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Clinical trial

Effects of inpatient energy management education and high-intensity interval training on health-related quality of life in persons with multiple sclerosis: A randomized controlled superiority trial with six-month follow-up

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ABSTRACT

Background: Fatigue is one of the most frequent symptoms in persons with multiple sclerosis (pwMS) and impacts health-related quality of life (HRQoL). A multidisciplinary rehabilitation approach is recommended for the treatment of fatigue in pwMS. However, high-quality evidence exists only for unimodal interventions, such as physical therapies/exercise or energy/fatigue management programmes. The primary objective of the current study was to test the hypothesis that a combination of inpatient energy management education (IEME) and high-intensity interval training (HIIT) is superior to a combination of progressive muscle relaxation (PMR) and moderate continuous training (MCT) for improving HRQoL at 6-month follow-up in fatigued pwMS.
Methods: A randomized (1:1) controlled superiority trial with fatigued pwMS >18 years of age, with Expanded Disability Status Scale (EDSS) score ≤6.5, recruited at the Valens clinic, Switzerland. Participants in the experimental group performed IEME twice and HIIT 3 times per week and those in the usual care group performed PMR twice and MCT 3 times per week, during a 3-week inpatient rehabilitation stay. Primary outcome was HRQoL (Physical and Mental Component Scales of the Medical Outcome Study 36-item Short Form Health Survey (SF-36)), assessed at entry to the clinic (T_0), after 3 weeks' rehabilitation (T_1) and 4 (T_2) and 6 (T_3) months after T_0. Secondary outcomes included SF-36 subscales, fatigue (Fatigue Scale for Motor and Cognitive Functions (FSMC)), mood (Hospital Anxiety and Depression Scale (HADS)), self-efficacy for performing energy conservation strategies (Self-Efficacy for Performing Energy Conservation Strategies Assessment (SEPECSA)), self-perceived competence in activities of daily living (Occupational Self Assessment (OSA)) and

Abbreviations: ADL, Activities of daily living; CI, Confidence interval; CPET, Cardiopulmonary exercise testing; EDSS, Expanded Disability Status Scale; EG, Experimental group; EQ-VAS, EuroQol-visual analogue scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; HADS, Hospital Anxiety and Depression Scale; HIIT, High-intensity interval training; HR_{peak}, Peak heart rate; HRQoL, Health-related quality of life; IEME, Inpatient energy management education; MCS, Mental Component Scale; MMRM, Mixed model for repeated measures; MMSE, Mini-Mental State Examination; MS, Multiple sclerosis; OSA, Occupational Self Assessment; PCS, Physical Component Scale; PMR, Progressive muscle relaxation; PROM, Patient-reported outcome measure; pwMS, Persons with multiple sclerosis; rpm, Revolutions per minute; SD, Standard deviation; SEPECSA, Self-Efficacy for Performing Energy Conservation Strategies Assessment; SF-36, Medical Outcome Study 36-item Short Form Health Survey; UC, Usual care; $\dot{V}O_{2peak}$, Peak oxygen consumption; $Watt_{peak}$, Peak wattage..

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cardiorespiratory fitness (peak oxygen consumption ($\dot{V}O_{2peak}$)). Data were analysed using a mixed model for repeated measures approach.

Results: A total of 106 pwMS (age (years): 49.75 (9.87), 66% female, EDSS: 4.64 (1.32)) were recruited. There were no significant group × time interaction effects in the primary and secondary outcomes. There were significant between-group differences in the pairwise comparisons of the group × time interaction in favour of the IEME + HIIT group at: (i) T_1 in cardiorespiratory fitness ($p = 0.011$) and SEPECSA ($p = 0.032$); (ii) T_2 in SF-36 mental health subscale ($p = 0.022$), HADS anxiety subscale ($p = 0.014$) and SEPECSA ($p = 0.040$); (iii) T_3 in SF-36 physical functioning subscale ($p = 0.012$) and SEPECSA ($p = 0.003$).

Conclusion: IEME + HIIT was not superior to PMR + MCT regarding the effects on HRQoL (SF-36 Physical and Mental Component Scales) at 6-month follow-up in pwMS. However, there were significant between-group differences in favour of IEME + HIIT in physical functioning and mental health (SF-36 subscales), anxiety (HADS), cardiorespiratory fitness ($\dot{V}O_{2peak}$) and self-efficacy (SEPECSA) at different measurement time-points that need to be considered in clinical practice.

