Effects of a 6-month exercise program on patients with multiple sclerosis

A randomized study

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Abstract—*Objective:* To improve walking and other aspects of physical function with a progressive 6-month exercise program in patients with multiple sclerosis (MS). *Methods:* MS patients with mild to moderate disability (Expanded Disability Status Scale scores 1.0 to 5.5) were randomly assigned to an exercise or control group. The intervention consisted of strength and aerobic training initiated during 3-week inpatient rehabilitation and continued for 23 weeks at home. The groups were evaluated at baseline and at 6 months. The primary outcome was walking speed, measured by 7.62 m and 500 m walk tests. Secondary outcomes included lower extremity strength, upper extremity endurance and dexterity, peak oxygen uptake, and static balance. An intention-to-treat analysis was used. *Results:* Ninety-one (96%) of the 95 patients entering the study completed it. Change between groups was significant in the 7.62 m (p = 0.04) and 500 m walk tests (p = 0.01). In the 7.62 m walk test, 22% of the exercising patients showed clinically meaningful improvements. The exercise group also showed increased upper extremity endurance as compared to controls. No other noteworthy exercise-induced changes were observed. Exercise adherence varied considerably among the exercisers. *Conclusions:* Walking speed improved in this randomized study. The results confirm that exercise is safe for multiple sclerosis patients and should be recommended for those with mild to moderate disability.

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In a chronic disease, such as multiple sclerosis (MS), the primary goal of exercise is to maintain and improve functional independence.[1] The beneficial effect of aerobic exercise on cardiorespiratory fitness, fatigue, and quality of life in patients with MS has been shown in independent studies.[2-4] Together with aerobic exercise, a comprehensive training program should also include exercises that increase muscular strength and endurance.[5]

The benefit of strengthening exercises on functional ability in MS remains to be determined. One earlier study indicated that 4 to 6 weeks of resistance training improved muscular strength and endurance in three and psychological well-being in all of the five subjects with a wide range of disability.[6] Lower limb muscle strength is related to walking speed.[7,8] It has been proposed that the prevention of walking deficits serves as a rationale for strengthening exercises in MS patients.[7] On the other hand, aerobic exercise, such as cycling or aquatics, may increase isometric strength, isokinetic force production, or muscle endurance in MS patients.[2,9] Further, aerobic exercise has been used to improve the functional gait of persons with MS.[10,11] These studies, with a small number of patients and without any control group, have only shown slight exercise-induced effects on walking velocity and gait measures.[10,11]

Typically, exercise studies in MS have been conducted in laboratory or otherwise well-controlled conditions.[2-4,6] Although these studies provide important knowledge regarding exercise responses in MS, it is essential to examine the effects of an exercise intervention performed under less ideal environments. Home exercise is a practical way of maintaining benefits obtained in formal rehabilitation settings.[12] Studies of populations other than MS indicate that home exercise is convenient, cost-effective, and efficient.[13-15]

The purpose of this study was to evaluate the effects of a progressive 6-month exercise program (3 weeks during inpatient rehabilitation followed by 23 weeks at home) on walking and other aspects of physical function in MS patients with mild to moderate disability.

Methods. *Design.* Patients were evaluated at baseline and at 6 months in a randomized controlled two-center intervention study. A trained, non-blinded, independent examiner carried out the clin-

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ical tests of physical function at the Masku Neurologic Rehabilitation Centre according to recommended guidelines.[16] Other measurements were carried out in the laboratory of the Research Department of the Social Insurance Institution.

The patients in the intervention group completed an exercise program of 26 weeks. At the time of baseline visits, the control patients were advised to avoid any greater changes in their physical activity habits during the next 6 months. These patients were contacted three times by phone before the follow-up visit.

