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Efficacy of high-intensity aerobic exercise on common multiple sclerosis symptoms

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Abstract

Objectives: Fatigue and walking impairment are disabling symptoms of multiple sclerosis (MS). We investigated the effects of progressive aerobic exercise (PAE) on fatigue, walking, cardiorespiratory fitness (VO_2max)**,** and quality of life in people with MS (pwMS).

Materials & Methods: Randomized controlled trial (1:1 ratio, stratified by sex) with a 24-week crossover follow-up and intention-to-treat analysis. Allocation to an exercise (24 weeks of PAE followed by self-guided physical activity) and a waitlist (24 weeks of habitual lifestyle followed by PAE) group. PAE comprised two supervised sessions per week; 30-60min, 65%-95% of maximum heart rate. Fatigue impact (Modified Fatigue Impact Scale; MFIS) and severity (Fatigue Severity Scale; FSS), walking ability (12-item MS Walking Scale; MSWS-12) and capacity (Six-Minute Walk Test; 6MWT, Six Spot Step Test; SSST), quality of life (Short Form 36 health survey; SF-36), and VO_2max were measured at baseline, 24 weeks, and 48 weeks.

Results: Eighty-six pwMS were enrolled. Following PAE between-group differences showed reductions in $MFIS_{total}$ (-5.3 [95% CI: -10.9;0.4], point estimate > clinical relevance), $MFIS_{physical}$ subscore (-2.8 [-5.6;-0.1]), and $MFIS_{psychosocial}$ subscore (-0.9 [-1.6;-0.2]), and an increase in VO_2max (+3.5 mL O_2/min/kg [2.0;5.1]). MSWS-12 (-5.9 [-11.9; 0.2]) and 6MWT (+14 m [-5;33]) differences suggested potential small walking improvements. No changes observed in FSS, SSST, or SF-36.

Conclusions: In a representative sample of pwMS, PAE induced a clinically relevant reduction in fatigue impact, whereas small and no effects were seen for walking and quality of life, respectively. The results need confirmation in a future trial due to the study limitations.

Registration: ClinicalTrials.gov: NCT02661555.

Key words: Exercise therapy, rehabilitation, fatigue, aerobic training.

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, and neurodegenerative disorder of the central nervous system with no existing cure.[1] Fatigue and walking impairment are two disabling and common symptoms of MS.[2] Together, these symptoms contribute substantially to self-rated health, compromising the patients' quality of life and participation in activities of daily living.[2] MS-related fatigue can be defined as "a lack of physical and/or mental energy that is perceived by the

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individual or the caregiver to interfere with usual and desired activities".[3] It is a multidimensional and complex symptom that, because of its multifaceted origins, has no clear etiology. So far, both central and peripheral explanatory fatigue mechanisms have been put forward.[4] Generally, the symptom is termed "primary fatigue" when it is directly related to disease mechanisms (e.g. inflammation, demyelination), while "secondary fatigue" is caused by non-disease-specific factors (e.g. physical inactivity, medication, sleep deprivation, depression).[3, 4] Previous studies report that 70–90% of people with MS (pwMS) experience fatigue, and 55% of pwMS describe fatigue as one of their worst symptoms, highlighting the impact of fatigue on health status in pwMS.[4] Another frequent MS symptom that is highly valued by both physicians and early and long-term MS patients is walking impairment.[5] Moreover, the prevalence of walking impairment is reported to increase from 32-100% across the adult life span in pwMS,[6] often producing a variety of consequences ultimately affecting quality of life.[7] Hence, both fatigue and walking impairment have important clinical implications in MS.

During the past 2 decades exercise has become accepted as a safe and powerful therapeutic strategy. Several systematic as well as narrative reviews have demonstrated that exercise is safe and leads to numerous positive effects in pwMS.[8, 9] Moreover, cumulating evidence support reductions of MS fatigue following exercise interventions.[10-12] Interestingly, a Cochrane review proposed aerobic exercise to be particularly potent in reducing self-reported fatigue in MS.[12] On top of that, aerobic exercise is well known to have beneficial physiological effects in terms of improving cardiorespiratory fitness (i.e. VO_2max), a crucial health and performance indicator for pwMS, which has also been associated with better walking performance.[13] However, existing studies hold limitations that could compromise the completeness, applicability, and reliability of previous results on the effects of aerobic exercise on MS fatigue. Among these limitations are: large heterogeneity regarding the applied fatigue scales, lack of statistical power, inappropriate designs to detect effects of exercise on fatigue, and limited reporting on patient characteristics, adverse events, and intervention characteristics.[14, 15] Specifically, the vast majority of previous aerobic exercise studies have applied low to moderate intensity interventions[12] despite the fact that high-intensity aerobic exercise leads to greater cardioprotective benefits and may be superior in ameliorating secondary MS fatigue through a higher increase in fitness and motor efficiency.[4, 16] Furthermore, interventions have generally been short lasting ≤12 weeks (and most often without follow-up), which is likely insufficient to induce potential cardiovascular, immunologic, neuroendocrine, and neurotrophic changes that may be required to improve primary MS fatigue.[4]

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Consequently, the aim of this project was to investigate the effects of a 24-week high-intensity progressive aerobic exercise (PAE) intervention followed by 24 weeks of follow-up on 1) self-reported fatigue impact and severity, 2) objectively measured walking capacity and VO_2max and self-reported walking ability, and 3) quality of life. We hypothesized that PAE would reduce fatigue impact and severity and improve walking capacity and ability, VO_2max as well as quality of life.