1. Introduction

Persons with multiple sclerosis (pwMS) show decreased physical activity levels (Kinnett-Hopkins et al., 2017) and cardiorespiratory fitness (Langeskov-Christensen et al., 2015) compared to healthy controls, associated with a reduced health-related quality of life (HRQoL) (Koseoglu et al., 2006). In addition, fatigue is reported by up to 80% of pwMS (Barin et al., 2018), making it one of the most frequent symptoms that impacts HRQoL (Amato et al., 2001). Fatigue is a complex and multidimensional symptom. The pathophysiological mechanisms of fatigue may be related directly to the MS disease (e.g., inflammation, demyelination, neurodegeneration) or to other factors that are not disease-specific (e.g., sleep disorders, depression, cognitive deficits, medication side-effects, chronically reduced activity) (Langeskov-Christensen et al., 2017). A multidisciplinary rehabilitation approach is recommended for the treatment of MS-related fatigue, including exercise and educational approaches in combination with medication (Asano and Finlayson, 2014; National Institute for Health and Care Excellence 2022). However, high-quality evidence exists only for unimodal interventions, such as physical therapies/exercise or energy/fatigue management programmes (Khan and Amatya, 2017).

Exercise is safe and well tolerated by pwMS, including high-intensity interval training (HIIT) (Dalgas et al., 2019; Campbell et al., 2018; Pilutti et al., 2014). Exercise is an effective supportive symptomatic treatment option in pwMS (Dalgas et al., 2019). We showed that, compared to moderate continuous training (MCT), 3 weeks of HIIT had superior effects in improving cardiorespiratory fitness (Schlagheck et al., 2021; Zimmer et al., 2018) and systemic concentrations of disease-associated biomarkers (Joisten et al., 2021) in pwMS. An acute bout of HIIT but not MCT has been shown to reroute the dysregulated kynurenine pathway of tryptophan degradation towards higher serum levels of kynurenic acid (Joisten et al., 2021). Kynurenic acid is attributed with neuroprotective and anti-inflammatory properties. Thus, the positive effects of HIIT on systemic concentrations of disease-associated biomarkers were hypothesized as a possible biological link contributing to the positive effects of exercise in pwMS (Joisten et al., 2021). Nevertheless, pwMS show decreased physical activity levels compared to healthy controls (Kinnett-Hopkins et al., 2017). "Lack of time" and "too tired" are amongst the most frequently reported barriers for pwMS not to exercise regularly (Asano et al., 2013). In this context, HIIT is an efficient and time-saving training option. However, the long-term effect of HIIT on HRQoL is unknown.

Recently, we developed a group-based inpatient energy management education (IEME) programme for a 3-week inpatient rehabilitation stay (Hersche et al., 2019a). IEME supports fatigued pwMS in managing their available energy resources and in implementing a well-balanced schedule of targeted exercise and recovery sessions into the daily routine. A randomized controlled feasibility trial investigating the effect of IEME compared with progressive muscle relaxation (PMR) has shown encouraging results; IEME improved various HRQoL dimensions (physical functioning, role limitations due to physical health, vitality and mental health) after 3 weeks, with a between-group effect in the physical functioning dimension in favour of IEME (Hersche et al., 2019b). A sustained effect of IEME compared to PMR was indicated by higher physical functioning at 4-month follow-up (Hersche et al., 2019b). However, it remains unclear if this positive effect is maintained until the 6-month follow-up.

Thus, the aim of this study was to investigate the effect of a combination of IEME and HIIT (experimental group; EG) compared to a combination of PMR and MCT (usual care at the Valens clinic, Switzerland; UC), with the treatments delivered during the 3-week inpatient rehabilitation stay. The primary objective was to test the hypothesis that IEME + HIIT is superior to PMR + MCT for improving HRQoL (Physical and Mental Component Scales of the Medical Outcome Study 36-item Short Form Health Survey (SF-36)) at 6-month follow-up in fatigued pwMS. Secondary outcomes included SF-36 subscales, fatigue, mood, self-efficacy for performing energy conservation strategies, self-perceived competence in activities of daily living (ADL) and cardiorespiratory fitness (peak oxygen consumption ($\dot{V}O_{2peak}$)).

2. Materials and methods

2.1. Study design

This was a two-armed single-blinded randomized controlled superiority trial. In addition to an individually tailored 3-week multidisciplinary inpatient rehabilitation programme, participants received an education approach (IEME or PMR) 2 days/week and exercised 3 days/ week (HIIT or MCT). Assessments were performed at entry to the clinic (baseline, T_0) and after a 3-week inpatient rehabilitation stay (T_1). Follow-up assessments were performed at 4 (T_2) and 6 (T_3) months after T_0. Detailed study design and procedures are given in the study protocol (Patt et al., 2021). The study was prospectively approved by the Swiss Ethics Committee of Eastern Switzerland (EKOS) (EKOS20/050; Project ID: 2020–00797; 9 April 2020), registered at ClinicalTrials.gov (NCT04356248; 22 April 2020) and conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed about the study and gave written informed consent prior to study inclusion.

