Fatigue, mood and quality of life improve in MS patients after progressive resistance training

U Dalgas1,2,3, E Stenager2, J Jakobsen3, T Petersen3, HJ Hansen3, C Knudsen1, K Overgaard1 and T Ingemann-Hansen1

Abstract
Fatigue occurs in the majority of multiple sclerosis patients and therapeutic possibilities are few. Fatigue, mood and quality of life were studied in patients with multiple sclerosis following progressive resistance training leading to improvement of muscular strength and functional capacity. Fatigue (Fatigue Severity Scale, FSS), mood (Major Depression Inventory, MDI) and quality of life (physical and mental component scores, PCS and MCS, of SF36) were scored at start, end and follow-up of a randomized controlled clinical trial of 12 weeks of progressive resistance training in moderately disabled (Expanded Disability Status Scale, EDSS: 3–5.5) multiple sclerosis patients including a Control group (n = 15) and an Exercise group (n = 16). Fatigue (FSS > 4) was present in all patients. Scores of FSS, MDI, PCS–SF36 and MCS–SF36 were comparable at start of study in the two groups. Fatigue improved during exercise by −0.6 (95% confidence interval (CI) −1.4 to 0.4) a.u. vs. 0.1 (95% CI −0.4 to 0.6) a.u. in controls (p = 0.04), mood improved by −2.4 (95% CI −4.1 to 0.7) a.u. vs. 1.1 (−1.2 to 3.4) a.u. in controls (p = 0.01) and quality of life (PCS–SF36) improved by 3.5 (95% CI 1.4–5.7) a.u. vs. −1.0 (95% CI −3.4–1.4) a.u. in controls (p = 0.01). The beneficial effect of progressive resistance training on all scores was maintained at follow-up after further 12 weeks. Fatigue, mood and quality of life all improved following progressive resistance training, the beneficial effect being maintained for at least 12 weeks after end of intervention.

Keywords
exercise therapy, Fatigue Severity Scale, Major Depression Inventory, MFI-20, SF-36, strength training

Introduction
Subjects with multiple sclerosis (MS) progressively develop impaired functional capacity.1–3 In addition, the disease is associated with fatigue,4 depressed mood5 and impaired quality of life (QoL).6 As many as 55% of all MS patients describe fatigue as one of the most severe symptoms.7 Increased risk of depression is another complication associated with multiple sclerosis,8 influencing daily activity. Also, QoL is impaired in MS, possibly reflecting functional disabilities, mental complications and altered social behavior.5

Endurance training in MS has the potential to reduce fatigue,9,10 influence mood scores beneficially10 and improve QoL scores.9,11,12 It is, however, almost unexplored whether progressive resistance training (PRT) has an effect on these scores in patients with MS. Two small non-controlled trials13,14 reported improvement of fatigue after 8–10 weeks of biweekly PRT, but there is no data on the effect of PRT on mood in MS. Romberg et al.15 observed no effect on QoL scores after 26 weeks of combined endurance training and PRT. Nonetheless, studies in otherwise healthy but depressed elderly subjects have reported beneficial effects of PRT both on scores of depression and of QoL.16

Recently, we conducted a randomized controlled trial (RCT) of 12 weeks in patients with MS and demonstrated that strength of knee flexors and extensors, walking performance and stair climbing improved. After PRT the effect was maintained 12 weeks after end of training.17 Also, we tested the hypothesis that MS patients after improvement of leg

1Department of Sport Science, University of Aarhus, Denmark.
2Department of Neurology, Soenderborg Hospital, Denmark.
3Department of Neurology, Aarhus University Hospital, Denmark.

Corresponding author:
Ulrik Dalgas, Department of Sport Science, University of Aarhus, Dalgas Avenue 4, 8000 Aarhus C, Denmark. Email: dalgas@sport.au.dk
strength and leg functioning after 12 weeks of PRT will improve their scores of fatigue, mood and QoL, and that these improvements will be maintained for a short period of time after end of training. We now report the effect of PRT on fatigue mood and QoL.

