6.66 mL/kg/min higher than that of women, regardless of the EDSS score.

Correlation analyses showed no significant relationships between disease duration and VO_2peak or between smoking and VO_2peak. These variables were, therefore, not considered for the multivariate regression analysis.

No relationship was found between leisure physical activity and VO_2peak. When participation in aerobic endurance exercise specifically was studied, it was found to increase model R^2 (42%) in relative VO_2peak, but this was due to one statistically very influential observation with an exceptionally high exercise amount of 10 hours per week (otherwise, the mean duration of aerobic exercise was 0.7 hours per week). We also examined if high amounts of aerobic endurance exercise would be related to VO_2peak. In this subgroup analysis we included those reporting of exercise ≥ 1 hour per week ($n = 21$). This analysis showed that aerobic endurance exercise ($P = 0.10$), sex ($P = 0.30$) and interaction between them ($P = 0.11$) were not significant predictors of VO_2peak, although the explained variance was 60% in absolute VO_2peak. In relative VO_2peak, the explained variance was 57% with aerobic endurance exercise ($P = 0.13$), sex ($P = 0.63$) and their interaction ($P = 0.05$) as independent variables. When excluding the one statistically very influential observation, the corresponding values for explained variance were 59% in absolute and 52% in relative VO_2peak. Aerobic endurance exercise was not significant ($P > 0.1$) in either of them. There was no interaction between aerobic endurance exercise and sex in either absolute or relative VO_2peak ($P = 0.32$ and $P = 0.91$, respectively).

Discussion

Our findings provide evidence that neurological disability, as measured by the EDSS, predicts the peak oxygen uptake of subjects with mild to moderate MS, indicating a relationship between disease severity and exercise capacity. Similar findings have been earlier reported by Ponichtera-Mulcare *et al.*,[8] who found a weak, inverse relationship between VO_{2max} and EDSS in 23 mildly to moderately disabled MS subjects (EDSS 1.0–6.0). Our results are also consistent with those of another study by Ponichtera-Mulcare *et al.*,[7] where VO_{2max} correlated moderately with the level of disability in 10 subjects with MS (EDSS 1.0–4.5). Opposite findings have been reported by Foglio *et al.*,[6] in whose study reduction in exercise capacity was associated with respiratory muscle dysfunction, but not to disease severity. In this investigation, however, the mean EDSS score (5.3) was higher than in the present study, and one third of the 24 patients were unable to perform the exercise test. Foglio *et al.* employed arm ergometry, which resulted in a high number of dropouts owing to poor upper limb co-ordination, whereas Ponichtera-Mulcare *et al.* used a leg cycling ergometer adapted for a patient sitting in a semirecumbent

position or compared three different modes of ergometry.[6–8] VO_2peak (or VO_{2max}) vary according to the test protocol and ergometrical mode used, which complicates comparison of our results with other studies.

Sex and EDSS together explained 29% of variance in relative VO_2peak. For absolute VO_2peak, the corresponding explanatory power was higher (42%). The results of men and women have been reported together in earlier studies of exercise capacity in MS. This may be misleading, as the aerobic capacity of adult women is 10–30% lower than that of adult men.[10] In our sample, 64% of the subjects were women and 36% men. The female:male ratio is about 2:1 in the MS population.[1] To our knowledge, ours is the first study to consider differences between sexes in VO_2peak in a large cohort of MS subjects highly representative of the general MS population with the known female predominance. When adding age to the relative VO_2peak regression model, we found that sex, EDSS and age together accounted for 38% of R^2. One possible explanation is that maximal aerobic capacity declines with age by about 10–11% per decade in women and 7–9% in men.[24,25] Another explanation is related to the nature of MS, as disease duration tends to be longer in older persons and the disability progression rate is also influenced by age.[26]

Our subjects were recruited from a waiting list for inpatient adaptation training courses. These rehabilitation courses are arranged by Social Insurance Institution in the Masku Neurological Rehabilitation Centre. The courses are meant for newly diagnosed patients, most of whom have had their diagnosis within the previous five years. A single patient can take part in the course only once. Every year about 200 patients take part in the adaptation training. In our opinion, our cohort is well representative for early MS population, as the incidence of MS in Finland is five per 100 000 per year,[27] which means 200–250 new diagnoses yearly.

To compare our results with those of other studies, with an identical mode of ergometry, we calculated the mean relative VO_2peak for men and women together. This was 23.6 mL/kg/min. Very similar VO_2peak values have been recently reported from two other MS studies. The VO_2peak in 20 MS subjects with a mean EDSS of 3.6 was 23.5 mL/kg/min in an investigation by Mulcare *et al.*[28] In another randomized study, VO_2peak at the end of a four-week intervention was 22.7 mL/kg/min in an MS exercise group (mean EDSS 4.5) and 22.3 mL/kg/min for an MS nonexercise group (mean EDSS 4.6). In this study, MS subjects' cardiorespiratory exercise capacity was up to 30% lower than in healthy controls.[14] This implies that the subjects of our study also had reduced exercise capacity. Another, a more direct way to evaluate the level of our subjects' VO_2peak is to compare these results with published normative data of healthy people.[10] The male subjects in our study reached a mean value of 27 mL/kg/min of relative VO_2peak. For men of mean age of 44 years, a value between 26 and 31 mL/kg/min in a general population indicates 'poor fitness' on a 7-point scale ranging from 'very poor' to 'excellent'. In our female subjects, also of a mean age of 44 years, relative VO_2peak was 21.7 mL/kg/min. This indicates 'poor' aerobic fitness (category range 22–25 mL/kg/min for women).[10] These comparisons suggest that our subjects' had reduced cardiorespiratory exercise capacity compared with healthy persons.

Arguably, some of our subjects did not reach their true maximum performance level during the exercise test. Because we did not know how close to their maximum the subjects would cycle, we decided to use the term VO_2peak instead of VO_{2max}. One male subject with an EDSS score of 5.5 had a maximal workload of 56 W and a value of perceived exertion of only 15/20 at peak exercise effort. Noticeably, this subject was unable to pedal rhythmically owing to motor weakness and effort related inco-ordination of the lower limbs. The maximal workload as a whole correlated weakly in both sexes with the cerebellar and pyramidal scores of the Functional Systems. This suggests that weakness or reduced co-ordination may have influenced exercise performance. On the other hand, in MS subjects with a very low level of disability (EDSS 0.0–2.0), the energy cost of exercise during cycle ergometry is not affected by these factors.[29] In our sample, the lowest EDSS scores were well represented: 45% of the subjects had an EDSS score of ≤ 2.0, 84% ≤ 3.5 and only 16% 4.0–5.5. EDSS scores from 0 up to 3.5 are based on symptoms (e.g., bladder function) and findings on neurological examination. Only EDSS scores > 4.0 are affected by walking ability.[9] Thus, impaired lower extremity function probably had a minor effect on exercise test results in our study.

Subjective fitness was consistently not related to objective measures of exercise capacity in our sample, only absolute VO_2peak was found to correlate weakly with self-perceived fitness in women. These findings differ from those of the healthy. According to Lamb, self-perceived fitness was significantly correlated with several objective fitness-related measures in 118 men and women.[22] We observed a correlation between perceived fitness and EDSS, suggesting that persons with MS already in relatively mild stages of disease estimate their fitness according to neurological symptoms instead of cardiorespiratory exercise capacity. However, this correlation was weak too. The correlation could be stronger in a sample of more severely handicapped subjects.