Materials & Methods

The present study conforms to the CONSORT 2010 guidelines.[17] It presents secondary data analyses from a randomized controlled trial (RCT) investigating the effects of aerobic exercise on brain health and cognition in pwMS (trial registered at ClinicalTrials.gov, identifier: NCT02661555). The primary analysis of this trial, investigating the effect of PAE on brain atrophy outcomes, has previously been published elsewhere (also covering study design and participants, flowchart, adherence data, baseline characteristics, and Six-Minute Walk Test (6MWT) and cardiorespiratory fitness (VO_2max) data).[18] Furthermore, a cross-sectional study (baseline data)[19] examining associations between cardiorespiratory fitness and cognitive performance and a longitudinal study examining the effect of PAE on cognitive performance[20] have also previously been published from the trial.

Study design and participants

This was a 24-week RCT with a cross-over follow-up. The first part of the study (i.e. 0 to 24 weeks) was *a priori* considered as the RCT part and the remainder as a follow-up part. This study design was chosen to reduce drop outs (i.e. with all receiving the intervention, either immediately or delayed), to replicate and potentially verify RCT intervention findings in the follow-up part, and to analyze follow-up data in the RCT intervention group.[18]

Eighty-six participants were recruited from Danish MS clinics. Detailed information on eligibility criteria along with recruitment process has been reported previously.[18, 19] Participants gave written informed consent. The study was approved by the ethical committee of the Central Denmark Region, Denmark (record no. 1-10-72-291-15).

Following inclusion and baseline testing, participants were randomized (1:1) to a PAE or waitlist group using block randomization, stratified by sex. The PAE group underwent supervised high-intensity PAE for 24 weeks, while the waitlist group continued their habitual lifestyle (including

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ongoing physiotherapy treatment). After 24 weeks, the waitlist group underwent the same PAE intervention, while the initial PAE group was encouraged to continue community based self-guided exercise without supervision of the researchers.[18] Figure 1 illustrates the study design and flowchart.

Progressive aerobic exercise intervention

Supervised PAE sessions were conducted twice weekly during the 24 weeks, with one continuous and one interval exercise session performed each week. The session volume increased from 30 to 60 min during the intervention while intensity increased from 65 to 95% of individual maximum heart rate. Exercise modality options included cycling, rowing, and cross training and were self-chosen by the participants from session to session. In order to increase participant motivation and adherence to the intervention along with variability in the exercise stimuli, the sessions alternated between continuous and interval exercise. From a pragmatic point of view, the intervention included two weekly training sessions, as it has previously shown sufficient to induce improvements in the maximal oxygen consumption velocity.[21] Also, 2 sessions per week allowed sufficient time for recovery and the opportunity to continue community-based exercise. Please see Langeskov-Christensen et al.[18] for further details on the exercise intervention.

Outcomes

At baseline (T0), after 24 (T24), and after 48 (T48) weeks, all participants performed a VO_2max test, the 6MWT, and the Six Spot Step Test (SSST), and completed questionnaires assessing fatigue impact (Modified Fatigue Impact Scale; MFIS), fatigue severity (Fatigue Severity Scale; FSS), walking ability (12-item MS Walking Scale; MSWS-12), and quality of life (Short Form (36) health survey; SF-36). Test sessions were separated by a minimum of 48 hours and a maximum of 10 days from the last exercise bout.

An incremental exercise test until exhaustion on a bicycle ergometer was applied to determine directly measured VO_2-max (Oxigraf O2CPX, Oxigraf Inc., Sunnyvale, CA, USA). For further details, see Langeskov-Christensen et al.[19] VO_2-max was considered a "compliance" outcome (i.e. did the aerobic exercise intervention improve the cardiorespiratory fitness as intended). Consequently, it was not included in relation to the research questions regarding fatigue, walking, and quality of life *per se*. Nonetheless, previous work from our group has demonstrated associations between VO_2-max in pwMS and parameters such as fatigue, walking, and quality of life[22], demonstrating the importance of VO_2-max as a health and performance marker in MS.

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To objectively assess walking capacity, the 6MWT was used. The 6MWT is a feasible, reproducible, and reliable measure in MS.[23] Participants were permitted habitual assistive devices during testing and were instructed to complete the 6MWT ”at their fastest speed and to cover as much distance as possible” on a 30-meter hallway pivoting at each end of the hall. The total distance walked after 6 min was registered.