2.2. Participants

PwMS referred for inpatient rehabilitation at the Valens clinic were screened for study eligibility at admission to the clinic. Inclusion criteria were: age >18 years; MS diagnosis (revised McDonald criteria Thompson et al. 2018) with relapsing-remitting, primary or secondary progressive MS phenotypes; Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score ≤6.5; Fatigue Scale for Motor and Cognitive Functions (FSMC) total score ≥43 (Penner et al., 2009); and literacy and understanding in German. Exclusion criteria were: cognitive impairment (22-point Mini-Mental State Examination score (MMSE) <21 (Newkirk et al. 2004); Hospital Anxiety and Depression Scale (HADS) depression subscale >11 (Zigmond and Snaith, 1983); concomitant cardiopulmonary or other neurodegenerative diseases in addition to MS; infections; pregnancy/intention to become pregnant; stem cell treatment within the last 6 months; and previous participation in an IEME or HIIT study. Participation was cleared by a physician before the start of the study. Recruitment and eligibility criteria are given in detail in the study protocol (Patt et al., 2021).

2.3. Interventions

All participants underwent a 3-week multidisciplinary inpatient rehabilitation programme, comprising physiotherapy to improve balance and walking ability (30–60 min, 5 times per week), strength training (30–45 min, 3 times per week), occupational therapy focusing on ADL (30 min, 2–3 times per week), neuropsychology addressing cognitive deficits (30 min, 2 times per week), social counselling and regular consultations with a physician, tailored to the individual needs of the patient. In addition, participants received a combination of an educative approach and a specific endurance exercise modality (IEME + HIIT, or PMR + MCT). Participants received IEME/PMR twice and HIIT/MCT 3 times per week during the 3-week inpatient rehabilitation stay.

The training intensity for HIIT/MCT was based on peak heart rate (HR_{peak}) in cardiopulmonary exercise testing (CPET) on a cycle ergometer at T_0, as described in Section 2.4.2. All training sessions were performed on a cycle ergometer (Cybex 750C Bike, Cybex International, Medway, MA, USA), with a 3-min warm-up and 3-min cool-down. Training sessions were heart rate monitored (Polar M200, Polar Electro Oy, Kempele, Finland), and were conducted by MS-experienced therapists. At the end of the 3-week inpatient rehabilitation stay, all participants received an individual training plan for exercising independently at home. Education sessions (IEME and PMR) were conducted by MS-experienced and trained occupational and physiotherapists, respectively.

Details of the interventions are given in the study protocol (Patt et al., 2021).

2.3.1. Experimental group (IEME + HIIT)

Inpatient energy management education (IEME). The aim of IEME is that fatigued pwMS learn to manage their energy resources efficiently so as to have a satisfying everyday life despite fatigue. IEME integrates the principles of patient education, the transtheoretical model of behaviour change, social cognitive theory, energy conservation strategies and cognitive-behavioural techniques (Hersche et al., 2019a). The IEME started with a 1:1 individual 1-h session, in which participants analysed their energy use. Subsequently, they participated in 5 1-h group sessions: break management; occupational balance; use of body and environment; simplifying activities; and effective communication. An individual 30-min session was then held to set goals for implementation of the learned energy conservation strategies at home.

High-intensity interval training (HIIT). Participants performed 5 1.5-min high-intensive intervals at a cycling cadence of 80–100 revolutions per minute (rpm), with the goal of reaching 95–100% HR_{peak}. Each completed interval followed a 2-min active break, including cycling at 20 watts (50–60 rpm), with the goal of reaching 60% HR_{peak}.

2.3.2. Usual care group (PMR + MCT)

Progressive muscle relaxation (PMR). PMR aims to foster mental relaxation by performing standardized relaxation exercises, including alternating muscle tension and relaxation of 11 muscle groups combined with deep breathing (Jacobson, 1938). Participants attended 6 1-h group sessions and, at the end of the 3-week inpatient rehabilitation stay, were encouraged to continue unsupervised PMR exercises at home.

Moderate continuous training (MCT). Participants cycled continuously for 24 min at 60–70 rpm and 65–70% HR_{peak}.

2.3.3. Reinforcement letter ("booster")

A "booster" was sent to all participants 6 weeks after discharge to remind them of the individual goals set at the end of their 3-week inpatient rehabilitation stay. Participants were reinforced to continue exercising (EG, UC), apply energy conservation strategies (EG), and performing PMR exercises (UC).

2.4. Outcomes and assessments

Demographic (age, sex, smoking status, education, employment status, housing situation) and anthropometric data (height, weight) were taken from participants' self-report. MS-related data (phenotype, EDSS score, time since diagnosis) were taken from medical records. Patient-reported outcome measures (PROMs) were assessed at all measurement time-points (T_0–T_3). At baseline (T_0) and after the 3-week inpatient rehabilitation stay (T_1), participants completed the PROMs at the Valens clinic and performed CPET. For follow-up assessments at 4 (T_2) and 6 months (T_3) after baseline, the PROMs were posted to the participants.