A secondary aim of the present study was to find out if any relationship occurs between exercise capacity and leisure physical activity in individuals with MS. Our findings are against such a relationship. Our subjects' exercise capacity was not significantly influenced even by the highest amount of aerobic endurance exercise. The results are in line with data on healthy adults, showing that leisure physical activity is a relatively minor contributor to VO_2peak in men and women across a broad age range of 18–95 years.[18] Our findings are in contrast to observations in healthy persons with an 'MS-like' age distribution of 25–55 years and also to those from patients with Parkinson's disease.[17,19] Canning *et al.* reported that sedentary Parkinsonian patients produced a lower percentage of predicted VO_2peak than those with a history of regular aerobic exercise.[19]

A major limitation of the present study is that the questionnaire used for determining physical activity was not specifically validated for persons with chronic diseases. Standardized questionnaires have been used to measure physical activity in subjects with MS, such as the Baecke Activity Questionnaire and the Seven-Day Physical Activity Recall Questionnaire.[14,15] The validity of these types of self-report measures may also, however, be poor in the MS population. For example, Ng and Kent-Braun showed that an accelerometer is more sensitive in detecting differences in MS subjects' physical activity than the Seven-Day Physical Activity Recall Questionnaire.[15] Good evidence does not exist for an assumption that the validity of a questionnaire would increase in parallel to its complexity. Some of the highest correlations between VO_{2max} measures and habitual physical activity have been obtained with a simple questionnaire including only a few key questions.[30]

Most of the physical activity questionnaires, including those used by us, assume that the subjects can accurately remember and report the type, duration and frequency of their physical activities during a certain time period. Godin and Shephard observed that self-reports of a low frequency of exercise are not closely associated with a poor fitness level.[30] Hence, our results may reflect an inaccurate perception of the relatively unfit subjects' leisure exercise behaviour, and it is possible that they overestimated the amount of their exercise.[31] The influence of seasonal factors, which are known to affect physical activity patterns,[32,33] cannot be excluded. Our data were collected over a six-month period from autumn to winter. In Finland, outdoor activities at this time of year may be limited compared with spring or summertime.

In the questionnaire, the amount of exercise was determined on the basis of sports and recreational activities only. Since the activity level was generally low in our subjects (Figure 1), it might have been appropriate to consider also household activities, or work-related activities, because some of our subjects were employed. These aspects have been taken into account in a recent scale, which was developed specifically for people with disabilities.[34]

Rosenthal and Scheinberg[35] suggested that the general exercise prescription for mildly impaired MS patients should resemble a regimen for the healthy as closely as possible. Furthermore, they recommended that 60 minutes is an optimal length for an aerobic exercise programme for subjects with low EDSS scores. Our findings are not fully in line with these guidelines. Because relative VO_2peak decreased linearly with increasing EDSS in our mildly impaired subjects (Figure 2), the rationale for using the same exercise prescriptions as for healthy subjects seems questionable. In our opinion, exercise prescriptions used for sedentary or unfit healthy persons would be more appropriate. It has been recommended that MS patients should undergo a graded exercise test before beginning an aerobic conditioning programme.[36] In clinical practice this is rarely possible. The present study should be useful for a clinical practitioner when planning aerobic exercise programmes for patients with the disease. If VO_2peak cannot be measured and the EDSS is known, the results of our study give predictive information about MS subjects' exercise capacity. For example, a person with an EDSS score of 2.5 can be expected to have reduced VO_2peak, which should be considered when prescribing the duration, frequency or intensity of exercise. Our subjects reported of breathlessness in 53% and sweating a little, or a good deal in 65% of aerobic exercise indicating that the intensity had been at least of moderate level in over half of the exercise sessions. Surprisingly, only 22% of the subjects did aerobic endurance exercise ≥ 1 hour per week, which can be regarded as a minimum level for developing and maintaining cardiorespiratory fitness.[37] Thus, special weight should be placed on ensuring that the duration and frequency of exercise are adequate, at least 30 minutes continuously three times per week.[37,38]

In conclusion, this cross-sectional study of men and women with mild to moderate MS showed that exercise capacity is inversely correlated with neurological impairment and disability. Our findings failed to show any evidence of a relationship between leisure physical activity and peak oxygen uptake. Further studies in MS are needed to evaluate the role of physical activity and its associations to physical performance capacity, perceived fitness, functioning, and general health. Research in this field should be extended to longitudinal studies designed to determine how physical activity patterns change in the course of disease progression.

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Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial

Jukka Surakka, Anders Romberg, Juhani Ruutiainen, Sirkka Aunola, Arja Virtanen, Sirkka-Liisa Karppi and Kari Mäentaka

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Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomized controlled trial

Jukka Surakka National Public Health Institute, Turku, **Anders Romberg**, **Juhani Ruutiainen** Masku Neurological Rehabilitation Centre, **Sirkka Aunola** National Public Health Institute, Turku, **Arja Virtanen, Sirkka-Liisa Karppi** Social Insurance Institution, Research Department, Turku and **Kari Mäentaka** National Public Health Institute, Turku, Finland

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Objective: To investigate the effects of aerobic and strength exercise on motor fatigue of knee flexor and extensor muscles in subjects with multiple sclerosis (MS).
Design: A randomized controlled trial.
Setting: At Masku Neurological Rehabilitation Centre, Masku, and the Social Insurance Institution, Research Department, Turku, Finland.
Subjects: Ninety-five MS patients with mild to moderate disability were randomized into exercise group ($n=47$) and a control group ($n=48$).
Intervention: Participants in the exercise group attended in a supervised exercise period of three weeks, which was followed by a home exercise programme lasting for 23 weeks. Patients in the control group continued with their normal living.
Outcome measures: Motor fatigue of knee flexor and extensor muscles was measured during a static 30-s maximal sustained muscle contraction. The decline in force (Nm) during the 30 s was recorded, and a fatigue index (FI) was calculated. Subjective fatigue was measured by using the Fatigue Severity Scale (FSS). The Ambulatory Fatigue Index (AFI) was calculated on the basis of a 500-m walking test. Assessment took place at baseline, at the third week (not for the control group) and at the 26th week. All outcome variables were analysed, men and women together, and some interesting contrasts were analysed by gender.
Results: Associations were observed with changes in extension FI and Expanded Disability Status Scale (EDSS) score and mean extension torque (Nm), but not with changes in FI and aerobic or strength exercise activity, mean AFI, mean FSS or in mean knee flexion torque. AFI was decreased in all subject groups ($p=0.007$). Motor fatigue was reduced in knee flexion ($p=0.0014$) and extension (ns) among female but not in male exercisers after six months of exercise. The exercise activity of women was 25% higher than that of the men.
Conclusions: Six months of exercise reduced motor fatigue in women, but not in men.

Address for correspondence: Jukka Surakka, National Public Health Institute, Department of Health and Functional Capacity, Peltolantie 3, FIN-20720 Turku, Finland. e-mail: jukka.surakka@ktl.fi

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Introduction

Patients with multiple sclerosis (MS) often describe fatigue as increased weakness with exercise or as an abnormal sense of tiredness. According to questionnaire studies, the prevalence of excessive fatigue in MS is 70–90%.[1–4]

The aetiology of MS fatigue is probably multifactorial, and in a recent review, Schwid *et al.*[5] suggested that components and mechanisms of fatigue should be investigated separately, and by gender[6] in order to broaden the knowledge of its characteristics and severity.

For many years MS patients were advised to avoid exercise because of excessive fatigue. Inactivity, however, may promote muscle deconditioning and decrease exercise tolerance. In a survey by Freal and co-workers,[1] 71% of patients described increased fatigue after heavy exercise, but on the other hand, 57% of the patients in the mentioned survey perceived that moderate physical exercise was helpful in controlling fatigue. Aerobic and strength exercise may reduce fatigue in MS patients.[7–10] Patients with mild to moderate physical impairment seem to benefit most from exercising.[11] Currently, physical exercise is actually recommended for MS patients to improve muscle performance,[11,12] and also to reduce fatigue.[12]

Different aspects of fatigue should be evaluated separately, both by means of subjective, self-reported questionnaires and by measuring the decline of strength during sustained muscle contraction.[13,14] Schwid *et al.*[14] found that people with MS had 12–18% higher fatigue indices than healthy subjects, when torque decline was measured during a 30-s sustained muscle contraction.

The purpose of this randomized controlled trial was to evaluate the effects of a six-month aerobic and strength exercise programme on the motor fatigue of knee extensor and flexor muscles in MS patients with mild to moderate disability.

Methods

Subjects

The design of this randomized controlled trial is shown in Figure 1. The study was approved by the Ethical Committee of the South-Western Finland District of Health Care. All of the subjects gave their written informed consent for participation in the study.