Patients. The patients were screened from a waiting list for inpatient rehabilitation at the Masku Neurologic Rehabilitation Centre, Masku, Finland, between 1999 and 2001. The inclusion criteria were diagnosis of clinically or laboratory supported MS,[17] a score of 1.0 to 5.5 on the Expanded Disability Status Scale (EDSS),[18] and age between 30 and 55 years. Patients were excluded if they had had a relapse 1 month before baseline, had a disease preventing participation in the prescribed exercise program, had engaged in regular exercise five or more times a week for at least 30 minutes/session during 3 months before admission, or showed signs of any other medical or mental conditions precluding participation. After initial screening, one of the authors (A.R.) contacted potential participants by phone. The purpose of the study was then explained to the patients, and they gave their approval to participation. After this, the patients were randomized and stratified by sex either to the exercise group (E group) or the control group (C group). The patients' final eligibility was determined 1) in the E group at admission to the 3-week inpatient rehabilitation course, and 2) in the C group at the baseline visit.

The study was approved by the Ethical Committee of the South-Western Finland District of Health Care. All patients gave their written informed consent to participation in the study. The study protocol and documents were reviewed regularly by an independent adjudication committee.

Neurologic examinations. Neurologic impairment and disability were determined using Kurtzke's Functional Systems Scales and EDSS. Each patient was assessed at baseline and at 6 months by the same neurologist. Information on disease and physical characteristics, as well as diseases other than MS, was collected. The number of relapses treated with steroids was recorded on the basis of patients' self-reports and confirmed with information from medical records.

Primary outcome. The primary outcome was walking speed, which was measured by two tests: a 7.62 m (25 ft) walk test (7.62 MWT), and a 500 m walk test (500 MWT).[19-21] In both tests the patients were asked to walk as fast as they could. In the 7.62 MWT, a 2 m path was used for acceleration before and deceleration after the actual test distance.[22] Photocell sensors (Newtest Powertimer System, Newtest Oy, Oulu, Finland) were used for timing. The mean time of two consecutive trials was included in the analysis. In the 500 MWT, the patients were instructed to walk from one end to the other of a straight 25-m course in a hallway. A stopwatch was used for timing. The total walking time and the time for the first and final lap were recorded.

Secondary outcomes. Maximal isometric torque of knee extensor and flexor muscles was measured using a dynamometer (HUR, Kokkola, Finland). This is a reliable method of measuring lower extremity strength in MS patients. The patients were tested in a seated position. Each patient was instructed to perform maximal extension and flexion contraction, and to maintain it for 5 seconds. Of the two attempts measured for each leg, the one with highest torque was used for analysis.

To assess upper extremity endurance, a weight lifting test was carried out.[23] The patients alternately raised their right and left arm holding a 7 kg (women) or 10 kg (men) dumbbell in both hands. The number of repetitions for both arms was recorded. Gross manual dexterity was measured using the Box and block test.[24]

An incremental exercise test on an electromagnetically controlled cycle ergometer (Rodby Ergometer RE 820, Södertälje, Sweden) was used for measuring peak oxygen uptake (VO_2 peak). The test protocol has been described in detail elsewhere.[25]

Static balance was assessed by the Equiscale, a clinical test of balance disorders in ambulatory MS patients consisting of eight items, each rating performance from 0 to 2. The overall top score of 16 points indicates excellent balance.[26]

Exercise program. The intervention in the E group consisted of physical training initiated at the time of inpatient rehabilitation (weeks 1 to 3) and followed by a progressive home-based exercise program (weeks 4 to 26). Ten supervised strength training and aerobic exercise sessions (five times each) were carried out during inpatient rehabilitation. Trained physiotherapists instructed the patients individually about an exercise program to be followed at home. At weeks 4 to 20, the program included three weekly strength training sessions and one aerobic exercise session. For the final weeks (21 to 26) one strength training session was added. At weeks 5, 8, 14, and 20, the patients were contacted by phone to monitor progression, to provide feedback and encouragement, and to answer questions.