2.4.1. Primary outcome

The primary outcome was change in Physical and Mental Component Scales (PCS and MCS, respectively) of the HRQoL over a 6-month period (T_0–T_3), assessed using the Medical Outcome Study 36-item Short Form Health Survey (SF-36) (Ware and Sherbourne, 1992). This generic PROM comprises 8 (0–100) subscales: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional health, and mental health. The 8 subscales were transformed into a PCS and a MCS, according to standard procedures (Ware, 1994), using normative data (mean and standard deviation (SD)) and weighting coefficients from the Swiss general population (Roser et al., 2019). Higher scores indicate better HRQoL.

2.4.2. Secondary outcomes

The 8 subscales of the SF-36 were reported as secondary outcomes.

Fatigue was assessed with the German version of the FSMC (Penner et al., 2009), a 20-item scale comprising 10 questions each assessing cognitive and motor fatigue, giving a total fatigue score of 20–100, with defined cut-off values, classifying patients as mildly (≥43), moderately (≥53) or severely (≥63) fatigued.

Anxiety and depression were assessed with the HADS (Herrmann-Lingen et al., 2011), a 14-item scale with 7 questions each on anxiety and depression. Items are rated on a 0–3 Likert scale, with higher scores indicating higher levels of anxiety or depression. The subscales range from 0 to 21, with scores >11 indicating severe anxious or depressive symptoms (Zigmond and Snaith, 1983).

Self-efficacy for performing energy conservation strategies was assessed with the Self-Efficacy for Performing Energy Conservation Strategies Assessment (SEPECSA) (Liepold and Mathiowetz, 2005), a 14-item scale on which participants ranked their confidence in using the energy conservation strategies learned during the IEME. The scores (1–10) were summed and divided by 14, with higher scores indicating higher confidence.

Self-perceived competence in ADL was assessed with the 21-item Occupational Self Assessment (OSA) scale (Kielhofner et al., 2010). The items represent participation in habits and roles, performance of skills, and volition for participation. Participants rate their self-perception of occupational competence on a 4-point scale, with raw scores ranging from 21 to 84. Raw scores are converted into interval data ranging from 0 to 100, with higher scores indicating higher competence.

Cardiorespiratory fitness was assessed with a CPET (Jaeger CPX, Germany) conducted on a cycle ergometer (ergoline 800, ergoline GmbH, Bitz, Germany) by blinded exercise scientists to determine $\dot{V}O_{2peak}$, $HR_{peak,}$ and peak wattage ($Watt_{peak}$). After a 2-min resting phase, followed by 3 min pedalling at 20 watts (warm-up), a ramp protocol with a continuous increase of 10 watts/min was performed to ensure an 8–12-min test period until subjective exhaustion. A 3-min cool-down was then performed at 20 watts. The CPET testing protocol is described in detail elsewhere (Wassermann et al., 2005).

2.5. Randomization and masking

Eligible pwMS underwent 1:1 stratified and concealed randomization, either to IEME + HIIT or to PMR + MCT. Independent employees conducted randomization, using version 1.5.2 of the Randomization in Treatment Arms software (RITA, EVIDAT, Kiel, Germany). Stratified randomization was performed using the minimization method according to Pocock & Simon (for review see Scott et al. 2002), using MS-phenotype (relapsing-remitting, primary progressive, secondary progressive), sex (male, female), age (<30, 30–39, 40–49, 50–59, 60–69, 70–80), disease severity (EDSS score) (<2, 2–2.5, 3–3.5, 4–4.5, 5–5.5, 6–6.5), levels of cardiorespiratory fitness ($Watt_{peak}$) (0–49 watts, 50–99 watts, ≥100 watts), HRQoL (EuroQol-visual analogue scale score (EQ-VAS) (Brooks, 1996)) (<65, 65–100) and fatigue (FSMC total score) (43–52, 53–62, ≥63) at baseline as strata.

The independent assessors conducting CPET were blinded to the group assignment of participants. Due to the nature of this study and the obvious differences between the 2 interventions, it was not possible to blind the therapists and participants to the intervention group assignment.

2.6. Sample size calculation

An a priori sample size calculation was carried out for investigation of the main hypothesis, using G*Power 3.1.9.2 software (Faul et al., 2007). As relevant effect size, a difference in mean SF-36 PCS/MCS scores between the IEME + HIIT group and the PMR + MCT group at 6-month follow-up, of at least $d = 0.5$, was defined. Level of significance (α) with Bonferroni correction for multiple comparisons (2 primary outcomes) was set at 0.025 and power (1–β) at 0.8. Patients' baseline scores were included in the model as covariate. Required sample size in such an analysis of covariance model can be calculated as $(1-\rho^2)*n$, where ρ is the correlation between patients' baseline and post-treatment outcome-scores, and n is the sample size that would have been required if a t-test of post-treatment outcome-scores was applied (Borm et al., 2007). An association between participants' scores at T_0 and at T_3 of $\rho = 0.65$ was estimated. The number needed to be recruited was 45 participants in each group (total $N = 90$). Based on previous studies (Zimmer et al., 2018; Hersche et al., 2019b) an 18% dropout was allowed for, resulting in a planned sample size of 106 participants.