The SSST was applied as an objective measure of walking performance. The test involves fast crisscross walking along a 5-m rectangular course, while kicking five blocks out of circles marked on the floor, and thereby extends traditional walking outcomes in pwMS by further challenging components of coordination and balance.[24] The SSST has an acceptable within- and between-day agreement and reliability, and valid timing can be performed by a handheld stopwatch.[25]

The MFIS and the FSS,[26] two of the most commonly used subjective fatigue assessments, were used to determine effects on fatigue impact and severity, respectively. The MFIS includes a total score and three subscores (physical, cognitive, and psychosocial). The FSS is a unidimensional, nine-item questionnaire providing an overall average score. The MFIS and the FSS are scaled so that higher scores indicate a greater impact or severity of fatigue, respectively. The reliability and precision of both scales are acceptable and provide researchers and clinicians with valuable information that can be used to interpret whether a change in MS fatigue impact or severity has occurred.[26]

The reliable, sensitive, and valid MSWS-12 was used to determine self-assessed limitations in walking ability.[27] The MSWS-12 has been reported to be an appropriate questionnaire in detecting clinically meaningful improvement after physical rehabilitation, with higher scores indicating a greater impact on walking than lower scores.[27]

To assess quality of life, the widely used SF-36 questionnaire was applied, covering a physical and a mental subscore.[28]

Statistical analysis

The power calculation for this study has been described elsewhere (the main RCT was powered towards brain volumetric changes).[18] Descriptive baseline variables modeled as continuous were assumed to follow a normal distribution. All analyses were performed using an intention-to-treat linear mixed effects model including all randomized participants. Patients who dropped out contributed with information in their respective groups until they dropped out. Data were analyzed using a mixed-effects analysis for repeated measures with time and group as fixed effects and patient ID as a random effect. Likelihood-ratio tests were used to test for equal/unequal standard

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deviations and correlations in the two groups for each outcome. Model validation was performed by inspecting the standardized residuals (i.e. QQ-plots, plots of the standardized residuals against the fitted values). Linear combinations of estimates were used to compute point estimates of group changes of interest (e.g. comparison of exercise and waitlist group changes from T0 to T24). Explorative within-group changes in the RCT part were only tested (using unadjusted *post hoc* linear pairwise comparisons) if a significant interaction was found but linear combinations of estimates showed no between group effect (i.e. MSWS-12, 6MWT). RCT intervention group follow-up data were analyzed using unadjusted *post hoc* linear pairwise comparisons to test within-group changes.

To further explore associations between relevant baseline and change values in the RCT part, we conducted *post hoc* univariate regression analyses to evaluate crude associations in the total sample. Descriptive and raw data were presented as mean (SD) or n (%) and changes were stated as mean [95% CI]. Consistent with contemporary statistical guidelines, the use of P values for secondary and other comparisons was toned down when interpreting the results of this study (i.e. P values were included but not in the conventional, dichotomous way).[29, 30] Rather, the "ATOM" (i.e. "Accept uncertainty. Be thoughtful, open, and modest.") recommendations from the The American Statistician were followed.[31]

Graphs were made using GraphPad Prism version 8.0.1. Statistical calculations were performed in Stata version 15.1. Statistical significance was set at $p<0.05$.

Results

Participants were recruited between 28 April 2016 and 10 October 2017. Among 148 pwMS assessed for eligibility and invited to participate, 86 were included and assessed in the trial. Of these, 64 completed the full 48 weeks of the trial (figure 1). There were 13 dropouts after 24 weeks (15.1%) and 9 additional dropouts after 48 weeks, producing a total dropout of 22 (25.6%). The various reasons for exclusions are detailed in figure 1.

Baseline (T0)

Baseline demographic and clinical characteristics of the study population are shown in Table 1. Wide ranges of age (23–64 years), disability (EDSS 0–6), and time since diagnosis (0–38 years) were observed in this sample with a distribution of relapsing-remitting (87.2%) and progressive (12.8%) MS patients.

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RCT findings (T0 to T24)

All longitudinal outcomes are presented in Table 2. Reductions were observed in $MFIS_{total}$ score (figure 2) and $MFIS_{physical}$ and $MFIS_{psychosocial}$ subscores, whereas VO_2max increased following 24 weeks of PAE. Moreover, results suggested a potential reduction in MSWS-12 (figure 3) and a potential increase in 6MWT. No between-group effects were observed in the $MFIS_{cognitive}$, FSS, SSST, and the $SF\text{-}36_{physical}$ and $SF\text{-}36_{mental}$ subscores.

Post hoc baseline analyses showed that VO_2max was associated with $MFIS_{total}$ ($r=-0.32$, $p<0.01$), MSWS-12 ($r=-0.45$, $p<0.01$), 6MWT ($r=0.63$, $p<0.01$), SSST ($r=-0.39$, $p<0.01$), $SF\text{-}36_{physical}$ ($r=0.34$, $p<0.01$), and FSS ($r=-0.20$, trend only: $p=0.08$), but not with $SF\text{-}36_{mental}$ ($r=-0.03$, $p=0.78$). When exploring the potential to change within each outcome, the change was associated with the baseline level in $MFIS_{total}$ ($r=-0.31$, $p<0.01$), FSS ($r=-0.34$, $p<0.01$), MSWS-12 ($r=-0.29$, $p=0.01$), SSST ($r=-0.46$, $p<0.01$), and the $SF\text{-}36_{physical}$ ($r=-0.28$, $p=0.02$) and $SF\text{-}36_{mental}$ ($r=-0.53$, $p<0.01$) subscores, but not for the 6MWT ($r=0.03$, $p=0.83$). Additional analyses showed that change in VO_2max was associated with change in 6MWT ($r=0.30$, $p=0.01$), MSWS-12 ($r=-0.21$, trend only: $p=0.08$), and $SF\text{-}36_{physical}$ ($r=0.22$, trend only: $p=0.06$), but not $MFIS_{total}$ ($r=-0.19$, $p=0.11$), FSS ($r=-0.18$, $p=0.13$), SSST ($r=-0.05$, $p=0.65$), and $SF\text{-}36_{mental}$ ($r=-0.07$, $p=0.54$).