Materials and methods

Study design

The present study is a controlled two-armed 12 week RCT including a post study follow-up period of 12 weeks. MS patients were randomized either to a progressive resistance training group (Exercise) or a control group (Control). The Exercise group completed a 12-week PRT program and was afterwards encouraged to continue training on their own without supervision or provision of training facilities. The Control group continued their previous daily activity level during the trial period. After end of the trial Controls were offered the same 12-week PRT intervention, as completed by the Exercise group.

Both groups were tested before (Pre), after 12 weeks of trial (Post) and at Follow-up at 12 weeks after the study end. The principal investigator (UD) supervised the exercise program and performed testing and data analysis. Testing consisted of subjects fulfilling four clinical scales in a quiet room without being disturbed. At all testing standardized instructions were applied. Also, a neurological examination, evaluation of isometric muscle strength and functional capacity were performed Pre and Post trial and at Follow up. A detailed description of these methods and results are published elsewhere.17

Before the study started, participants gave informed consent and the study was approved by the local scientific ethics committee (Videnskabsetisk Komité, Aarhus Amt, journal no. 20060088) and performed in accordance with the Helsinki Declaration 2. The study was registered at www.clinicaltrial.gov (NCT00381576).

Subjects

All participants were recruited among MS patients scheduled at the out-patients’ MS Clinic, Aarhus University Hospital during a 5-month period (May–October, 2006). To study a well defined disease entity, only patients with relapsing–remitting MS were included. Out of 426 MS patients 106 patients fulfilled the following study criteria: definite relapsing–remitting MS according to McDonald criteria,18 Expanded Disability Status Scale (EDSS) between 3.0 and 5.5 with a pyramid function score ≥2.0, ability to walk ≥100 m, no need for help with transportation to training facility, age >18 years and accept of diagnosis and treatment (no sign of crisis reaction, which was regularly evaluated by the team taking care of the patient). Patients were excluded if they suffered from dementia, alcoholism or had a pacemaker implanted, had any serious medical co-morbidities, had had an MS attack within the last 8 weeks, were pregnant or had trained systematic resistance training within the last 3 months. During the study the participants were excluded if they had an attack influencing the pyramidal functions or if they participated in less than 80% of the training sessions. The level of disability among the participants (EDSS 3–5.5 with 2 or more in pyramid function score) was chosen because these patients have some functional impairment but still have a preserved gait function needed for study participation. During a 17-month period (2 November 2006 to 3 March 2008), 38 MS patients were included after concealed randomization and blinded pre-testing. At post-testing and testing at follow-up neither the investigators nor the participants were given access to previous test results. During the randomization procedure the participants were stratified with respect to gender either to the Exercise group (n = 19) or the Control group (n = 19). One subject dropped out of the study because training worsened lower back pain. All other drop-outs were caused by circumstances unrelated to the intervention (Figure 1).

Progressive resistance training

The PRT intervention consisted of 12 weeks of resistance training of the lower extremities performed twice weekly (Monday and Thursday). Following a 5-min warm up on a stationary bicycle, patients performed five different exercises, namely leg press, knee extension, hip flexion, hamstring curl and hip extension. The participants were instructed to perform all exercises at a fast concentric phase and a slow eccentric phase. A resistance training protocol can be described in terms of sets, repetitions and load. A set is a group of exercise repetitions performed without rest and load is expressed as the repetition maximum (RM, e.g. 8RM indicating the heaviest load that can be lifted at eight repetitions at proper technique, meaning that 8RM is a heavier load than 10RM). In terms of sets, repetitions and load the progression model was as follows: Week 1–2: three sets of 10 repetitions at a load of 15RM; Week 3–4: three sets of 12 repetitions at a load of 12RM; Week 5–6: four sets of 12 repetitions at a load of 12RM; Week 7–8: four sets of 10 repetitions at a load of 10RM; Week 9–10: four sets of eight repetitions at a load of 8RM, Week 11–12: three sets of eight repetitions at a load of 8RM. Between sets and exercises a rest period of approximately 2–3 min was allowed. To ensure progression all training sessions were supervised. Most of the training sessions were carried out in groups of 2–4 subjects. If a participant
missed a training session it was attempted to substitute the session on an alternate day.