2.7. Statistical analysis

Outliers in the data-set, defined as z-scores >3 or <–3, were replaced with the variable mean ±3 SD. Baseline demographics and clinical characteristics were summarized using frequency (percentage) and mean (SD).

Between-group differences over time were assessed using a mixed model for repeated measures (MMRM) approach, with group, time and group × time interaction as fixed effects (type III sums of squares, compound symmetry (CS) covariance structure over time). Pairwise comparisons of estimated marginal means of the group × time interaction were computed, with Bonferroni adjustment to control for alpha error accumulation. For these pairwise comparisons, Cohen's d with 95% confidence interval (95% CI) was calculated as effect size measure. The respective baseline score of each parameter was included in the model as covariate. Data were analysed without imputation of missing observations; i.e. all available data from all randomized participants were included in the model.

For statistical analysis, SPSS 28 (IBM, Armonk, NY, USA) was used. Results were considered statistically significant if p-value ≤0.05. Due to multiple testing of the primary outcome (SF-36 PCS and MCS), alpha was adjusted in this case and a p-value ≤0.025 was considered statistically significant.

3. Results

Participants were recruited between 13 July 2020 and 19 October 2021. Follow-up was completed on 11 May 2022. During the recruitment period, 182 pwMS with an EDSS score ≤6.5 entered the Valens clinic and were assessed for eligibility. A total of 106 pwMS were included and randomized into 2 intervention groups. Baseline demographics and clinical characteristics are shown in Table 1. One participant had missing data for primary and secondary outcomes at T_1 (0.9%). At T_2 and at T_3, 6 (5.7%) and 7 (6.6%) participants did not return the questionnaires, respectively (Fig. 1). No adverse events occurred.

3.1. Compliance with treatment protocol

3.1.1. Experimental group (IEME + HIIT)

One subject declined to participate due to organizational issues. Of the 52 IEME participants, 3 dropped out during the intervention period due to "no need". Participants attended a mean of 4.7 IEME sessions (34/

Table 1
Baseline demographics and clinical characteristics.

	IEME + HIIT ($n = 53$)	PMR + MCT ($n = 53$)
Age (years)	49.98 (10.90)	49.51 (8.81)
Sex		
Male	19 (35.85)	16 (30.19)
Female	34 (64.15)	37 (69.81)
Weight (kg)	70.87 (16.62)	73.76 (16.42)
Height (cm)	170.49 (10.44)	170.20 (8.71)
Body-mass index (kg/m^2)	24.33 (5.22)	25.48 (5.68)
Smoking status		
Smoker	12 (22.64)	16 (30.19)
Non-smoker	41 (77.36)	37 (69.81)
Level of education		
Lower-secondary education	6 (11.32)	2 (3.77)
Upper-secondary education	21 (39.62)	28 (52.83)
Tertiary level education	26 (49.06)	23 (43.40)
Employment status		
Full-time	7 (13.21)	4 (7.55)
Part-time	20 (37.74)	23 (43.40)
Self-employed	3 (5.66)	1 (1.89)
Not employed	23 (43.40)	25 (47.17)
Housing		
Single	9 (16.98)	12 (22.64)
Cohabiting	44 (83.02)	41 (77.36)
Time since diagnosis (years)	15.02 (9.35)	11.79 (8.37)
EDSS score	4.61 (1.41)	4.67 (1.23)
MS phenotype		
Primary progressive	6 (11.32)	9 (16.98)
Secondary progressive	20 (37.74)	18 (33.96)
Relapsing-remitting	27 (50.94)	26 (49.06)
HRQoL (EQ-VAS)	58.85 (20.64)	61.08 (16.16)
SF-36 Physical Component Scale	25.39 (10.12)	26.87 (9.72)
SF-36 Mental Component Scale	46.65 (13.09)	45.16 (13.28)
Fatigue (FSMC total score)	71.15 (14.05)	67.62 (12.91)
HADS depression	4.15 (2.38)	4.83 (2.61)
$\dot{V}O_{2peak}$ relative (mL/min/kg)	19.67 (5.82)	18.39 (6.25)

Continuous data are presented as mean (SD) and categorical data as frequency (%).
IEME: inpatient energy management education; HIIT: high-intensity interval training; PMR: progressive muscle relaxation; MCT: moderate continuous training; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; HRQoL: health-related quality of life; EQ-VAS: EuroQol-visual analogue scale; SF-36: Medical Outcome Study 36-item Short Form Health Survey; FSMC: Fatigue Scale for Motor and Cognitive Functions; HADS: Hospital Anxiety and Depression Scale; $\dot{V}O_{2peak}$: peak oxygen consumption.