The inclusion criteria were: age between 30 and 54 years, definite diagnosis of MS,[15] Expanded Disability Status Scale (EDSS) score of 1.0–5.5,[16] willingness to participate and to exercise at home according to instructions. The exclusion criteria were: a cardiovascular disease or a musculoskeletal disorder that would hinder the patient from completing the exercise programme, relapse in MS less than one month before the baseline, intensive and regular physical exercise – at least five times a week, at least 30 min each time – during the preceding three months, and any medical, psychological or other reason indicating that the patient would not be able to complete the intervention programme.

After having confirmed their eligibility by telephone interview, the subjects were stratified by gender and randomized to an exercise or a control group. The randomization procedure was done by the project statistician with SAS software (version 8.2, SAS Institute, Inc, Cary, NC, USA).

At the baseline, the two groups were similar for anthropometric characteristics, EDSS scores, disease duration, Fatigue Severity Scale (FSS) scores and Ambulatory Fatigue Index (AFI) (Table 1).

The supervised exercise programme

Five supervised resistance and five aerobic exercise sessions were carried out during the three-week rehabilitation course. Aerobic exercises were conducted in a pool and on alternate days with resistance exercise.

The aerobic programme included varying forms of gymnastic exercises in shoulder-deep water (temperature approx +28°C). The workout schedule in the pool was as follows: 5–7 min warming up, 20–25 min aerobic exercises, 5–8 min cooling down. The targeted exercise intensity was 65–70% of age-predicted maximal heart rate. If a patient was unable to take part in the aquatic programme, it was replaced by an ergometry exercise session of 30–35 min.

The resistance exercise programme was of circuit type. After about 10 min of warming up, the patients performed 10 exercises with 10–15 repetitions in two sets. The total circuit consisted of the following exercises: (1) scapular adduction, (2) hip extension, (3) arm pull down, (4) seated abdomen,

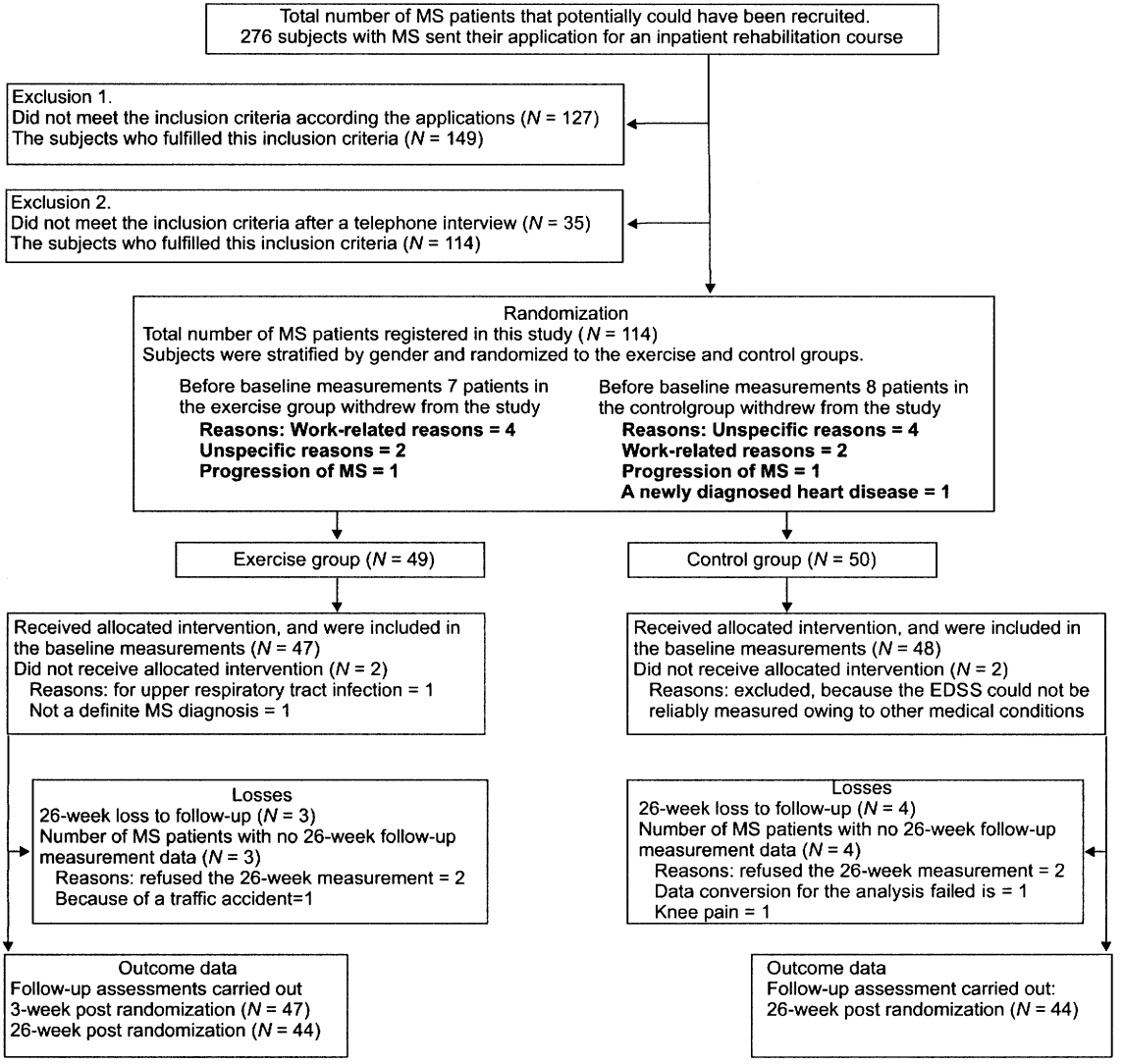

Figure 1 Flow diagram of the study.

(5) hip abduction, (6) triceps push, (7) seated back, (8) leg curl, (9) biceps brachii curl, (10) knee extension.

The exercises were performed using pressurized air resistance machines (exercises 1, 4, 5, 7, 8, 10), or weight stack machines (exercises 3, 6, 9) or against gravity (exercise 2). The load was 50–60% of the maximum load lifted at one time (i.e., one-repetition maximum, 1RM). After the third session, the loads were re-evaluated individually and, if needed, decreased or increased. Rest periods of 1 min between the exercises were applied. Both circuits were followed by a 4-min pause. The pause after the second circuit was followed by a cool-down period consisting of muscle stretching.

The home exercise programme

The patients were instructed to continue exercising for 23 weeks at home. The patients were

Table 1 Baseline characteristics of the female and male exercising and control MS groups

Variable	Exercise group ($n=47$)		Control group ($n=48$)	
	Women ($n=30$)	Men ($n=17$)	Women ($n=31$)	Men ($n=17$)
Age (years)	43±6	45±6	44±7	44±7
Height (cm)	165±5	177±6	167±6	176±8
Weight (kg)	65±12	77±12	72±12	83±16
Years since diagnosis	6±6 (0–22)	6±7 (1–23)	6±7 (0–28)	5±6 (0–19)
EDSS	2.0±0.8 (1–4.0)	2.9±1.2 (1–5.5)	2.5±1.0 (1–4.0)	3.1±1.2 (2.0–5.5)
FSS	4.6±1.6 (1.2–6.7)	4.6±1.6 (1.4–6.2)	4.7±1.2 (2.7–7.0)	4.5±1.1 (2.4–6.7)
AFI	4.1±7.1 (−16.7–21.7)	7.0±10.4 (−10.7–32.3)	5.1±6.8 (−14.8–19.6)	6.7±11.8 (−10.7–43.5)
Relapsing-remitting course (n)	28	10	25	12
Primary progressive course (n)	1	3	3	4
Secondary progressive course (n)	1	4	3	1

EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; AFI, Ambulatory Fatigue Index.
Values are means±SD, range or number of subjects.

provided with an individual progressive exercise programme instructed by a physiotherapist during the rehabilitation course. The weekly number of exercise sessions was four during weeks 1–17 and five during the last six weeks (18–23). The main aim of the home exercise programme was to improve muscular strength. The knee extensor and flexor muscles were exercised to an equal extent.