Replication (T24 to T48)

All PAE group findings from the RCT part were replicated and verified in the waitlist group in the follow-up part; i.e. the same effect of PAE was observed even though it was postponed by 24 weeks.

Follow-up (T24 to T48)

Generally, fatigue impact improvements attained during the RCT part appeared to had diminished at follow-up after 24 weeks of self-guided physical activity (Table 2), although point estimates did not reach the same magnitude as in the RCT part ($MFIS_{total}$ change: +3.0 [–0.3;6.2], $p=0.08$; $MFIS_{physical}$ change: +1.4 [–0.4;3.2], $p=0.13$; $MFIS_{psychosocial}$ change: +0.2 [–0.3;0.7], $p=0.53$). Similarly, the potential effects on self-assessed walking ability seemed to diminish (MSWS-12 change: +3.0 [–0.9;6.9], $p=0.14$), while the potential effect on 6MWT was maintained at follow-up (6MWT change: –6.6m [–17.6;4.32], $p=0.24$). The VO_2max improvement attained during the RCT

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part disappeared at follow-up (-2.8 mL/min/kg, [-3.8;-1.8], p<0.01). $MFIS_{cognitive}$, FSS, and SF-36 scores showed no changes.

Discussion

To the best of our knowledge, this study is the first single-blinded RCT to assess the efficacy of progressive long-term high-intensity aerobic exercise on MS-related fatigue impact and severity, walking ability and capacity, and quality of life in a representative sample[32] of mildly to moderately impaired pwMS. We found that 24 weeks of supervised PAE, when compared to habitual lifestyle, led to a mean reduction in total fatigue impact (i.e. -5.3 in the $MFIS_{total}$ score) which can be regarded as clinically meaningful based on recent findings showing that a change of at least 4 points on the MFIS constitutes a clinically significant difference in fatigue (figure 2).[33] Furthermore, the $MFIS_{physical}$ and $MFIS_{psychosocial}$ subscores improved after the PAE intervention indicating less impact of fatigue on physical and psychosocial functioning. Also, PAE improved cardiorespiratory fitness while the effects on walking ability (MSWS-12) and capacity (6MWT) suggested potential small improvements, although these latter findings should be interpreted cautiously given the uncertainty around the point estimates for these outcomes. Even though these improvements appeared to have diminished after 24 weeks of follow-up, the associated point estimates did not reach the same magnitude as in the RCT part suggesting a potential small long-term effect of PAE on MS-related fatigue and potentially on walking too. These findings partly support our hypothesis and are further supported by an almost identical replication of findings in the second part of the study (week 24-48). However, contrary to our hypothesis no between-group effects were observed in the FSS, $MFIS_{cognitive}$ subscore, SSST, and the $SF\text{-}36_{physical}$ and $SF\text{-}36_{mental}$ subscores.

As this is the first study to apply long-term high-intensity PAE in pwMS, direct comparison to previously published studies is not possible. One previous study compared 24 weeks of Tai-Chi yoga (two weekly sessions of 90 minutes) to controls and found that the Fatigue Scale of Motor and Cognitive Functions (FSMC) deteriorated in the control group, whereas it remained stable in the Tai Chi group.[34] Another study compared an Ai-Chi aquatic program (two weekly sessions for 20 weeks) to a control group and showed an improvement in the $MFIS_{physical}$ subscore.[35] Although these results somewhat support the findings of the current study, the results are limited by methodological issues such as a lack of randomization, higher baseline EDSS scores in the control vs. intervention group, no detailed dose of training, and low to moderate intensity exercise.[34, 35]

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Two additional studies reported no interaction effects when comparing 26 weeks of inpatient rehabilitation (plus home-based exercise) vs. controls[36] and Iyengar yoga classes (plus home program) or weekly bicycle exercise classes (plus home exercise) vs. controls,[37] respectively. Again, these studies applied low to moderate intensity interventions and different fatigue scales than the current study,[37] hampering the comparison with the current study. Overall, these few previous long-term (i.e. ≥ 20 weeks) exercise studies assessing MS-related fatigue show mixed results, significant heterogeneity between trials, and moderate methodological quality (e.g. inclusion of non-fatigued participants in studies not targeting the therapy on fatigue specifically). Interestingly, a recent aerobic exercise trial specifically assessed fatigue as the primary outcome (with the CIS20r fatigue subscore, MFIS, and FSS) and included participants with a predefined severe level of fatigue (i.e. mean baseline FSS=5.3; MFIS= 41.2).[38] In this study, a 16-week partly supervised intervention, primarily consisting of low to moderate intensity exercise three times a week, did not lead to a clinically meaningful reduction in fatigue impact or severity when compared to controls. While the TREFAMS-ACE study was designed to assess fatigue as the primary outcome and the current study was not, there are study similarities (sample size, number of patients in the intention-to-treat analysis, comparable baseline FSS scores, aerobic exercise intervention) that justify some comparison. On the other hand, study differences include that the current study applied supervised exercise throughout the entire intervention, a longer intervention period involving a higher volume of high-intensity aerobic exercise, and better adherence both in terms of completed sessions and prescribed workload.[18] These differences may explain why participants in the TREFAMS-ACE study did not increase their cardiorespiratory fitness, despite a low level at baseline, which may also explain why only a small post-intervention effect on fatigue levels was observed in these patients (i.e. mean change: CIS20r fatigue subscore = -4.7, $MFIS_{total}$ = -1.8).[38] Of note, a recent study from our group investigated the pathophysiological pathways explaining the potential positive effects of exercise on fatigue in MS.[4] This scoping review identified more than 30 pathophysiological fatigue pathways holding the potential to alleviate MS fatigue through cardiovascular, immunologic, neuroendocrine, and neurotrophic changes as well as through symptomatic improvement of deconditioning, sleep disorders, and depression.[4] Such findings highlight the multidimensionality and complexity of MS fatigue. Therefore, future exercise studies exploring these pathways of MS fatigue, using a more mechanistic approach and both subjective and objective measures distinguishing primary and secondary fatigue in well-characterized pwMS are highly warranted.