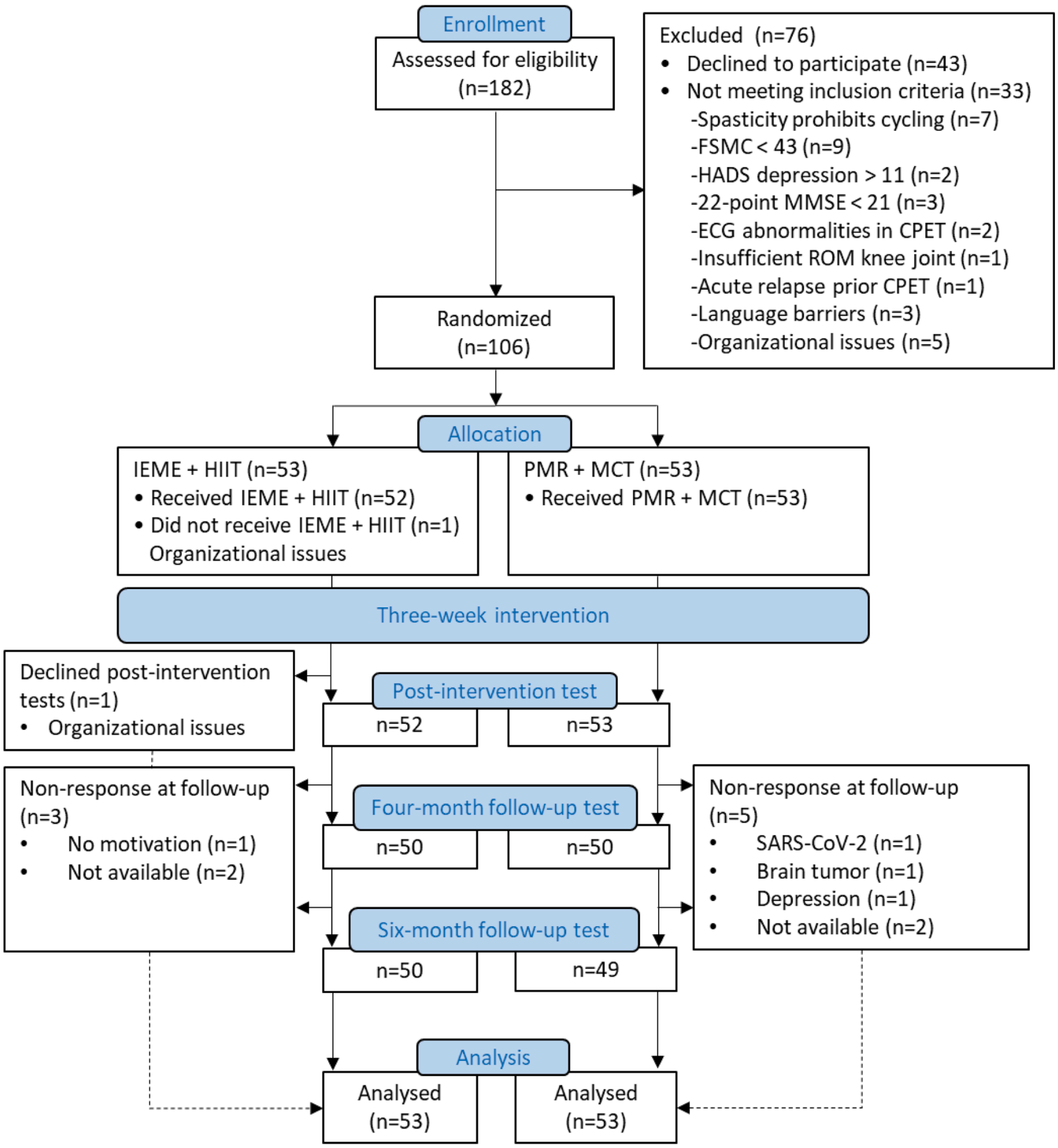

Fig. 1. Study flow diagram.
IEME: inpatient energy management education; HIIT: high-intensity interval training; PMR: progressive muscle relaxation; MCT: moderate continuous training; FSMC: Fatigue Scale for Motor and Cognitive Functions; HADS: Hospital Anxiety and Depression Scale; 22-point MMSE: 22-point Mini-Mental State Examination score; ECG: electrocardiography; ROM: range of motion; CPET: cardiopulmonary exercise testing.

52 participants ≥5 sessions, 11/52 participants 4 sessions, 7/52 participants <4 sessions). Mean training intensity for the 52 HIIT participants was 102.64% HR_{peak} and they attended a mean of 6.63 sessions (40/52 participants ≥ 6 sessions, 12/52 participants <6 sessions).

3.1.2. Usual care group (PMR + MCT)

Two participants dropped out of PMR during the intervention period (discomfort in group setting ($n = 1$), difficulty relaxing ($n = 1$)). Participants attended a mean of 4.87 PMR sessions (31/53 participants ≥5 sessions, 11/53 participants 4 sessions, 11/53 participants <4 sessions). Mean training intensity for the 53 MCT participants was 79.48% HR_{peak} and they attended a mean of 7.53 exercise sessions (49/53 participants ≥6 sessions, 4/53 participants <6 sessions).