Strength training. At weeks 1 to 3, an adaptation of circuit resistance training method was used. The patients did 10 exercises with 10 to 15 repetitions in two sets. The total circuit included four exercises for both lower and upper extremities, and two exercises for the trunk. At weeks 4 to 26, the strengthening exercises mainly reproduced the exercises of weeks 1 to 3. Two exercises were done in a standing position for imitation of walking patterns. The patients were given two elastic bands (Theraband), one for the lower and the other for the upper extremities. At weeks 4 to 8, the program included two sets of 10 to 12 repetitions of each exercise. At week 9, the amount of repetitions was increased to 12 to 15. At week 15, new, stiffer elastic bands were delivered. Now, the repetitions were decreased to 10 to 12 for the rest of the exercise period.

Aerobic exercise. For weeks 1 to 3, aquatic training was chosen as a mode of aerobic exercise. For weeks 4 to 26, the patients were encouraged to continue with aquatic training, or with their earlier preferred mode of other aerobic exercise.

Exercise adherence. The patients kept a diary for each day of exercise. Adherence was determined for all exercise and for strength training and aerobic exercises separately using the number of exercise sessions reported as a percentage of exercise sessions prescribed for the home exercise period.

Sample size. Sample size was based on calculation for the 7.62 MWT. We defined a change of 20% to indicate a clinically meaningful improvement.[27] To detect a difference of this magnitude between the groups, a minimum of 62 patients was needed to provide 80% power at two-sided $\alpha = 0.05$. In sample size estimation we used as a reference a study in which the EDSS ranged from 1.0 to 3.5.[28] Because we also considered patients with higher EDSS scores, and to allow for a reasonable dropout rate, we aimed to recruit a total of 100 patients.

Statistical analysis. The baseline characteristics between groups were compared using the *t*-test, Wilcoxon's test, Mantel-Haenszel-test, or the χ^2 test. Primary and most secondary outcomes were analyzed using the general linear mixed model with repeated measures. Group and sex were included in the model as a between subject factor and time as a within subject factor. Covariate adjustment was applied if any imbalance was detected between groups, or if the covariate correlated with the outcome. As potential covariates, we chose EDSS and established biologic determinants of physical function. 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 analysis. The effect size statistic was calculated for the measures of the primary outcome. To interpret effects sizes, we used Cohen's classification, where a value of 0.2 is small, 0.5 medium, and 0.8 or higher is large.[29] All statistical analyses were done using the SAS for Windows package (SAS Institute, Cary, NC).

Results. *Patients.* Over an 8-month period in 2001, 276 patients were screened, and of these 114 were randomized to either the E or the C group. Data from 95 patients were included in the analyses (figure). Baseline subject characteristics were similar in both groups in most of the variables (table 1). There were no differences between the groups at baseline in either pyramidal functions ($p = 0.11$) or cerebellar functions ($p = 0.46$) of Kurtzke's Functional Systems Scales.

Disease progression. No change ($p = 0.93$) over time was seen in neurologic status as measured by EDSS. The

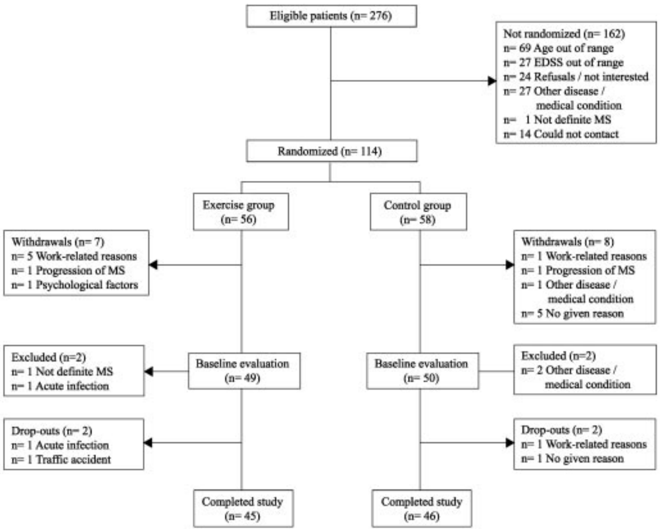

Figure. Flow chart showing the number of patients from screening to completion of the study. EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

group-by-time interaction in EDSS over the study period was also nonsignificant ($p = 0.16$).