The home exercise programme included eight resistance exercises for the same muscle groups that were trained during the first three weeks. The subjects were equipped with two elastic bands (Theraband®; Akron, Ohio, USA), one for the lower, one for the upper extremities. During weeks 1–5 patients performed each exercise in two sets of 10–12 repetitions. In the sixth week, the number of repetitions was increased to 12–15. In week 12, they were given new, stiffer elastic bands, and the number of repetitions was decreased to 10–12 for the rest of the exercising period. For the duration of the exercise period, six months was deemed appropriate to achieve training effects.[17,18] The proportions of strength exercise and aerobic exercise of all home exercises were 75% and 25%, respectively. The patients in the control group did not participate in any exercise programme, instead, they were asked to continue with their normal living.

Exercise activity

Subjects kept a daily diary in which they recorded the duration and intensity of exercise, level of general condition (before and after the exercise), and any symptoms following the exercise. During the home exercise period the subjects were contacted four times by phone to allow the research staff to monitor their adherence and progress, to answer any questions, and provide individual feedback and encouragement.

Measurements

Leg flexor and extensor torque and motor fatigue were measured by using a knee muscle dynamometer (Ab HUR®; Oy, Kokkola, Finland). The measurement methods have been described previously.[19] Participants in the exercise group were assessed at the baseline, at three weeks and at six months. The control group was assessed at the baseline and at six months. All outcome variables were analysed men and women together, and some interesting contrasts were analysed by gender.

Torque (Nm) during the 30-s fatigue measurement

The decline in mean torque of 1 s (Nm) was calculated in 1-s intervals from the time point of maximum value of the muscle torque (TPM) to the end of the recording (30 s). The highest mean value of 1 s during the period 0–5 s was chosen as the TPM.

Fatigue Index (FI)

The area under force curve (AUFC, where force (F) is giving the moment, Nm) calculation starts from the TPM during the first 5 s. The AUFC from this point to the end of the contraction (30 s) is divided by the hypothetical AUFC that would be obtained if the patient sustained the same maximal force (F) until the end of the 30 s.[19] Fatigue index (FI) is given as:

$$FI = 100\% \times [1 - (AUFC_{TPM-30} / (F_{max,\,0-5} \times (TPM - 30))]$$

This FI has proven to be a reliable method of assessing motor fatigue in MS patients.[19]

Fatigue Severity Scale (FSS)

Perceived fatigue was measured by the FSS developed and validated by Krupp and co-workers.[20]

Ambulatory Fatigue Index (AFI)

The patients' ambulatory ability was assessed by means of a 500-m walking test.[21] The test was carried out on a 50-m course. The patients were asked to walk at their maximum speed instead of 'comfortable pace'. The time was recorded for the first and the final lap, and AFI was calculated by dividing the velocity during the final 50-m lap by the velocity during the initial 50-m lap.[14,21]

Statistical analysis

Multivariate analysis with repeated measures was used to examine potential changes in FI, AFI and FSS. Group (exercise versus control) and gender were used as between-subject factors and time and side as within-subject factors. The EDSS score, AFI and FSS were used as fixed covariates and the duration of aerobic and strength exercise activity in the exercise group, and the maximal and mean torque (Nm) values were used as variable covariates to find out the associations of these variables with the FI. The results from the three-week supervised period were also analysed to establish possible learning effects related to the measurement; this analysis was done only for the exercise group. Validity of the models was evaluated by means of residual analysis. The results are presented in baseline FI(%) (mean ± SEM) and mean changes (±SEM) with 95% confidence intervals (CI). The analyses were based on the torque measured from the right leg (there were no differences between right or left leg). The Pearson correlation coefficients were used to describe the association between the FI in flexion and extension and FSS, AFI and EDSS. P-values of less than 0.05 were considered to indicate statistical significance. SAS statistical software was used in all statistical calculations (version 8.2, SAS Institute, Inc, Cary, NC, USA).

Results

Women completed 62% (29 h) and men 53% (23 h) of the pre-planned strength exercise sessions (75 times) at home (with elastic bands). When aerobic and strength exercise sessions were combined, 98% (63 h) of women and 85% (53 h) of men completed the targeted amount of exercise sessions (75+24 times). The realized proportion of strength exercises were 46% (29 h of 63 h) in women, and 43% (23 h of 53 h) in men. The most frequent aerobic exercises (number of sessions) were: walking ($n=42$), cycling ($n=35$), swimming ($n=17$) and cross-country skiing ($n=10$). One woman showed exceptionally high aerobic exercise frequency (266% of the targeted exercise frequency). When her data were omitted the aerobic and strength exercise frequency in women was 92% (59 h). In the exercise groups no association was observed between FI and the amount of aerobic or strength exercise as covariate.

In knee extension, the FI was −3.3% lower in female exercisers after six months of exercising, while the controls showed an increase of 4.3% (Table 2). There were no differences in the changes of FI in knee extension between male exercisers and male controls. In both groups the FI tended to increase from baseline by six months (Table 2).

Table 2 Fatigue at baseline and change at 26 weeks assessed by fatigue index (FI) and fatigue index covariates (FI cov)

	Extension		Flexion	
	FI (%)	FI cov (%)	FI (%)	FI cov (%)
Female exercise group ($n=30$)				
Baseline mean ± SEM	27.3 ± 2.6	28.3 ± 2.1	23.9 ± 2.4	No association with the covariates was observed
Change mean ± SEM (CI) at 26 weeks	−3.3 ± 2.5 (−8.2, 1.6)	−3.0 ± 1.5 (−6.0, 0.1)	−1.9 ± 1.8 (−5.4, 1.6)	
Female control group ($n=31$)				
Baseline mean ± SEM	22.4 ± 2.6	25.9 ± 2.1	16.7 ± 2.4	No association with the covariates was observed
Change mean ± SEM (CI) at 26 weeks	4.3 ± 2.5 (−0.7, 9.4)	1.8 ± 1.5 (−1.2, 4.9)	5.3 ± 1.8 (1.7, 8.8)*	
Male exercise group ($n=17$)				
Baseline mean ± SEM	24.9 ± 3.7	23.2 ± 3.1	23.1 ± 3.9	No association with the covariates was observed
Change mean ± SEM (CI) at 26 weeks	2.0 ± 3.6 (−5.1, 9.1)	3.7 ± 2.3 (−0.8, 8.2)	2.8 ± 3.3 (−3.7, 9.3)	
Male control group ($n=17$)				
Baseline mean ± SEM	25.3 ± 3.5	24.2 ± 2.9	25.3 ± 3.8	No association with the covariates was observed
Change mean ± SEM (CI) at 26 weeks	1.8 ± 3.3 (−4.8, 8.4)	1.5 ± 2.0 (−2.5, 5.5)	2.4 ± 3.1 (−3.9, 8.78)	

*Statistically significant change ($p<0.05$).
The baseline FI and change at 26 weeks were measured for female and male exercise and control groups, using a 30-s static fatigue test of knee extension and flexion. The percentage (%) values are given as mean ± SEM and 95% confidence interval (CI). The adjusted covariates were EDSS score, and mean torque (Nm) of 1 s during the first 5 s.

However, in knee extension the group*gender*time interaction was not significant, which reflects that the changes were statistically equivalent in men and women. Statistically significant covariates were EDSS score ($p=0.04$), maximal torque ($p=0.001$) and mean torque ($p=0.0004$). Changes in FI with these adjustments are also shown in Tables 2 and 3.

The exercising men reached the maximal torque level faster than the exercising women did in knee extension and flexion torques (Nm) at six months. Additionally, the torque decline after the TPM was greater and faster in men than in women.

In knee flexion, the group*gender*time interaction was significant ($p=0.0140$). The difference between the female exercisers and controls was even greater than in knee extension, with less fatigue in exercisers (−1.9%) and significantly increased fatigue (5.3%) in controls (Table 2). There were no differences in the changes of flexion fatigue between male exercisers and controls (Table 2). In flexion no association between FI and covariates was observed. The effects of side (left or right leg) were not significant either in extension or in flexion.