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Although the MSWS-12 and 6MWT between-group differences only approached clinically relevant changes, explorative *post hoc* pairwise comparisons revealed within-group time effects in the PAE group showing an improvement in the MSWS-12 (i.e. -7.7 points [-11.9;-3.5], $p<0.01$) which lies within the range (i.e. -6.30 to -8.85 points) previously suggested to represent a meaningful change on this scale (figure 3)[39, 40] and an improvement in the 6MWT (i.e. +27.2m, [13.8;40.5], $p<0.01$) exceeding the clinically meaningful change of 21.6m.[18, 27] Interestingly, these effects were observed in an MS sample comprising only 15% (12% in the PAE group, 18% in the waitlist group) with mild walking impairment (according to a recently used cut-off value of 400m in the 6MWT, with no clinical validation).[41] These data corrobate previous observations following 5 weeks of aerobic exercise interventions[42] and cautiously suggest that participants improved walking ability and capacity at a clinically relevant level. Moreover, specificity (i.e. you become good at what you practice) is a key word in professional sports but also for patient populations. Since most PAE sessions were performed on bicycle ergometers in the present study, perhaps larger improvements in walking ability and capacity are achievable when applying exercise modalities that further challenge coordination and balance, while still challenging the cardiorespiratory system (e.g. cross-country walking / running).

An important aspect of the present study is whether the aerobic exercise intervention is applicable in clinical practice. Whilst acknowledging that implementation in most cases will require individually tailored exercise prescription and initial supervision from an instructor, we believe it is possible to implement the present aerobic exercise intervention for several reasons. First, the exercise frequency (2days/week) and duration (30-60min) are realistic to most patients (at least to those interested in exercise), as none of the participants of the present study had any issues regarding the frequency or duration. Second, the applied exercise equipment is standard and thus accessible in most rehabilitation and fitness centers. Third, the applied progression model only requires a heart rate monitor, with the majority of these enabling setting of different heart rate exercise zones (e.g. 65-75% of estimated heart rate max). Thus, the present intervention offers a novel intervention that can rather easily be adopted in clinical practice.

Lastly, the *post hoc* exploratory correlation analyses showed that VO_2max was associated with most of the applied outcomes at baseline. Although we cannot infer causality from these associations, we

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can speculate that VO_2max is a marker of long-term / lifetime aerobic exercise participation, with high cardiorespiratory fitness potentially translating into scoring better in these outcomes. Moreover, the analyses exploring the potential to change within each outcome underline the importance of including already impaired (e.g. fatigued, less ambulatory) patients in studies assessing the efficacy of interventions aimed at these symptoms. Surprisingly, only 6MWT change was associated with VO_2max change highlighting the aerobic/endurance component of the 6MWT.[43] Perhaps this explains why we observed potential improvements in the 6MWT but not in the SSST which primarily challenges coordination and balance. However, the lack of association between changes in VO_2max and $MFIS_{total}$ suggests that the observed reduction in fatigue impact is mediated not solely by VO_2max change but also by other pathways.[4]

Despite the strengths of this trial (e.g. long-term supervised exercise intervention, inclusion of follow-up period, replication of intervention findings, careful standardization of methodology, inclusion of representative MS sample) there are limitations that must be considered when interpreting the results. Fatigue, walking, and quality of life were secondary outcomes as the main study was powered towards brain atrophy.[18] Thus, the present study merely classifies as an explorative study in regard to these outcomes. However, the present study enrolled more participants than most previous studies on this topic. Moreover, 38.4% (according to a cut-off value of 38 on the MFIS [44]) or 60.5% (according to a cut-off value of 5 on the FSS [45]) of the patients in this sample could be classified as fatigued at baseline, leaving little room for improvement in many of the patients. Studies that specifically include fatigued patients are thus needed to consolidate the current findings. Additionally, questionnaires which lack specificity to MS were used (e.g. SF-36) potentially limiting their meaningfulness. Lack of blinding also constitutes a limitation. Patient and exercise supervisor blinding were not possible given the obvious treatment differences, and the primary assessor of the reported outcomes was similarly not blinded to the treatments. Moreover, additional strata criteria such as MS phenotype and MRI outcomes could have improved group homogeneity. Also, the dropout rate in the RCT part (15.1%) lowers the power of the results. However, due to the study design it was possible to replicate the intervention in the waitlist group, which consolidated the observed changes. Importantly, while the increased dropout rate can be viewed as a concern, this was not directly caused by the high-intensity PAE, which was well tolerated, with no serious adverse events and good adherence (i.e. 93.3 ± 5.4% completed sessions). Lastly, 52 eligible patients declined to participate, indicating selection bias. Finally, no monitoring

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of physical activity behavior was undertaken, disallowing detection of potential changes in physical activity levels between groups in the RCT part and assessment of adherence to self-guided exercise after crossover.