3.2. Effect of treatment on primary and secondary outcomes

Mean scores for primary and secondary outcomes at all measurement time-points are shown in Table 2. Type III tests of fixed effects (group, time and group × time interaction) for the primary and secondary outcomes are shown in Table 3.

The MMRM did not show statistical significance for the group × time interaction for the primary and secondary outcomes. There was statistical significance for the main effect of time for all primary and secondary outcomes, except SF-36 role limitations due to emotional health.

3.2.1. Primary outcome

Pairwise comparisons of the group × time interaction were not statistically significant in the mean SF-36 PCS and MCS scores between the EG and UC group at any time-point (see Fig. 2A and 2B, respectively, and

Table 2
Raw scores of primary and secondary outcomes.

	Descriptive analysis Mean (SD) N							
	IEME + HIIT				PMR + MCT			
	T_0	T_1	T_2	T_3	T_0	T_1	T_2	T_3
SF-36 Physical Component Scale	25.39 (10.12) 53	30.97 (11.46) 52	28.97 (11.84) 50	29.12 (11.64) 50	26.87 (9.72) 53	31.42 (10.41) 53	29.65 (11.85) 50	27.09 (11.16) 49
SF-36 Mental Component Scale	46.65 (13.09) 53	53.76 (10.70) 52	48.98 (12.69) 50	47.96 (12.21) 50	45.16 (13.28) 53	51.95 (10.97) 53	45.83 (12.64) 50	45.34 (12.56) 49
SF-36 Physical functioning	42.17 (21.04) 53	52.21 (23.59) 52	48.60 (22.99) 50	47.70 (23.22) 50	44.81 (22.30) 53	52.36 (23.01) 53	47.90 (27.85) 50	43.67 (25.06) 49
SF-36 Role limitations due to physical health	33.96 (36.39) 53	55.77 (42.19) 52	46.50 (41.35) 50	48 (44.56) 50	28.30 (30.24) 53	51.89 (40.39) 53	41 (41.88) 50	34.69 (40.12) 49
SF-36 Bodily pain	57.53 (28.63) 53	66.69 (26.35) 52	63.12 (25.58) 50	62.42 (26.64) 50	65.51 (30.38) 53	69.74 (26.12) 53	68.50 (24.57) 50	63.04 (29.64) 49
SF-36 General health	47.89 (18.28) 53	55.73 (18.85) 52	49.64 (19.35) 50	48.80 (18.95) 50	49.81 (18.13) 53	55.32 (17.60) 53	49.10 (19.41) 50	48.69 (16.64) 49
SF-36 Vitality	41.13 (19.08) 53	55.58 (17.05) 52	47.70 (20.23) 50	45.10 (21.68) 50	36.89 (14.49) 53	53.96 (16.42) 53	40.30 (18.36) 50	39.18 (17.39) 49
SF-36 Social functioning	64.39 (26.10) 53	78.38 (24.39) 52	70.50 (26.34) 50	69.25 (23.31) 50	65.80 (26.31) 53	78.81 (22.51) 53	68.50 (26.99) 50	64.03 (27.20) 49
SF-36 Role limitations due to emotional health	72.96 (37.59) 53	83.97 (31.99) 52	74.67 (37.23) 50	74.67 (38.43) 50	68.55 (43.07) 53	76.11 (40.50) 53	71.33 (39.27) 50	69.39 (42.40) 49
SF-36 Mental health	69.21 (17.66) 53	81.23 (12.61) 52	74.80 (14.99) 50	72.56 (14.32) 50	70.79 (16.87) 53	80.60 (12.88) 53	70.80 (16.03) 50	69.88 (16.70) 49
FSMC total score	71.15 (14.05) 53	66.13 (16.64) 52	68.37 (18.07) 49	69.48 (16.25) 50	67.62 (12.91) 53	63.32 (14.93) 53	66.08 (17.69) 49	67.16 (16.28) 49
HADS total score	9.26 (4.95) 53	5.71 (4.65) 52	8.14 (4.83) 49	8.53 (4.92) 49	10.11 (5.34) 53	6.98 (5.28) 53	9.98 (6.83) 50	9.86 (6.44) 49
HADS anxiety score	5.11 (3.27) 53	2.88 (2.63) 52	3.84 (2.64) 49	4.39 (3.06) 49	5.28 (3.49) 53	3.79 (3.38) 53	5.14 (3.87) 50	4.76 (3.57) 49
HADS depression score	4.15 (2.38) 53	2.85 (2.59) 52	4.31 (2.87) 49	4.14 (2.71) 49	4.83 (2.61) 53	3.19 (2.50) 53	4.84 (3.34) 50	5.10 (3.40) 49
SEPECSA	7.32 (1.58) 53	8.09 (1.46) 52	7.99 (1.47) 49	8.02 (1.37) 49	6.88 (1.66) 53	7.32 (1.63) 53	7.14 (1.92) 50	7.05 (1.60) 49
OSA competence	61.98 (10.84) 53	66.12 (10.65) 52	63.47 (11.05) 49	62.02 (11.49) 48	60.85 (8.75) 52	64.67 (10.92) 52	60.37 (9.87) 49	60.85 (10.32) 48
$\dot{V}O_{2peak}$ relative (mL/min/kg)	19.67 (5.82) 53	21.50 (5.81) 50	–	–	18.39 (6.25) 53	19.95 (6.36) 53	–	–