Women in the exercise group improved significantly their fatigue resistance in knee extension during the 23-week home exercise period. In knee flexion, the achieved improvements had

Table 3 Fatigue at baseline and change at 0–3, 3–26 and 0–26 weeks in the male and female groups assessed by fatigue index (FI) and fatigue index covariates (FI cov)

	Extension		Flexion	
	FI (%)	FI cov (%)	FI (%)	FI cov (%)
Female exercise group ($n=30$)				
Baseline mean ±SEM	27.3±2.2	26.3±2.0	23.9±2.0	
Change mean ±SEM (CI) 0–3 weeks	0.0±1.3 (−2.7, 2.6)	1.4±1.4 (−1.4, 4.2)	−1.6±1.6 (−4.8, 1.6)	No association with the covariates was observed
Change mean ±SEM (CI) 3–26 weeks	−3.3±1.4 (−6.0, −0.6)*	−2.8±1.3 (−5.5, −0.2)*	−0.2±1.6 (−3.5, 3.0)	
Change mean ±SEM (CI) 0–26 weeks	−3.3±1.3 (−6.0, −0.6)*	−1.4±1.4 (−4.3, 1.3)	−1.8±1.6 (−5.1, 1.4)	
Male exercise group ($n=17$)				
Baseline mean ±SEM	24.8±3.1	23.5±2.9	21.9±2.9	
Change mean ±SEM (CI) 0–3 weeks	0.4±2.0 (−3.5, 4.3)	2.0±2.0(−2.0, 6.1)	2.1±2.3(−2.4, 6.7)	No association with the covariates was observed
Change mean ±SEM (CI) 3–26 weeks	1.8±2.0 (−2.1, 5.7)	0.3±2.1 (−3.9, 4.5)	2.0±2.3 (−2.6, 6.5)	
Change mean ±SEM (CI) 0–26 weeks	2.2±2.0 (−1.7, 6.0)	2.3±2.1 (−1.9, 6.6)	4.1±2.3 (−0.4, 8.7)	

*Statistically significant change ($p<0.05$).
The baseline FI and the changes from baseline to 3 weeks, from 3 to 26 weeks, and from baseline to 26 weeks were measured in female and male exercise groups, using a 30-s static fatigue test of knee extension and flexion. The percentage (%) values are given as mean ±SEM with 95% confidence interval (CI). The adjusted covariates were EDSS score, and mean torque (Nm) of 1 s during the first 5 s.

already occurred during the first three weeks of exercising (Table 3). In men no improvement could be observed. In knee extension, EDSS score ($p=0.01$) and mean torque ($p=0.0003$) were statistically significant covariates. These adjustments slightly decreased the improvement observed in the exercising women.

A positive correlation was found at the baseline, between the FI in knee extension and EDSS in the male exercise group ($r=0.66$, $p<0.01$). No other correlations between the FI and AFI, EDSS or FSS were found.

The time effect was statistically significant for the AFI both in the exercise and control groups (change and confidence intervals), 2.44 (0.67–4.21), $p=0.007$, and nearly significant for the FSS, 0.17 (−0.02 to 0.36), $p=0.07$. No significant gender or group interactions were observed in AFI or in FSS.

Discussion

In the present study, exercising women but not men showed reduced motor fatigue after an exercise period of six months. The amount of reduction was not related to the amount of exercise. Other

reasons related either to MS or to individual physiology may explain the lack of exercise effect in men. It can be speculated that six months was too long for a training period and that the progression of the disease may have hidden some positive training effects, especially in men. Perhaps, if we had followed up the training effects more frequently (e.g., once a month), we might have obtained a more comprehensive picture of the training effects on motor fatigue. Morganti *et al.*[22] showed in their one-year resistance training programme in healthy older women that the greatest increases in strength were achieved in the first three months.

The relapsing-remitting type of multiple sclerosis is present in 80% of MS patients, with a female predominance of approximately 60–70%.[23] In our study, there were more subjects with a progressive course of MS among the men than among the women. Male exercisers also had a higher mean EDSS score than female exercisers, in spite of equal duration of MS. High EDSS scores and high FI values were associated in the male but not in the female exercise group. Gender differences observed in the EDSS among our subjects are in line with previous studies. In MS, disability progresses faster in men than in women.[23–25] It can be speculated that deconditioning of muscles was evident only in men in our study.

Kent-Braun and co-workers[26] studied the skeletal muscle composition, strength and enzyme activity in MS patients (mean EDSS score 4.0). They found that the MS patients' muscles had the same characteristics as disused muscles: fewer type I (slow twitch) fibres, smaller muscle fibres, greater tendency to supply energy by anaerobic pathways and to have impaired skeletal muscle oxidative capacity. They proposed that the chronically reduced maximum discharge rates, and altered motor unit activation might induce changes in skeletal muscle characteristics.

In our study, the EDSS and torque were associated with fatigue in knee extension, but not in flexion, in which the strength is lower. Previous studies speak both for and against an association between weakness and motor fatigue. Schwid and co-workers[14] concluded that strength and motor fatigue are distinct features, but Djaldetti and co-workers[13] observed that static fatigue was more pronounced when weakness was present. De Haan and co-workers[10] proposed that fatigue can be reduced by increasing the muscle mass. According to Schwid *et al.*,[14] fatigue may have several forms (weakness, fatigue or both). The authors did not find any relationships between static and dynamic fatigue within the same muscle group.

The torque decline was greater and faster in male than in female exercisers after a few initial seconds of measurement in this study. A similar trend was observed in our previous paper[19] among mild-to-moderately affected MS patients. Women's performance remained probably at a submaximal level, while men performed with maximal effort. The absolute muscle force was lower in women than in men. However, since women were performing the same relative work as men did, the oxygen demand in their working muscles may have been lower. Further, the vascular occlusion during the performance may correlate with the force of muscle contraction. With reduced vascular occlusion in muscles, the metabolic clearance should consequently be faster during a prolonged performance. Thus, both decreased oxygen demand and better metabolic clearance in women may explain the observed gender differences in fatigue.[27–29]

Perceived fatigue (measured by FSS) in our study tended to increase in all subjects after 26 weeks of follow-up. Previous studies indicate that perceived fatigue is distinct from motor fatigue.[5,30] Sharma and co-workers[30] suggested that MS-related fatigue has both central and peripheral components, such as impaired metabolism and altered muscle excitation components – contraction coupling. Our finding is consistent with the study of Sharma *et al.*,[30] where they proposed the lack of association between perceived fatigue and FI to indicate that the origin of motor fatigue is related with dysfunction of upper motor neurons and/or muscles. Previous studies are contradictory concerning whether fatigue is of central or peripheral origin or both,[5,6,10,14,30,31] therefore it may be appropriate to talk about signs of muscle fatigue and signs of perceived fatigue.[6]

During the first three weeks, we did not observe any learning effects in the measurements, except that the exercising women improved their fatigue resistance in knee flexion. It is possible that our exercise programme was optimal for flexor muscles, because of water gymnastics and because of the fact that knee extensor and flexor muscles were

Clinical messages

- Motor fatigue can be successfully reduced in mildly impaired female MS patients by aerobic and strength exercise.
- The exercise should preferably be as specific as possible concerning the muscle group and exercise intensity for achieving reduced fatigue in knee extensor and flexor muscles in subjects with MS.

exercised at gym with the same type of device as was used for the fatigue measurement.[32]

Subjects in this study were chosen from MS patients who had sent their application to participate in an inpatient rehabilitation course. This is a potential source for bias. The attitude of all of them may well have been positively turned towards physical exercise. Another limitation is that the subjects were no more than mildly or moderately disabled. Therefore, exercise intervention trials among severely affected patients are needed before generalizations concerning the entire MS population can be made.

Also, to ensure better statistical power, the male exercise group should have been larger.

Our study showed that aerobic and strength exercise can reduce motor fatigue in MS patients as has earlier been proposed by Kent-Braun *et al.*[8] and de Haan *et al.*[10] The exercise mode used in our study, exercises for the whole body, was perhaps not optimal for the purpose of improving fatigue resistance in knee muscles. The physiological enhancements normally achieved by exercising may not be the same in MS patients in whom different muscle groups are affected in various and unpredictable ways. Therefore, the exercise effect might have been more pronounced if the exercises had mainly focused on leg extension and flexion, and also with a greater proportion of strength exercises. Furthermore, of all aerobic exercises, walking was the most popular exercise mode, and that did probably not provide sufficient intensity to reduce fatigue in men (e.g., to achieve muscle hypertrophy).[33] Further studies are needed to find out the optimal exercise mode and intensity for improving motor fatigue resistance in MS patients. The changes in ambulatory endurance (measured by AFI) were similar for all subjects. An explanation may be the relatively low reliability of AFI intraclass correlation coefficient (ICC) 0.36 in subjects with MS and 0.21 in healthy subjects).[14] The reliability of the FI used in our study has been shown to be good (ICC 0.68–0.86).