Primary outcome. In exercisers, the 7.62 MWT time decreased by 12% (95% CI 16% to 7%, $p < 0.001$) relative to baseline. The C group also improved on the 7.62 MWT with a mean decrease of 6% (95% CI 11% to 2%, $p = 0.002$) in walk time. On the 500 MWT, mean walk time decreased by 6% in the E group (95% CI 10% to 2%, $p < 0.001$), whereas the time in the C group remained unchanged (mean change 0%, 95% CI −3% to 4%, $p = 0.99$). For change between groups, the group-by-time effect was significant in the 7.62 MWT, the 500 MWT, and the first 50 m lap of the 500 MWT (table 2). EDSS was a significant covariate ($p < 0.001$) in all variables of walking; on the 500 MWT, worsening by a 1.0 unit in EDSS denoted a slowing of about 47 seconds in walking time. Age was found a significant covariate in the 7.62 MWT ($p = 0.01$) and in the first 50 m lap of the 500 MWT ($p = 0.02$). The results of the primary outcome were not influenced by height, weight, or body mass index.

Ten (22%) patients in the E group improved ≥20% on the 7.62 MWT vs one patient (2%) in the C group ($p = 0.01$). Effect size on the 7.62 MWT was medium (0.50) in the E group and negligible (0.19) in the C group. On the 500 MWT, effect size was small (0.26) in the E group and negligible (0.02) in the C group.

Secondary outcomes. In the E group, knee flexion strength increased significantly. In the C group, the change in knee flexion strength was significant only on the right side. Improvements in lower extremity strength were greater in the E group than in the C group, but none of the between-group differences were significant (table 3). The E group improved significantly on upper extremity endurance (UEE) vs the C group: the mean change on the right UEE was 2.9 (95% CI 0.7 to 5.1) repetitions for the exercisers and 0.2 (95% CI −2.0 to 2.4) repetitions for the control patients ($p = 0.02$). The differences on the left UEE were 3.1 (95% CI 1.1 to 5.0) and 0.3 (95% CI −1.7 to 2.3) repetitions ($p = 0.01$).

Both groups improved over time on the Box and blocks tests; the average increase in number of blocks removed was 2.4 (95% CI 1.1 to 3.7) in the dominant hand and 1.3 (95% CI 0.1 to 2.5) in the nondominant hand. The difference between groups was not significant for either dominant ($p = 0.64$) or nondominant ($p = 0.84$) hand.

After adjusting for age ($p < 0.001$), sex ($p < 0.001$), and EDSS ($p = 0.001$), no group-by-time interaction ($p = 0.93$) was seen in the VO_2 peak. Further, no change over time was observed in static balance in either group.

Exercise adherence. Mean exercise adherence was 93 ± 46% for all exercise, 59 ± 31% for strength training, and 185 ± 144% for aerobic exercise. The proportion of exercisers doing less than one third of the prescribed strength training was 24%, and of prescribed aerobic exercise 9%. No exercise-related injuries were reported. Over the course of the trial, 11 relapses (5 in the E group, 6 in the C group) in nine patients were treated with steroids.

Discussion. The results of this randomized study show that long-term exercise led to significant and clinically meaningful changes in the walking speed of patients with mild to moderate MS. This was accompanied by significant improvements in upper extremity endurance. The intervention showed no effect between the groups on lower extremity