**Fatigue**

Fatigue was primarily tested using the one-dimensional Fatigue Severity Scale (FSS). As explanatory parameters the Multidimensional Fatigue Inventory (MFI-20) was performed, also. The FSS has been validated in MS patients and the test–retest reproducibility is acceptable. Also, FSS has a Danish version. MFI-20 is validated in various groups of patients, with acceptable reproducibility. Also, MFI-20 has a Danish version with a Danish reference material. The MFI-20 covers five dimensions of fatigue including General Fatigue (GF), Physical Fatigue (PF), Reduced Activity (RA), Reduced Motivation (RMO) and Mental Fatigue (MF). For both the FSS and MFI-20 scale higher scores indicate increased fatigue. A FSS score of 4 was used as cut-off value for definition of fatigue.

**Mood**

Mood scores were obtained using the Major Depression Inventory (MDI), which is developed and validated in Denmark. MDI scores between 20–24 indicate mild depression, scores of 25–29 moderate depression and scores above 29 severe depression.

**Quality of life**

Measures of health related QoL were obtained using the SF-36 questionnaire. SF-36 is translated to Danish and has been validated and tested for reliability in healthy Danes and includes a Danish reference material. The questionnaire comprises eight dimensions covering physical, mental and social aspects of health. For each dimension a score from 0 to 100 was calculated according to standard procedures. Subsequently, scores were transformed into a physical component scale (PCS) and a mental component scale (MCS), higher scores indicating a better QoL.

**Muscle strength and functional capacity**

Data extract from the publication on leg muscle strength (isometric knee extensor strength, KE MVC) and functional capacity (functional capacity score, FS) are shown in Table 2 in this paper. These data are shown to allow correlations between muscle strength and function and changes in fatigue, mood and QoL scores.
Statistics

As described elsewhere, the primary outcome measures of the study were KE MVC and FS. All other measures were secondary outcomes. However, the main focus of this part of the study was on changes of QoL, mood and fatigue in the Exercise and Control groups during the 12 weeks of trial. Secondary parameters were changes of QoL, mood and fatigue score after 12 weeks of self-guided physical activity (Exercise_{follow-up} − Exercise_{post} vs. Exercise_{post} − Exercise_{pre}) as well as changes of QoL, mood and fatigue score in the Control group after 12 weeks of PRT (Control_{follow-up} − Control_{post} vs. Control_{post} − Control_{pre}). Only participants completing the entire study (trial and follow up) were included in the final analysis.

At baseline pre-values were either compared using a Wilcoxon–Mann–Whitney test or an unpaired t-test for categorical and continuous variables, respectively. A Wilcoxon–Mann–Whitney test was used to compare differences between Pre and Post values in the Exercise group vs. the Control group. A Wilcoxon signed rank test on paired observations was used to compare Post and Follow-up values in the Exercise group and Pre vs. Post changes with Post vs. Follow-up changes in the Control group. Furthermore, correlation analyses (Spearman) were performed to assess associations between changes in selected questionnaire scores, muscle strength and functional capacity during the intervention period. The correlation analyses were performed on collapsed data from both groups and from all study arms. In the correlation analyses MDI and SF-36 scores were included as corrected as well as uncorrected for the influence of fatigue (MDI: Item 3 excluded; SF-36: Item 'Vitality' excluded). All statistical analysis was performed using a 5% limit of significance. Data are presented using mean ± SD.

### Results

Table 1 shows demographic data and information about severity, duration and treatment of MS in the Control and the Exercise groups without any differences between groups. Table 2 shows that scores of fatigue, mood and QoL at study start were similar in the two groups. Also, Table 2 shows the effect of PRT on knee extension strength and on a combined function test performance score. In the Exercise and Control group no subjects at baseline had FSS scores below the cut-off point of 4, indicating that all subjects were fatigued. In the Exercise group one subject was classified as having mild depression at baseline whereas none of the control subjects were depressed.