In conclusion, 24 weeks of PAE induced a clinically relevant reduction in fatigue impact in a representative sample of pwMS, whereas small and no effects where seen for walking and quality of life, respectively. The results need confirmation in a future trial due to the study limitations (e.g. fatigue was a secondary outcome in this clinical trial).

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Conflict of Interest Statement

LGH has received research support, travel grants and/or teaching honoraria from Biogen and Sanofi. UD has received research support, travel grants, and/or teaching honoraria from Biogen, Merck Serono, Novartis, and Sanofi Genzyme. TP has received research support from Biogen, Merck, Roche, Alexion, Sanofi Genzyme, and Novartis. HHN has received research support, travel grants and/or teaching honoraria from Biogen, Merck Serono, Novartis, Sanofi Genzyme, Teva and Roche. No other authors have any disclosures.

Data Availability Statement

Access to the data that underlie the results reported in this article will be given, on reasonable request, to investigators whose proposed use of the data has been approved by a review committee identified by the authors of this study. Once access is granted, data will be available through The Danish National Archives at https://www.sa.dk/en/ (note: please contact the corresponding author at mach@ph.au.dk).

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Author contributions

• Conception or design of the work: ML-C, UD, ES

• Data collection: ML-C, LGH, HBJ, HHN, TP

• Data-analysis: ML-C, LGH, UD

• Interpretation of data: All

• Drafting the work and/or revising it: ML-C, LGH, UD

• Final approval of the version to be published: All

• Agreement to be accountable for all aspects of the work: All

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Table 1: Baseline characteristics

	Progressive aerobic exercise (n = 43)	**Waitlist (n = 43)**
Women	26 (60%)	26 (60%)
Age (years)	44.0 (9.5)	45.6 (9.3)
Height (cm)	173.5 (10.5)	174.3 (9.5)
Weight (kg)	77.4 (19.5)	74.0 (13.5)
Body-Mass Index (kg/m²)	25.5 (4.6)	24.3 (3.7)
Expanded Disability Status Scale score	2.7 (1.4)	2.8 (1.6)
Time since diagnosis (years)	10.9 (7.9)	8.6 (6.0)
Disease-modifying treatment use	38 (88%)	32 (74%)
MS type		
- Relapsing-remitting	41 (95%)	34 (79%)
- Primary progressive	2 (5%)	4 (9%)
- Secondary progressive	0 (0 %)	5 (12%)
Cardiorespiratory fitness (ml/min/kg)	28.2 (6.9)	28.6 (7.7)
Fatigued according to MFIS / FSS*	16 (37%) / 27 (63%)	17 (40%) / 25 (58%)

Note: Data are presented as mean (SD) or n (%).

Abbreviations: MS, multiple sclerosis. MFIS, Modified Fatigue Impact Scale. FSS, Fatigue Severity Scale.

*Fatigue defined according to cut-off values of 38 on the MFIS[44] or 5 on the FSS [45].

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Table 2. Cardiorespiratory fitness, walking, and self-reported outcomes.

	Progressive aerobic exercise			Waitlist			Between-group change	p value
	T0	T24	T48	T0	T24	T48	Δ (T0 to T24)	
Cardioresp. fitness (mL O_2/min/kg)	28.2 (6.9)	32.1 (7.3)	29.2 (7.6)	28.6 (7.7)	28.4 (7.6)	33.5 (7.4)	3.5 [2.0;5.1]	<0.001
MFIS (a.u)								
Total	32.6 (13.4)	25.6 (15.0)	28.1 (13.9)	32.7 (16.6)	31.2 (17.8)	20.9 (15.1)	-5.3 [-10.9;0.4]	0.066
Physical	13.6 (6.1)	10.4 (7.6)	11.6 (7.4)	14.7 (9.2)	14.1 (8.8)	8.4 (6.9)	-2.8 [-5.6;-0.1]	0.045
Psychosocial	2.3 (1.7)	1.7 (1.6)	1.9 (1.7)	2.0 (1.6)	2.2 (2.0)	1.1 (1.3)	-0.9 [-1.6;-0.2]	0.013
Cognitive	16.7 (8.1)	13.5 (8.5)	14.6 (7.9)	16.0 (8.3)	15.0 (8.8)	11.4 (8.0)	-1.5 [-4.4;1.4]	0.295
FSS (a.u)	4.9 (1.5)	4.7 (1.5)	4.5 (1.6)	5.0 (1.2)	5.0 (1.4)	4.4 (1.4)	0.0 [-0.5;0.5]	0.971
6MWT (m)	531 (103)	579 (97)	571 (103)	521 (129)	537 (133)	593 (116)	14 [-5;33]	0.139
SSST (s)	8.0 (3.2)	7.1 (2.2)	7.0 (2.7)	8.6 (5.8)	7.2 (2.7)	6.3 (2.3)	0.4 [-0.2;1.0]	0.200
MSWS-12 (a.u)	29.7 (27.9)	21.1 (26.2)	23.2 (25.5)	33.6 (29.1)	31.6 (27.3)	19.2 (21.3)	-5.9 [-11.8;0.1]	0.056
SF-36 (a.u.)								
Physical	46.6 (9.9)	48.1 (9.0)	48.5 (9.2)	44.4 (9.2)	45.5 (8.9)	49.2 (8.5)	-0.1 [-2.7;2.6]	0.959
Mental	48.6 (11.3)	50.9 (9.0)	49.6 (10.4)	49.7 (11.7)	50.4 (11.8)	54.0 (9.6)	1.6 [-3.0;6.2]	0.478