Table 1 *Baseline characteristics of study patients*

Variable	Exercise group, n = 47	Control group, n = 48	p Value
Men/women	17/30	17/31	0.94
Age, y	43.8 ± 6.3	43.9 ± 7.1	0.94
Height, cm	169 ± 7.9	170 ± 7.8	0.56
Weight, kg	69.6 ± 13.4	75.6 ± 14.6	0.04
BMI, kg/m^2	24.2 ± 3.7	26.0 ± 4.4	0.03
Years after first symptoms (min–max)	9.7 ± 7.7 (1–25)	9.6 ± 7.8 (1–37)	0.92
Years after diagnosis (min–max)	6.0 ± 6.5 (0–23)	5.5 ± 6.4 (0–28)	0.79
EDSS, median (min–max)	2.0 (1.0–5.5)	2.5 (1.0–5.5)	0.07
Using disease-modifying drugs, n (%)	19 (40)	26 (54)	0.18

Values are mean ± SD, unless otherwise noted.

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

Table 2 Results of 7.62 m (7.62 MWT) and 500 m (500 MWT) walk tests at baseline and 6-month changes (95% CI) in walking times

	Exercise group		Control group		
	Baseline mean ± SD	Change mean (95% CI)	Baseline mean ± SD	Change mean (95% CI)	p Value*
7.62 MWT (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
500 MWT					
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)	0.008
Time for 1st 50m (s)	30.4 ± 5.9	−2.31 (−3.23 to −1.39)	31.1 ± 6.3	−0.90 (−1.83 to 0.04)	0.006
Time for final 50m (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

* Of change between groups with group by time interaction.

strength, VO_2 peak, static balance, or manual dexterity. The clinical relapses of MS were evenly distributed between the two groups, showing that exercise has no detrimental effect on MS activity.

Our study adds important data on exercise responses in MS. Previously, three other randomized studies have examined the effects of regular exercise in MS patients.[2,4,30] Unlike our study, two of them used aerobic training under supervision as an intervention. Their exercise period was also shorter than ours: 4, 8, and 15 weeks.[2,4,30]

We observed an improvement of 12% (7.62 MWT) and 6% (500 MWT) in walking speed in exercisers compared to 6% and no change in control patients. According to effect size statistics, the exercise group showed moderate or slight improvements in walk tests vs negligible changes in the control group. The fact that 22% of the exercisers exceeded the threshold of 20% improvement on the 7.62 MWT indicates a true change in function.[27,31] Walking speed can be considered a key indicator of MS patients' general mobility already at the early stages of the disease.[32,33] Thus, there is a need to maintain and improve walking speed and other components of gait. Two earlier nonrandomized exercise studies in the field have given negative results.[10,11]

We chose walking speed as the primary outcome for several reasons. Restricted walking affects MS patients' ability to participate in family, social, vocational, and leisure activities. In addition, walking speed, in the psychometric sense, is a continuous variable with a sensitivity to change over time superior to traditional ordinal scales such as EDSS.[20,31] Third, walking deficits are major determinants of overall impairment in ambulatory MS patients.[20] This was made concrete by our finding that a 1-point increase on EDSS meant about 47 seconds slower walking on the 500 MWT. We applied two walk tests, because the 7.62 MWT is basically a test of walking speed, whereas the 500 MWT measures ambulatory endurance.[20]

Although muscle strengthening was emphasized in the home exercise, we were unable to show any significant difference between the groups in knee flexor and extensor strength. A possible explanation is training specificity: the greatest strength gains occur when the same exercise type is used for both training and testing.[34] Our measurement method, recording maximal static torque by a dynamometer, differed from exercises consisting of dynamic performance. In contrast to lower extremity strength, exercise resulted in improved upper extremity endurance, as measured by the dynamic weight lifting test. This supports the influence of training specificity, since one of the two home exercises for upper extremities closely resembled the test.

Our earlier cross-sectional study found no relationship between exercise capacity and leisure physical activity.[25] The overall results on the VO_2 peak are comparable to this. Yet 20 patients in the exercise group increased their VO_2 peak by an average of 27%. It is likely that many of the exercisers increased their total volume of exercise, which in turn would have contributed to beneficial effects on the VO_2 peak. For some reason as many as 25 patients in the control group also improved their VO_2 peak (mean increase 14%). This may be a consequence of the unblinded study design.