### Effects of 12 weeks of PRT

Fifteen patients in the Exercise group and 16 in the Control group completed the study. No subjects were excluded because of lack of training session compliance.

EDSS and body weight remained unchanged during trial in both groups of MS patients. Participants in the Exercise group completed a total of 23.9 (95% confidence interval (CI) 23.7–24) sessions out of the planned 24 PRT sessions.

#### Fatigue

All subjects were fatigued with a FSS > 4. Figure 2 shows that the FSS score changes improved significantly in the Exercise group versus the Control group ($p < 0.05$). Also, changes of General Fatigue of the MFI-20 scale improved significantly in the Exercise group versus the Control group ($p < 0.05$, Table 2). No explanatory dimensions of the MFI-20 scale differed significantly between the two groups (Table 2).

#### Mood

Figure 2 shows that the MDI score changes improved significantly after resistance training in the Exercise group vs. the Control group ($p < 0.05$).

### Table 1. Demographic data at baseline

<table>
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<th></th>
<th>Control</th>
<th>Exercise</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Numbers</td>
<td>16 (6/10%)</td>
<td>15 (5/10%)</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.1 ± 8.4</td>
<td>47.7 ± 10.4</td>
<td>0.67</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168.9 ± 12.3</td>
<td>169.8 ± 9.4</td>
<td>0.81</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.9 ± 15.2</td>
<td>70.1 ± 14.2</td>
<td>0.55</td>
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<tr>
<td>EDSS (arbitrary units)</td>
<td>3.9 ± 0.9</td>
<td>3.7 ± 0.9</td>
<td>0.53</td>
</tr>
<tr>
<td>Time since diagnose (years)</td>
<td>8.1 ± 6.0</td>
<td>6.6 ± 5.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Immunomodulatory treatment (%)</td>
<td>11/5</td>
<td>7/8</td>
<td>0.28</td>
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</table>

Data are given as mean ± SD.
Table 2. Changes in questionnaire score, muscle strength and functional capacity before (pre) and after (post) 12 weeks of RCT and 12 weeks later at follow-up (↑ = improved SF-36; ↓ = improved FSS, MFI-20 and MDI)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Time effect</th>
<th>Exercise</th>
<th>p-value</th>
<th>Group effect</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Follow-up</td>
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<td>Control post–pre</td>
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<td></td>
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<td></td>
<td>vs. follow up–post</td>
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<td>Pre</td>
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<td>Follow-up</td>
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<td>vs. follow up–post</td>
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<td></td>
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<td></td>
<td>Control post–pre</td>
<td></td>
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</table>

<table>
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<tr>
<th></th>
<th>Control</th>
<th>p-value</th>
<th>Exercise</th>
<th>p-value</th>
<th>Group effect</th>
<th>p-value</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Exercise post–pre</td>
<td></td>
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</table>
Quality of life. Figure 2 shows that the changes of the SF-36 physical component improved significantly in the Exercise group vs. the Control group ($p < 0.05$). There was no significant ($p = 0.09$) difference between the two groups for the SF-36 mental component (Table 2).

Effects of PRT at follow-up

At follow-up 12 weeks later no significant deterioration occurred in comparison with post trial values of scores of fatigue, mood or QoL.

Effects of 12 weeks of post-trial PRT in the Control group

Participants in the Control group completed an average of 22.6 (95% CI 21.5–23.7) sessions out of 24 planned PRT sessions during the 12 weeks’ exercise period after the trial.

Fatigue. There was no significant beneficial effect on the changes of the FSS score after resistance training (Table 2). However, the general fatigue score of the MFI-20 scale improved significantly as compared to the previous control period ($p < 0.05$). No other scores of the MFI-20 questionnaire showed significant improvements after resistance training as compared to the previous control period (Table 2).

Mood. There was no significant effect of the MDI score in controls after resistance training as compared to the trial period (Table 2).

Quality of life. The change of the SF-36 mental component after resistance training improved significantly as compared to the previous control period ($p < 0.05$, Table 2). No significant improvement in SF-36 physical component occurred after resistance training as compared to the previous control period (Table 2).

