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ORIGINAL COMMUNICATION

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

**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 nil. 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

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## 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 im-

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pairment 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 programme 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 retranslated 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 programme 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 programme 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 $\chi^2$ -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 % $\alpha$-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 were 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, $\geq 0.20$ a small, $\geq 0.50$ a medium and $\geq 0.80$ a large effect size [3].

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

## Results

Fig. 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

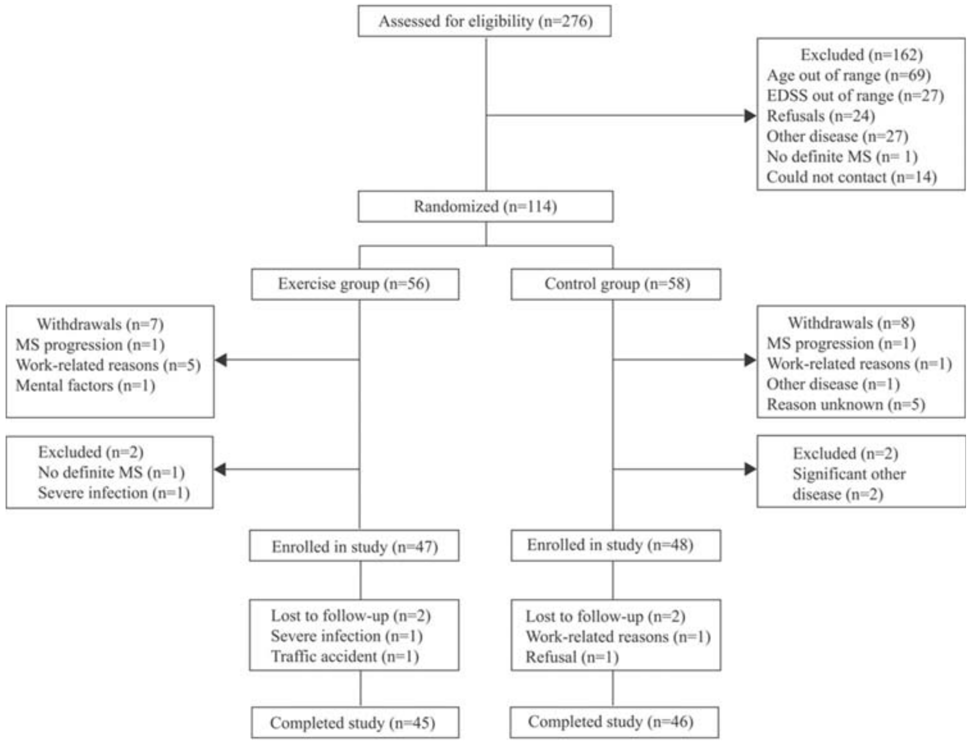


**Fig. 1** Flow diagram of the randomised controlled study

**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 (2–3.5) |
| 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

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) [23, 25]. 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

**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 ($p > 0.2$)

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 favouring 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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