To ensure unbiased group comparison provided by randomization, an intention-to-treat analysis was used. The justification for our approach was evidenced by the large variance in exercise adherence

Table 3 Changes in maximal isometric knee muscle strength at 6 months

	Exercise group		Control group		
	Mean change (95% CI)	p Value	Mean change (95% CI)	p Value	Between-group difference, p value
Knee extension, right (Nm)	7.2 (−2.7 to 17.2)	0.24	5.0 (−4.8 to 14.8)	0.55	0.65
Knee extension, left (Nm)	5.9 (−1.7 to 13.5)	0.18	0.1 (−7.4 to 7.6)	1.00	0.42
Knee flexion, right (Nm)	9.6 (3.7 to 15.5)	<0.001	7.0 (1.2 to 12.8)	0.01	0.28
Knee flexion, left (Nm)	10.1 (3.6 to 16.6)	<0.001	4.4 (−1.9 to 10.8)	0.27	0.48

among the exercisers—intention-to-treat analysis reflects what might occur in actual clinical practice. Overall exercise adherence (93%) was excellent. However, the adherence rate of 59% for strength training fell markedly below the intended amount. In other studies using home-based resistance training, the adherence with the intervention protocol has been higher (78% or 95%).[15,30] Continuous guidance and support may be crucial in home exercise.[13] In our study, the frequency of the four phone contacts may have been insufficient to motivate the patients to exercise as requested.

Our study has several limitations. The assessment of exercise adherence was based on self-report diaries. Our impression was that some of the exercisers did not record their training conscientiously. Also, a possible source for observational bias is that the person who assessed walking speed was not completely blinded to group allocation. We tried to overcome this weakness by following strictly the practical guidelines set for independent assessment in randomized controlled trials.[16] Finally, we had to complete the random allocation of the patients to groups before fully confirming their eligibility. The explanation is logistic: all study patients were on the waiting list for inpatient adaptation training courses organized nationally in a rehabilitation center. The course date was negotiated individually with each patient, considering working or family life. Because of possible long traveling distances, the patients could not be examined before admission. Thus, randomization had to be done before setting the date of the inpatient course. We believe that the post-randomization exclusions were justified because the patients never received the intervention, and because an independent adjudication committee systematically reviewed all these patients.[35]