In conclusion, the outcomes of the present study show that aerobic fitness and strength exercising reduces motor fatigue in MS subjects with low or moderate disability. This study indicates that the exercise mode was more feasible among the less disabled women than the more disabled men. There might also be a physiological female gender advantage.

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Long-term exercise improves functional impairment but not quality of life in multiple sclerosis

Anders Romberg[1]; Arja Virtanen[2]; Juhani Ruutiainen[1]

[1]Masku Neurological Rehabilitation Centre, 21251 Masku, Finland
[2]Research Department, Social Insurance Institution, 20720 Turku, Finland

Corresponding author:
Anders Romberg
Masku Neurological Rehabilitation Centre
P.O. Box 15
FIN-21251 Masku
FINLAND
Tel: + 358 2 439 2111
Fax: + 358 2 439 2112
e-mail: anders.romberg@ms-liitto.fi

Abstract

Regular exercise is important for patients with multiple sclerosis (MS) to maintain their functional ability and general health. The aim of this study was to determine whether a long-term exercise program has any effect on functional impairment or health-related quality of life (HRQOL) in subjects with mild to moderate MS. In a randomised controlled trial, subjects in the intervention group (n = 47) exercised according to a progressive exercise program, mainly consisting of resistance training, for six months. Subjects in the control group (n = 48) received no intervention. The subjects were assessed at baseline and at six months using the Multiple Sclerosis Functional Composite (MSFC), the Expanded Disability Status Scale (EDSS), the Functional Independence Measure (FIM), the MS Quality of Life-54 (MSQOL-54) questionnaire and the Centre for Epidemiologic Studies Depression Scale (CES-D). The drop-out rate was low (4%) with 91 subjects completing the study. At six months, the exercising subjects showed improvement on the MSFC (mean score change 0.114, 95% confidence interval [CI] 0.010 to 0.218), whereas the control subjects showed deterioration (mean score change -0.128, 95% CI -0.232 to -0.025). The change between groups was statistically significant (interaction, p = 0.001). Consistent with the physical nature of the intervention, the change predominantly occurred in leg function/ambulation. The effect seen in the EDSS, FIM, MSQOL-54 or CES-D was none. These findings indicate that MSFC is more sensitive than EDSS in the detection of improvement in functional impairment as a result of regular exercise. The unfavourable results from HRQOL do not rule out the possibility that other types of exercise programs may improve it in MS.

Key words: MS; rehabilitation; exercise; functional composite; quality of life

Introduction

Multiple sclerosis (MS) is the most common chronic disabling disease of the central nervous system in young adults. Despite significant progress in the development of disease-modifying drugs, pharmacological therapy alone does not represent optimal care in MS [15]. Exercise, a low-cost non-invasive intervention, has recently been recognized as a feasible form of self-management for persons with the disease [36]. Current evidence indicates regular exercise is beneficial in MS [7,19,27,28,30]. Studies of exercise interventions in subjects with MS have, however, been unable to show that neurological impairment, measured by the Expanded Disability Status Scale (EDSS) [16] could be decreased by exercise. This may, at least in part, depend on the shortcomings of the applied measure.

The EDSS is by far the most widely used rating scale in MS [34]. Mainly to overcome the psychometric limitations of the EDSS [34,41], a new measure assessing impairment and disability in MS, the Multiple Sclerosis Functional Composite (MSFC), has been introduced [6]. MSFC is a multidimensional measure of functional impairment including tests of leg function/ambulation (Timed 25-Foot [7,62 m] Walk Test [TWT]), arm/hand function (Nine Hole Peg Test [9HPT]) and cognitive function (Paced Auditory Serial Addition Test [PASAT]) [6,33]. It considers the cognitive and arm/hand dimensions better than EDSS [6]. It is also more closely linked to brain pathology detected by MRI [33].

Health-related quality of life (HRQOL) refers to those dimensions of quality of life that are affected by health status and may be influenced by health care [18]. HRQOL has been accepted as an essential domain in clinical research and treatment of subjects with MS [21]. Progressive and disabling MS has a considerable effect on HRQOL [24,29]. Thus, interventions focusing on the maintenance or improvement of HRQOL would be desirable.

Exercise is an appealing strategy for the improvement of quality of life. In MS, the effects of exercise on behavioural and psychological outcomes, such as HRQOL or depression, have not been adequately studied [36]. Only one controlled trial has verified the benefit of an exercise programme in MS in terms of HRQOL. Petajan and co-workers showed that 15 weeks of aerobic training resulted in significant improvements on the Sickness Impact Profile [27].

The aim of the present study was to determine whether a long-term exercise program reduces functional impairment, measured by the MSFC and improves HRQOL in MS subjects with mild to moderate disease severity.

Methods

Subjects

In this randomised, controlled study with a 6-month follow-up, subjects with an age between 30 and 55 years, clinically and/or laboratory-defined MS [31] and an EDSS score of 1.0 to 5.5 (inclusive) were considered eligible. The exclusion criteria were relapse during the preceding month, intensive exercise at least 5 times a week at least 30 min /session regularly for 3 months before admission, a serious disease other than MS or any other reason precluding participation in a progressive exercise program.

The subjects were recruited from a waiting list for inpatient rehabilitation at the Masku Neurological Rehabilitation Centre. Screening for eligibility based on admission records. Thereafter, possible participants were interviewed by phone. Then, the potentially eligible subjects were stratified by sex and randomly assigned either to the exercise intervention or to the control group. The subjects' final eligibility was confirmed at admission for inpatient rehabilitation in the exercise group or at baseline testing in the control group.

The study protocol was approved by the Ethical Committee of the South-Western Finland District of Health Care. Informed consent was obtained from all subjects before entry to the study.

Measures

Impairment. The MSFC was administered according to standardized instructions [9]. First, the patients performed the TWT twice. The mean time (in seconds) of the trials was considered for the analysis. Next, the 9HPT was done twice with the dominant as well as with the non-dominant hand with the mean time (in seconds) for each hand being analysed. Finally, the PASAT (3 second version) was done once; the score was the number of correct answers. A trained assessor, not otherwise involved in the study, conducted the MSFC assessments.

The scores on each measure were converted to a Z-score, and the composite score was then calculated as recommended by the Administration and Scoring Manual for the Multiple Sclerosis Functional Composite Measure [9]. To create an internal reference population, the means and standard deviations of the baseline visits for all patients were used.

Neurological impairment and disability were evaluated using Kurtzke's Functional Systems Scales and EDSS [16] by two experienced neurologists. To ensure intra-rater reliability, the patients were assessed by the same neurologist at baseline and at 6-months.

Disability. Disability was assessed using the Functional Independence Measure (FIM). FIM has 18 items each with a 7-point scoring system based on the type and amount of assistance required for basic life activities [12]. The total score ranges from 18 to 126, with higher scores indicating higher levels of independence. The reliability and validity of FIM in MS patients has been shown in independent studies [2,34]. FIM assessments were done by nurses specially trained and certified to use the instrument.

Health-related quality of life. The disease-specific Multiple Sclerosis Quality of Life-54 questionnaire (MSQOL-54) was used to assess HRQOL. The MSQOL-54 was developed to combine generic quality of life aspects of the Short Form 36-Item Health Survey Questionnaire (SF-36) with MS-targeted dimensions and ratings for the overall quality of life [38]. As a result, 18 disease-specific items were added to the original 36 items of the SF-36. The 54 items are divided into 12 multi-item and two single-item scales. Evidence supports the reliability and validity of the MSQOL-54 [35,38,39].