Note: Raw data are stated as mean (SD). Changes are stated as mean [95% CI]. Gray font indicates follow-up data, which were not part of the RCT part of the study.

Abbreviations: a. u., arbitrary units. MFIS, Modified Fatigue Impact Scale. 6MWT, Six-Minute Walk Test. FSS, Fatigue Severity Scale. SSST, Six Spot Step Test. MSWS-12, 12-item Multiple Sclerosis Walking Scale. SF-36, Short Form (36) health survey.

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Figure legends

Figure 1 Flow diagram. “Worsening of symptoms” covers worsening of walking or vision. Dropouts due to physical problems were, except for “physical fatigue”, not related to the exercise intervention.

Figure 2 Mean changes (with 95% CI) in $MFIS_{total}$ scores in the two groups in the RCT part (left) and follow-up part (right). Dashed lines show the clinically meaningful change threshold of 4 points [33]. A negative change represents an improvement in fatigue.

Figure 3 Mean changes (with 95% CI) in MSWS-12 scores in the two groups in the RCT part (left) and follow-up part (right). Dashed lines show the threshold for a meaningful subject-level change in walking ability [39, 40]. A negative change represents an improvement.

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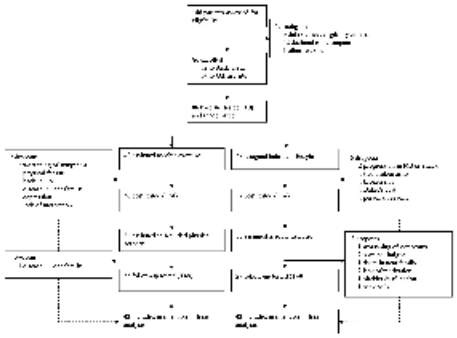

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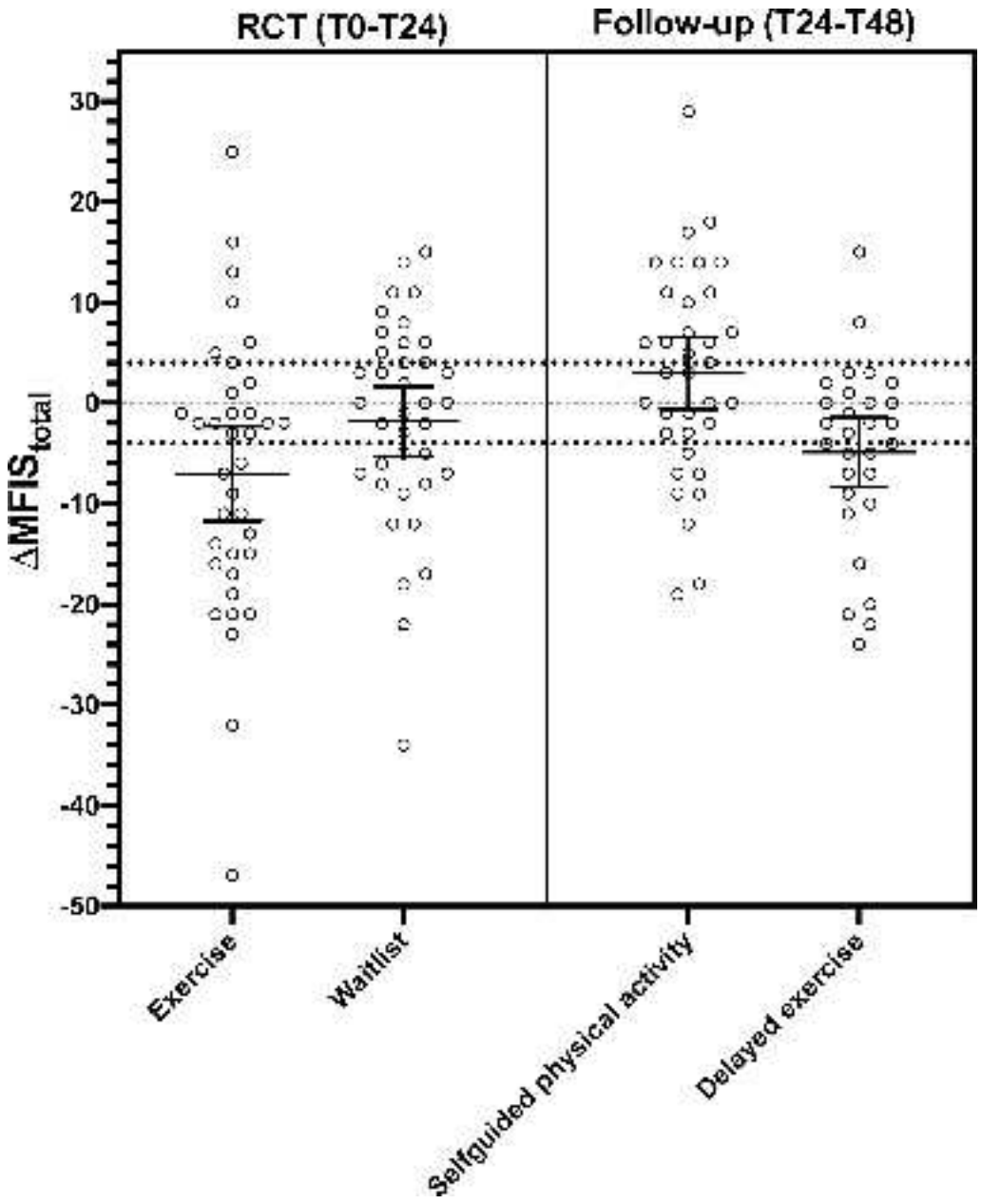