Correlations. Changes of the FSS scores during resistance training correlated with changes of mood scores and the mental component score of SF-36, but not with the physical component score of SF-36. The changes of mood score correlated with the physical as well as the mental component score of the SF-36 score. Furthermore, changes in mood scores and physical component scores correlated with changes in functional capacity scores. When the SF-36 scores were corrected for items concerning fatigue the correlations between mood scores and physical component scores and between mood scores and functional capacity scores were no longer significant (Table 3).
Discussion

The results of the present study demonstrate that supervised resistance training of the lower extremity improves scores of fatigue, mood and QoL in subjects with relapsing–remitting MS. Furthermore, the improvements attained during resistance training, were maintained for at least 12 weeks of self-guided physical activity. The observations that resistance training in MS improves fatigue, mood and QoL could partly be reproduced in the Control group during the post trial follow-up period. As hypothesized the effect of resistance training in MS is versatile improving fatigue, mood as well as QoL.

Fatigue

Our data showed a small but significant improvement of the FSS score in the Exercise group versus the Control group. Furthermore, changes in general fatigue on the MFI-20 scale improved significantly in the Exercise group versus the Control group. Our data, therefore, indicate that resistance training has a beneficial effect on MS fatigue. This finding is interesting because fatigue is a frequent and severe symptom among patients with MS.4 As many as 55% of all MS patients report that fatigue is one of the most disabling symptoms.7 Furthermore, a recent review concluded that the effectiveness of both pharmacological and psychosocial/psychological interventions counteracting MS fatigue at best is modest and often absent.29

Traditionally, a cut-off score of 4 have been applied to define fatigue because only 5% of healthy controls were reported to have scores above this level.10 However, in a mixed group of healthy Norwegian subjects between 40–60 years average FSS scores of 3.9–4.0 were found, which made the authors suggest that a cut-off value of 5 should be applied.30 It was, however, also stated that further validation of this cut-off point were needed.30 Nonetheless, data from our study showed that participants did experience fatigue before the intervention [Baseline: 5.5 (95% CI 5.0–6.0) and 5.8 (95% CI 5.4–6.1) in the Control and Exercise groups, respectively] corresponding to a level reported in other studies.31,32 Despite the fact that recruitment of our subjects was based on EDSS score rather than fatigue, all participants had FSS scores above the cut-off point of 4, indicating that the subjects are well suited for the present study. Furthermore, when comparing the five dimensions of the MFI-20 scale it was found that a mixed group of healthy Danish subjects between 40–49 years (GF:7.0; PF:6.2; RA:4.2; RMO:3.6; MF:5.0)23 scored lower than our subjects [Exercise group: GF:12.9 (95% CI 10.9–14.9); PF:12.1 (95% CI 9.7–14.5); RA:11.0 (95% CI 9.1–12.9); RMO:7.8 (95% CI 6.3–9.3); MF:10.6 (95% CI 8.0–13.2)] before the study.

The present study support the findings of the few existing reports examining the effects of resistance training on fatigue in MS patients. In a non-controlled study White et al.13 reported a reduction in fatigue score evaluated with the Modified Fatigue Impact Scale after 8 weeks of lower extremity resistance training. In another non-controlled study Dodd et al.14 using a qualitative approach, also reported reduced fatigue in seven out of nine patients after 10 weeks of biweekly training.

Endurance training has the potential to reduce fatigue, but findings are inconsistent, some studies showing an effect4,10,33 whereas others do not.11,12,24–26

Table 3. Relationships between changes of scores of fatigue (FSS), mood (MDI), quality of life physical (PCS) and mental (MCS) component, knee extensor muscle strength (KE MVC) and functional capacity score (FS)