The items of the SF-36 are almost identical to those of the RAND 36-Item Health Survey 1.0 (RAND-36), only the scoring of two subscales (general health and bodily pain) is slightly different [14,40]. A Finnish version of the RAND-36 has been available since 1999, and its reliability and validity has been comparable with the results obtained for the RAND-36 and SF-36 in international studies [1]. Guidelines for the cross-cultural adaptation of HRQOL measures were used to translate the 18 disease-specific items of the MSQOL-54 into Finnish [13]. First, a professional translator, with experience from medical sciences, translated the original question items into Finnish. The draft was checked and corrected by two of the researchers (AR, JR) and an MS nurse expert on HRQOL. Thereafter, the Finnish version

was re-translated into English by an independent specialist (a medical doctor). The publisher of the original MSQOL-54 gave her permission for the use of the scale after having commented on the back translation. Finally, the Finnish version was re-evaluated by the work group in collaboration with a professional translator. A few minor modifications were made to the wording of some items to make them more suitable to Finnish culture. The final version was then tested on 10 MS patients whose level of disability was similar to that of the subjects of the present study.

The MSQOL-54 item results were transformed linearly to 0 - 100 scores and final scale scores were created by averaging items within the scales. A higher score in each scale indicates a better HRQOL. Physical health composite (PHC) and mental health composite (MHC) scores were calculated as a weighted sum of selected scale scores [38].

Depression. Depressive symptoms were measured using the Centre for Epidemiologic Studies Depression Scale (CES-D), a self-report questionnaire consisting of 20 items, each rating answers from 0 to 3 [32]. The total score ranges from 0 to 60, and a score of 16 or greater is indicative of clinical depression. The CES-D has high internal consistency, acceptable test-retest reliability, and good construct validity in both clinical and community samples [20,32].

Intervention

The exercise intervention lasted for 26 weeks. At weeks 1-3, the exercisers participated in an inpatient rehabilitation program. During the rehabilitation period, exercise consisted of supervised training in groups. This included five resistance training sessions and five aerobic training sessions. At weeks 4-26, exercise was continued at home according to instructions given by physiotherapists at the time of inpatient rehabilitation.

The progressive home exercise program will be described in detail in another report. In brief, it combined resistance training (3-4 times a week) with aerobic endurance training (once a week). The main emphasis was on resistance training. For this purpose, the subjects were provided with elastic bands (Theraband®). In the course of the home exercise period the subjects were contacted four times by phone to encourage them to adhere to the program and to answer training-related questions. The subjects had been instructed to record all completed training sessions in an exercise diary.

The subjects of the control group received no intervention, and they were offered an inpatient rehabilitation course at the end of the study. For the time of follow-up, these subjects were asked to avoid changes in their physical activity habits. They were contacted three times by phone before the final evaluation at 6 months.

Statistical analysis

The t-test or Wilcoxon's test for continuous variables and the χ^2 -test for categorical variables were used to verify the success of randomization. The changes in impairment, disability, HRQOL, and depression were determined by the mixed-models analysis of variance, which does not require complete data on each participant. Sex and group were considered between-group factors and time a within-subject factor. Changes within groups were evaluated by contrasts with confidence intervals if interaction between group and time was significant at less than 10% α-level. The strength of associations between subject characteristics and intervention outcomes was checked using correlation analysis. On this basis, a series of covariate analyses were done to determine the influence of age, education, employment status, and disease duration on the MSFC score and the influence of employment status, EDSS, and depression on the PHS and MHS of the MSQOL-54. The covariates were considered fixed, because they were only collected at baseline (age, disease duration, education, employment status) or no change was seen at follow-up (EDSS, depression). An intention-to-treat approach was used in all analyses for the subjects on whom at least baseline data was collected.

The magnitude and clinical relevance of the change scores were evaluated by the effect size statistic. According to Cohen's benchmarks, a value of 0 to 0.19 denotes negligible, ≥ 0.20 a small, ≥ 0.50 a medium and ≥ 0.80 a large effect size [3].

The SAS® for Windows package (SAS institute, Cary, NC, USA) was used for all analyses.

Results

Figure 1 shows the study profile. A sample of 276 subjects with MS was screened. The entry criteria were met by 114 subjects. Of them, 56 were assigned to the exercise group and 58 to the control group. Following post-randomization withdrawals and exclusions, 95 subjects

were available for statistical analysis. Table 1 summarizes their baseline characteristics. Ninety-one subjects completed the study.

Impairment. Table 2 shows how the exercise group improved and the control group deteriorated on the MSFC score and its Z-components. The within-group changes were significant on the MSFC score in both groups and, in addition, on the TWT in the exercise group. In exercisers, the change in MSFC components was dominant on the TWT, but in controls on the 9HPT. For change between groups, group-by-time interaction was significant in all variables except the PASAT. Addition of covariates to the linear mixed models of the MSFC did not influence the observed changes.

The effect size of the MSFC score change was 0.16 for the exercise group and -0.18 for the control group. Forty-four percent of subjects in the exercise group vs. 20% in the control group showed improvement on the MSFC score.

EDSS remained unchanged over the course of the intervention ($p = 0.16$, for interaction between groups). The average increase in the EDSS was 0.1 point in exercisers (effect size -0.09) and the average decrease 0.1 point in controls (effect size 0.09).

Disability. No change in disability was seen in either group ($p = 0.84$, for interaction between groups) as measured by FIM. The mean increase in the FIM total score was 0.3 points (in both groups) with an effect size of 0.15 in the exercise group and 0.04 in the control group. FIM showed a marked ceiling effect; in the total sample 63% of the subjects had a score of at least 124 at baseline.

Health-related quality of life. The percentage of missing data on the MSQOL-54 was very low (0.02% of all items). No significant between-group differences were found in any of the MSQOL-54 scale scores at baseline or after the intervention. In terms of effect sizes, the exercise group showed slight improvement on four scales and negligible changes on ten scales. Accordingly, the control group improved slightly or showed a slight decline on one scale, whereas on 12 scales the change was negligible (table 3).

The scores on the PHC and MHC of the MSQOL-54 were stable with no differences between groups. Effect sizes showed negligible changes in both groups (table 3). When adjusted for

covariates, a slight sex-by-time ($p = 0.078$) and an EDSS ($p = 0.064$) effect on the PHC was seen. Depression had a strong influence on HRQOL as shown by the highly significant ($p < 0.001$) effect of the CES-D scores on both the PHC and the MHC.

Depression. The mean baseline CES-D score was 14.7 (SD 10.5) in the exercise group, and 15.6 (SD 9.5) in the control group. Compared to baseline, the 6-month CES-D scores were slightly higher in the exercise group, but no group-by-time interaction ($p = 0.47$) emerged. The effect sizes indicated negligible changes in both groups.

Discussion

The results of this study show that functional impairment, measured by MSFC, improved significantly in subjects with MS exercising regularly for 6 months. In a control group, receiving no such intervention, functional impairment worsened. The change in the MSFC in exercisers was seen above all in the TWT, which was to be expected because the intervention focused on motor function, i.e. strengthening of the limbs. In control subjects, significant deterioration occurred both in the TWT and 9HPT. Opposite to results on the MSFC, neither within- nor between-group differences were seen in the "golden standard" measures of disability such as EDSS or FIM.

To date, intervention studies using MSFC as an outcome measure have all been clinical drug trials [5,23,25]. To our knowledge, this is the first study to report the effects of a rehabilitation intervention on MSFC. Our results are well in keeping with studies evaluating the effects of interferon beta-1a or methylprednisolone treatment in MS [5,23,25]. Like these trials, we found MSFC to be more sensitive than EDSS in detecting changes in function.

In our study, the exercisers showed a mean improvement of 0.114 vs. a mean deterioration of 0.128 in control subjects on the MSFC score. The improvement was less than in subjects receiving methylprednisolone due to a relapse (mean improvement 0.56 to 0.92) [25,23]. In a study examining the effects of interferon beta-1a on the disease progression, the mean decrease on the MSFC score was 0.36 in the treatment group and 0.49 in the placebo group over a 2-year interval [5]. The wide variation in MSFC changes over different studies is probably related to differences in the type and length of the intervention. On the other hand, it has been shown that the use of different reference populations has an effect on Z-scores and,

consequently, on MSFC scores [37]. Like Cohen et al [5], we applied an internal reference population where the means and standard deviations of the baseline measurements for all study patients were used. An external reference population has also been used [25], or the reference population has not been reported at all [23].