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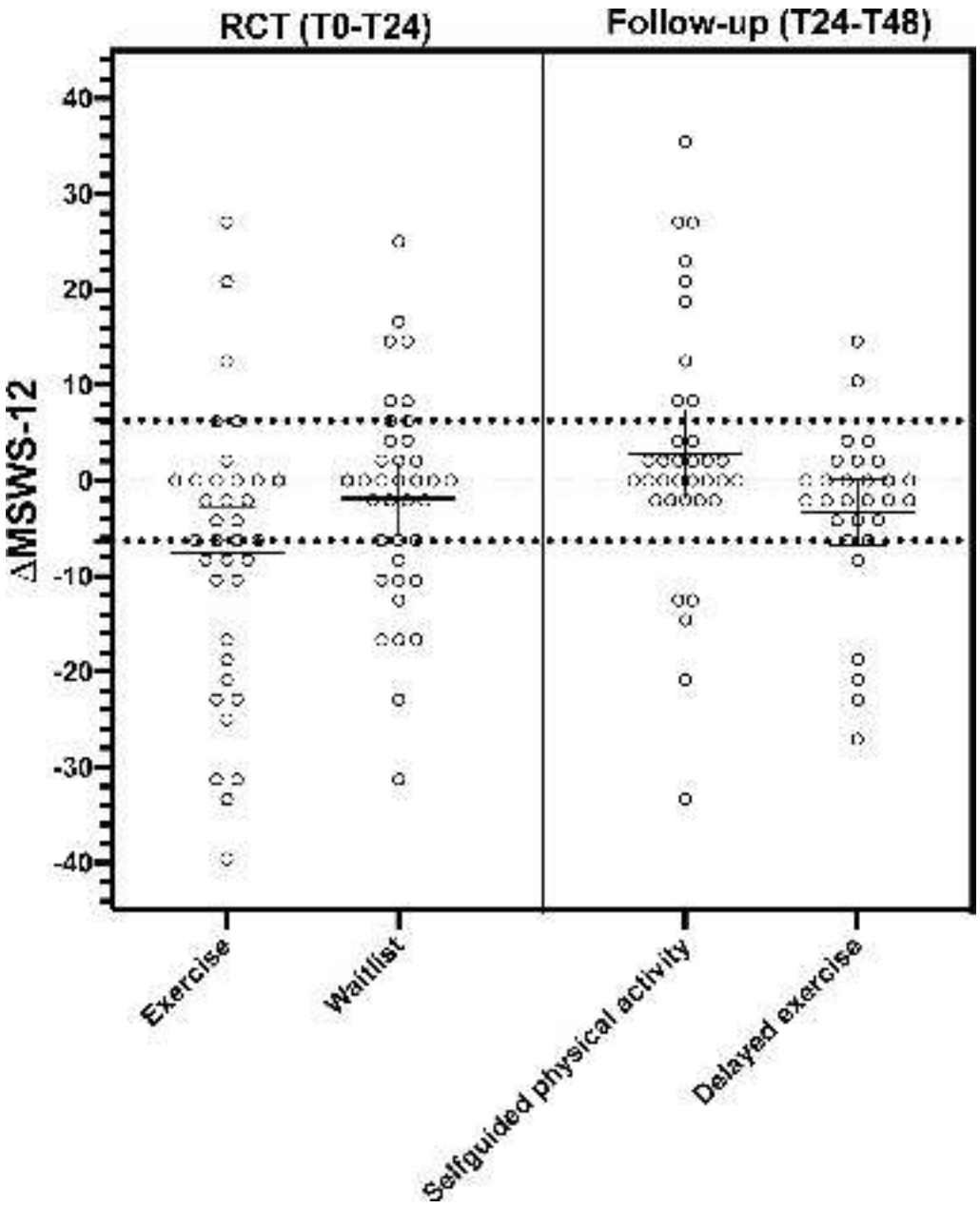

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