<table>
<thead>
<tr>
<th>Correlated parameters</th>
<th>Scores</th>
<th>Corrected scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>p-value</td>
</tr>
<tr>
<td>FSS vs. MDI</td>
<td>0.35</td>
<td>0.006</td>
</tr>
<tr>
<td>FSS vs. PCS</td>
<td>-0.11</td>
<td>n.s.</td>
</tr>
<tr>
<td>FSS vs. MCS</td>
<td>0.39</td>
<td>0.002</td>
</tr>
<tr>
<td>FSS vs. KE MVC</td>
<td>0.14</td>
<td>n.s.</td>
</tr>
<tr>
<td>FSS vs. FS</td>
<td>-0.05</td>
<td>n.s.</td>
</tr>
<tr>
<td>MDI vs. PCS</td>
<td>-0.26</td>
<td>0.044</td>
</tr>
<tr>
<td>MDI vs. MCS</td>
<td>-0.45</td>
<td>0.0003</td>
</tr>
<tr>
<td>MDI vs. KE MVC</td>
<td>-0.21</td>
<td>n.s.</td>
</tr>
<tr>
<td>MDI vs. FS</td>
<td>-0.31</td>
<td>0.017</td>
</tr>
<tr>
<td>PCS vs. MCS</td>
<td>-0.25</td>
<td>0.049</td>
</tr>
<tr>
<td>PCS vs. KE MVC</td>
<td>0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>PCS vs. FS</td>
<td>0.26</td>
<td>0.046</td>
</tr>
</tbody>
</table>

<sup>a</sup>MDI, PCS and MCS corrected for the influence of fatigue scores; n.s., non-significant.
Consequently, resistance training seems to be at least as successful as endurance training in reducing fatigue in MS patients. A few studies have studied the effect of combined resistance and endurance training on MS fatigue. Fragozo et al. reported that 20 weeks of combined training 3 days a week reduced Chalder's score for fatigue, whereas no effect was found by Surakke et al. after 23 weeks of combined training at home.

Interestingly, studies that reported an effect of endurance training on fatigue either used the multidimensional Modified Fatigue Impact Scale (MFIS) or the Multidimensional Fatigue Inventory (MFI). All studies, except one, that were unable to demonstrate an effect of endurance training used the one-dimensional FSS. This finding could indicate that the FSS is not as sensitive a measure of MS-related fatigue as some of the multidimensional scales. Nevertheless, a significant reduction of FSS scores was observed following PRT in the present study.

No correlations were found between changes of fatigue and muscle strength or functional capacity indicating that other factors explain the improvements seen in fatigue. One factor could be mood which is supported by the weak but significant correlation between the changes of these two variables. A weak correlation persisted when questions regarding fatigue was removed from the mood score. The direction of this relationship was, however, not examined in this study. Other intervention studies examining fatigue and mood have, also, found a relationship between mood and fatigue. Bakshi et al. have suggested that fatigue and mood share common underlying mechanisms such as psychological factors or brain lesions in specific neural pathways. An alternative mechanism explaining the improved fatigue score could be an improved central muscle activation. A recent study by Andreasen et al. showed that patients experiencing both primary and secondary fatigue had impaired central muscle activation. Data from sedentary healthy subjects have shown that resistance training has the potential to improve central muscle activation, but this needs to be addressed in MS patients in future studies.

Endurance and resistance training can be considered two extremes of a continuum constituting basic physical exercise. Consequently, this leads to the suggestion that exercise in general has the potential to reduce fatigue in MS patients. However, studies on the effectiveness of different training modalities and the influence of training intensity and frequency on MS fatigue are warranted.

**Mood**

The incidence of depression is increased in MS. In the present study only one of the participating subjects in the Exercise group could be characterized as having mild depression at baseline. After the trial the MDI score of this subject was no longer above the cut-off level for mild depression. To our knowledge the present study is the first to evaluate the effects of resistance training on mood scores. A significant decrease was seen in the MDI score in the Exercise group versus the Control group. Compared to data of healthy Danish subjects aged 35–49 years with a MDI score of 7.26 participants had a score of 10.3 (95% CI 7.0–13.5) at study start and a score of 7.9 (95% CI 5.2–10.6) after exercise. Studies examining the effects of endurance training on mood scores in MS patients have reported improvements or no effect. Thus, both endurance and resistance training seem to have the potential to beneficially influence mood and depression in MS patients.