The MSFC is prone to practice effects. Of the three MSFC components, PASAT has been shown to be the most susceptible to practice effects. A similar effect on 9HPT may also be considerable, but it has not been observed in the TWT [4]. A limitation of the present study was that we were unable to eliminate the possible practice effects. If practice effects influenced the results, they were, however, similarly distributed in both groups. The problem could have been overcome by organizing pre-baseline testing sessions, but this was not possible because of logistic reasons. Apparently, the need for pre-baseline testing can be considered a practical disadvantage in using the MSFC. Another limitation in our study, like in most trials evaluating effectiveness of clinical rehabilitation, was the lack of placebo treatment and the difficulty of keeping the assessors or the patients blinded. Thirdly, the study subjects were randomized before fully confirming their eligibility, which led to post-randomization withdrawals and exclusions. The limitation is related to the fact that the potential study subjects from all over the country were on the waiting list for inpatient rehabilitation courses and randomization had to be done before setting the date of the inpatient course. To ensure unbiased analysis, an independent expert group carefully reviewed all subjects who withdrew before baseline evaluation (n = 7 + 8) or were excluded after it (n = 2 + 2)[8].

The exercise intervention had no significant effect on HRQOL, in disagreement with another study [27]. This may be due to differences in the intervention or in the used measure. In our study, the subjects exercised - after the initial 3-week rehabilitation period - for 23 weeks alone at home, whereas in the study of Petajan et al exercise was done in small groups under supervision for 15 weeks. Social isolation with a lack of support from other exercisers may have contributed to our subjects' modest results in HRQOL. We cannot completely rule out the possibility that the intervention effects were not detected because of the psychometric limitations (marked floor and ceiling effects and poor responsiveness) of the MSQOL-54 [10]. The Sickness Impact Profile - the measure used by Petajan et al [27] - is, however, subject to similar limitations [11].

Although no statistically significant changes were seen in HRQOL there was an overall trend, consistent with the results of the MSFC, for improvement in MSQOL-54 scale scores favoring the intervention group. This implication was supported by the effect size results (table 3). Depression strongly influences HRQOL of MS patients [24,35]. Our results are in agreement with this, as we found a major effect of depression, as measured by CES-D, in the mental and physical health composite scores of the MSQOL-54.

In a randomised study, with a 6-month intervention, participation in yoga classes combined with home practice was compared to aerobic exercise or a waiting list control group [22]. The results of this trial are nearly similar to those of ours in many respects. Yoga as well as aerobic exercise produced a significant improvement only in vitality (energy and fatigue) out of the eight subscales of the SF-36. Furthermore, no differences emerged between the three groups in either depression or cognitive function.

We considered it important to assess components of health status, such as HRQOL and depression, not captured by impairment or disability measures. The exercise program employed had no effect on depression. This is in line with a large meta-analysis concluding that it is not possible to determine indisputably the effectiveness of exercise on reducing symptoms of depression [17]. Yet, in a randomized trial with persons 60 years or older, aerobic but not resistance exercise, significantly lowered depressive symptoms over time [26]. Thus, the exercise program of our study, mainly consisting of resistance training, may not have been optimal for the reduction of depression.

Our study gives promising evidence that the disability progression of MS can be compensated for by regular exercise. Exercising at home seems a practical and low-cost option for the maintenance of functional ability in ambulatory subjects with MS, as also shown by another recent study [7]. Our findings indicate that the MSFC is a more responsive measure than the EDSS or the FIM to show intervention effects in a MS population up to an EDSS score of 5.5. Further studies are needed to evaluate the usefulness of MSFC in the detection of change due to other types of rehabilitation interventions and involving more severely disabled patients.

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Table 1 Subject characteristics at baseline.

Variable	Exercise Group n = 47	Control Group n = 48
Age, years, mean ± SD	43.8 ± 6.3	43.9 ± 7.1
Female sex	30 (63%)	31 (65%)
Married / cohabiting	17 (36%)	12 (25%)
Employment status		
Full- or part-time employed	29 (62%)	26 (54%)
Retired	18 (38%)	22 (46%)
Education length		
< 9 years	8 (17%)	13 (27%)
9 - 12 years	25 (53%)	21 (44%)
≥ 13 years	14 (30%)	14 (29%)
Disease duration, years, mean ± SD (min - max)	6.0 ± 6.5 (0 - 23)	5.5 ± 6.4 (0 - 28)
EDSS score, median (interquartile range)	2.0 (1.5 - 3.5)	2.5 (2.0 - 3.5)
FIM score, mean ± SD (min - max)	123.4 ± 2.1 (116 - 126)	123.9 ± 2.3 (117 - 126)

Differences between groups were not statistically significant for any of the variables.

EDSS = Expanded Disability Status Scale; FIM = Functional Independence Measure.

Table 2 Changes in the MSFC score and the component Z-scores at 6 months.

	Exercise group		Control group		
Variable	Mean change (95% CI)	p-value	Mean change (95% CI)	p-value	p-value*
MSFC	0.114 (0.010 to 0.218)	0.031	-0.128 (-0.232 to -0.025)	0.015	0.001
TWT	0.185 (0.041 to 0.328)	0.012	-0.119 (-0.261 to 0.023)	0.101	0.004
9HPT	0.071 (-0.038 to 0.180)	0.200	-0.106 (-0.214 to 0.003)	0.056	0.025
PASAT	0.092 (-0.115 to 0.298)	0.379	-0.161 (-0.366 to 0.045)	0.124	0.088

MSFC = Multiple Sclerosis Functional Composite; TWT = Timed 25-Foot Walk Test; 9HPT = Nine Hole Peg Test; PASAT = Paced Auditory Serial Addition Test. *Of change between groups with group-by-time interaction.

Table 3 MSQOL-54 scale scores (mean ± SD) of the two study groups and magnitude of change (effect size) in each scale.

	Exercise group			Control group		
Scale	Baseline	6 months	Effect size	Baseline	6 months	Effect size
Physical function	73,9 ± 18,0	70,4 ± 20,3	-0,19	68,7 ± 21,3	67,7 ± 21,9	-0,05
Role limitation - physical	40,4 ± 40,9	43,3 ± 41,4	0,07	38,7 ± 38,9	42,9 ± 39,3	0,11
Role limitation - emotional	60,3 ± 42,1	68,9 ± 37,9	0,20	65,3 ± 42,4	65,9 ± 40,1	0,02
Pain	67,4 ± 25,1	66,8 ± 22,5	-0,02	74,3 ± 20,2	72,0 ± 22,2	-0,12
Emotional well-being	71,1 ± 20,9	73,2 ± 18,9	0,10	71,4 ± 18,3	73,0 ± 20,5	0,09
Energy	57,9 ± 23,1	58,8 ± 22,3	0,04	54,7 ± 19,9	56,5 ± 21,2	0,09
Health perception	47,8 ± 19,7	51,9 ± 18,5	0,21	48,3 ± 17,2	51,3 ± 17,9	0,17
Social function	72,7 ± 21,8	75,9 ± 20,4	0,15	76,4 ± 17,3	77,2 ± 19,7	0,05
Cognitive function	69,5 ± 25,6	71,1 ± 20,8	0,06	76,4 ± 17,3	72,8 ± 22,2	-0,21
Health distress	69,9 ± 22,2	73,0 ± 21,0	0,14	70,9 ± 22,2	72,1 ± 23,4	0,05
Sexual function	67,2 ± 27,5	68,5 ± 29,7	0,05	69,8 ± 18,7	75,9 ± 26,3	0,33
Sexual satisfaction	58,5 ± 34,7	66,1 ± 33,8	0,22	57,3 ± 33,0	58,2 ± 33,8	0,03
Change in health	43,1 ± 25,9	52,2 ± 26,6	0,35	50,5 ± 26,0	49,5 ± 24,4	-0,04
Overall quality of life	68,0 ± 16,9	69,5 ± 18,8	0,09	66,4 ± 16,0	68,7 ± 17,4	0,15
Physical health composite	61,7 ± 18,2	63,0 ± 17,8	0,07	62,1 ± 14,7	63,3 ± 16,6	0,09
Mental health composite	67,5 ± 21,7	71,2 ± 20,6	0,17	68,7 ± 19,4	70,4 ± 21,3	0,09

None of the differences between groups were significant either at baseline ($p > 0.1$) or at 6 months ($p > 0.2$)