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References

1. Durstine JL, Painter P, Franklin BA, Morgan D, Pitetti KH, Roberts SO. Physical activity for the chronically ill and disabled. Sports Med 2000;30:207–219.
2. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol 1996;39:432–441.
3. Ponichtera-Mulcare JA, Mathews T, Barrett PJ, Gupta SC. Change in aerobic fitness of patients with multiple sclerosis during a 6-month training program. Sports Med Train Rehabil 1997;7:265–272.
4. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. Mult Scler 2002;8:161–168.
5. ACSM Position stand on the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 1998;30:975–991.
6. Svensson B, Gerdle B, Elert J. Endurance training in patients with multiple sclerosis: five case studies. Phys Ther 1994;74:1017–1026.
7. Thoumie P, Mevellec E. Relation between walking speed and muscle strength is affected by somatosensory loss in multiple sclerosis. J Neurol Neurosurg Psychiatry 2002;73:313–315.
8. Haghani H, Marks R. Relationship between maximal isometric knee extensor and flexor strength measures, age and walking speed of healthy men and women ages 18–74. Physiother Can 2000;52:33–38.
9. Gehlsen GM, Grigsby SA, Winant DM. Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis. Phys Ther 1984;64:653–657.
10. Gehlsen G, Beekman K, Assman N, Winant D, Seidle M, Carter A. Gait characteristics in multiple sclerosis: progressive changes and effects of exercise on parameters. Arch Phys Med Rehabil 1986;67:536–539.
11. Rodgers MM, Mulcare JA, King DL, Mathews T, Gupta SC, Glaser RM. Gait characteristics of individuals with multiple sclerosis before and after a 6-month aerobic training program. J Rehabil Res Dev 1999;36: 183–188.
12. Solari A, Filippini G, Gasco P, et al. Physical rehabilitation has a positive effect on disability in multiple sclerosis patients. Neurology 1999;52:57–62.
13. King AC, Haskell WL, Barr Taylor C, Kraemer HC, DeBusk RF. Group- vs home-based exercise training in healthy older men and women. A community-based clinical trial. JAMA 1991;266:1535–1542.
14. Robertson MC, Devlin N, Gardner MM, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 1: Randomised controlled trial. BMJ 2001;322:697–701.
15. Capodaglio P, Facioli M, Burroni E, Giordano A, Ferri A, Scaglioni G. Effectiveness of a home-based strengthening program for elderly males in Italy. A preliminary study. Aging Clin Exp Res 2002;14:28–34.
16. Siemonsma PC, Walker MF. Practical guidelines for independent assessment in randomized controlled trials (RCTs) of rehabilitation. Clin Rehabil 1997;11:273–279.
17. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13:227–231.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–1452.
19. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. Mult Scler 1999;5:244–250.
20. Schwid SR, Goodman AD, Mattson DH, et al. The measurement of ambulatory impairment in multiple sclerosis. Neurology 1997;49:1419–1424.
21. Schwid SR, Thornton CA, Pandya S, et al. Quantitative assessment of motor fatigue and strength in MS. Neurology 1999;53:743–750.
22. Romberg A, Virtanen A, Ruutiainen J. 7.62 m (25 ft) Walk Test—with or without acceleration-deceleration phase? In: Battistin L, Dam M, Tonin P, eds. Proceedings of the 3rd World Congress in Neurological Rehabilitation. Bologna: Monduzzi Editore, 2002;301–304.
23. Rytökoski U, Puukka P, Talo S. Biodisabilities in relation to other disease consequences in the functional assessment of patients with chronic low back pain. Int J Rehabil Res 1997;20:225–244.
24. Goodkin DE, Hertsgaard D, Seminary J. Upper extremity function in multiple sclerosis: improving assessment sensitivity with box-and-block and nine-hole peg tests. Arch Phys Med Rehabil 1988;69:850–854.
25. Romberg A, Virtanen A, Aunola S, Karppi S-L, Karanko H, Ruutiainen J. Exercise capacity, disability and leisure physical activity of subjects with multiple sclerosis. Mult Scler 2004;10:212–218.
26. Tesio L, Perucca L, Franchignoni FP, Battaglia MA. A short measure of balance in multiple sclerosis: validation through Rasch analysis. Funct Neurol 1997;12:255–265.
27. Kaufman M, Moyer D, Norton J. The significant change for the Timed 25-foot Walk in the Multiple Sclerosis Functional Composite. Mult Scler 2000;6:286–290.
28. Goodkin DE, Priore RL, Wende KE, et al. Comparing the ability of various composite outcomes to discriminate treatment effects in MS clinical trials. Mult Scler 1998;4:480–486.
29. Cohen J. Statistical power analysis for the behavioral sciences, revised ed. London: Academic Press, 1977.
30. DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. Arch Phys Med Rehabil 2004;85:290–297.
31. Schwid SR, Goodman AD, McDermott MP, Bever CF, Cook SD. Quantitative functional measures: what is a reliable change? Neurology 2002;58:1294–1296.
32. Holden MK, Gill KM, Magliozzi MR. Gait assessment for neurologically impaired patients. Standards for outcome assessment. Phys Ther 1986; 66:1530–1539.
33. Benedetti MG, Piperno R, Simoncini L, Bonato P, Tonini A, Giannini S. Gait abnormalities in minimally impaired multiple sclerosis patients. Mult Scler 1999;5:363–368.
34. Morrissey MC, Harman EA, Johnson MJ. Resistance training modes: specificity and effectiveness. Med Sci Sports Exerc 1995;27:648–660.
35. Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002;325:652–654.