**Quality of life**

To our knowledge there are no other reports examining the effects of resistance training on QoL in subjects with MS. A significant increase was found of the physical component of the SF-36, whereas a trend was seen for the mental component (p = 0.09) in the Exercise group, only. This is an interesting finding because it is known, that QoL is reduced in MS patients. In particular, the physical component score of 41.4 (95% CI 37.5–45.3) was impaired in our participants as compared with healthy Danish subjects, who had a score of 50.4. In contrast, the mental component scores of 54.3 (95% CI 50.4–58.2) in MS vs. 54.1 in healthy Danish subjects are similar. In general, data describing the effects of endurance training on QoL scores have shown beneficial effects. QoL measures like SF-36 and multiple sclerosis quality of life (MSQOL) have been used as questionnaires for MS (HAQUAMS) and POMS all have shown improvements for items regarding vitality, social functioning, mood, energy, fatigue, anger, sexual function and depression.

**Are the observed changes clinically relevant?**

In general this study revealed small but significant improvements of fatigue, mood and QoL. Therefore, it is relevant to ask whether these findings have clinical significance. In the Exercise group the FSS improved from 5.8 (95% CI 5.4–6.1) to 5.2 (95% CI 4.4–6.0). The fatigue score is, therefore, approaching the cut-off score of 5.0 proposed by Lerdal et al. and at the Follow-up test the score had actually fallen below the cut-off score 4.9 (95% CI 4.3–5.5). According to the cut-off score by Lerdal et al. the change does have clinical relevance for most patients, whereas only a few subjects came below the cut-off score of 4.0 proposed by Krupp et al.
Regarding the MDI score the participants were not depressed at study start although the score was higher than seen in healthy controls. The MDI distinguishes between no, mild, moderate and severe depression. If clinical relevance is defined as a change from one category to another then the observed improvements have no clinical relevance and a study including only depressive MS patients as participants would be a prerequisite. On the other hand, it might be of importance to MS patients to know that 12 weeks of exercise can normalize their MDI score.

The observed changes in both fatigue and mood are obtained after only 12 weeks of training and a prolonged training period, therefore, might lead to further improvements. In MS patients further improvements occur in measures of physical capacity such as maximal oxygen consumption (VO2-max) when the training program lasts 6 months (VO2-max improvements after 3 and 6 months were 10 and 15%, respectively). The present study, therefore, may point out the direction of change but not necessarily the potential size of the improvements.

Limited reproducibility in the Control group
After 12 weeks of exercise in the Control group only some of the changes seen in the Exercise group after exercise could be reproduced. Although the FSS score showed a trend towards an improvement in the Control group, no changes were seen in MDI score and in PCS of the SF-36. These discrepancies complicate the interpretation of the data, and emphasizes that these data are secondary outcome measures which the study was not powered to measure. Another explanation for the discrepancies could be, that the participants in the Control group might have felt that they were deselected at the expense of the participants in the Exercise group because of the 12 week ‘waiting period’ despite our attempts to make all participants feel equally important.

Limitations and methodological issues
This study has several limitations that should be kept in mind when interpreting the results. First of all, the participants represent a selected group of relapsing–remitting MS patients. It seems reasonable to expect that MS patients having an EDSS score between 0 and 3 in general would be able to tolerate and benefit from resistance training. However, it is more questionable whether the results can be generalized to the more severely impaired MS patients (EDSS > 5.5). In these patients the training intervention would need to be much more individualized due to considerable differences of functional capacity. Secondly, the participants and some of the supervising investigators were not blinded to the intervention. It is, however, very difficult to blind participants to exercise intervention because placebo exercise intervention often will be revealed by participants. Thirdly, we chose a design in which social interaction could influence the effects of resistance training. Consequently, a cause and effect relationship cannot be established based on the present study. Future studies examining the effects of PRT on fatigue, mood and QoL should, therefore, consider the inclusion of a group receiving ‘placebo exercise’ in the study design despite the associated difficulties.

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