SF-36: Medical Outcome Study 36-item Short Form Health Survey; FSMC: Fatigue Scale for Motor and Cognitive Functions; HADS: Hospital Anxiety and Depression Scale; SEPECSA: Self-Efficacy for Performing Energy Conservation Strategies Assessment; OSA: Occupational Self Assessment; $\dot{V}O_{2peak}$: peak oxygen consumption; T_0: baseline; T_1: 3 weeks; T_2: 4 months; T_3: 6 months.

Supplementary Tables 1 and 2, respectively).

3.2.2. Secondary outcomes

In pairwise comparisons of the group × time interaction, the EG group had significantly higher scores than UC at: (i) T_1 in the $\dot{V}O_{2peak}$ and the SEPECSA; (ii) T_2 in the SF-36 mental health and SEPECSA; (iii) T_3 in the SF-36 physical functioning and SEPECSA; and the EG group had significantly lower scores than UC at T_2 in HADS anxiety (Fig. 2C–G, and Supplementary Tables 3–7).

4. Discussion

This randomized controlled trial did not show a superiority of IEME + HIIT compared with PMR + MCT regarding the effects on the primary outcome HRQoL (SF-36 Physical and Mental Component Scales (PCS and MCS, respectively)) at 6-month follow-up in fatigued pwMS. This finding contradicts the main study hypothesis.

This is the first study of the effect of a combination of IEME + HIIT on HRQoL (SF-36 PCS and MCS) during a 3-week inpatient rehabilitation stay with 6-month follow-up. For comparison with other studies, several differences need to be considered. Hersche et al. (2019b) found improvements in physical functioning (SF-36 subscale) in favour of IEME compared with PMR after 3 weeks' intervention without endurance training and at 4-month follow-up. The current study used the SF-36 PCS and MCS and combined IEME with HIIT and PMR with MCT. Endurance exercise has beneficial effects on physical domains of HRQoL (Reina-Gutiérrez et al., 2022), but, to our knowledge, there are no studies of the effects of HIIT vs MCT on HRQoL in pwMS. Dalgas et al. (2010) found significant improvements in an exercise group compared with a passive control group after a 12-week progressive resistance training intervention in fatigued pwMS on the PCS, but not the MCS of the SF-36. The current study did not use a passive control group, which may explain the

Table 3
Type III tests of fixed effects for primary and secondary outcomes.

	Group	Time	Group × Time
SF-36 Physical Component Scale	0.480	<0.001*	0.417
SF-36 Mental Component Scale	0.165	<0.001*	0.661
SF-36 Physical functioning	0.106	<0.001*	0.112
SF-36 Role limitations due to physical health	0.335	<0.001*	0.738
SF-36 Bodily pain	0.739	0.009*	0.389
SF-36 General health	0.613	<0.001*	0.892
SF-36 Vitality	0.274	<0.001*	0.238
SF-36 Social functioning	0.298	<0.001*	0.422
SF-36 Role limitations due to emotional health	0.251	0.087	0.956
SF-36 Mental health	0.081	<0.001*	0.157
FSMC total score	0.947	<0.001*	0.970
HADS total score	0.236	<0.001*	0.740
HADS anxiety score	0.079	<0.001*	0.189
HADS depression score	0.746	<0.001*	0.433
SEPECSA	0.002*	<0.001*	0.240
OSA competence	0.534	<0.001*	0.639
$\dot{V}O_{2peak}$ relative (mL/min/kg)	0.066	<0.001*	0.079

SF-36: Medical Outcome Study 36-item Short Form Health Survey; FSMC: Fatigue Scale for Motor and Cognitive Functions; HADS: Hospital Anxiety and Depression Scale; SEPECSA: Self-Efficacy for Performing Energy Conservation Strategies Assessment; OSA: Occupational Self Assessment; $\dot{V}O_{2peak}$: peak oxygen consumption.

lack of significant differences between groups in the SF-36 PCS and MCS.

The IEME + HIIT group had significantly higher scores in mental health and physical functioning (SF-36 subscales) at 4- and 6-month follow-ups, respectively, compared with the PMR + MCT group. This is partly in line with Hersche et al. (2019b), with higher physical functioning after 3 weeks IEME, and at 4-month follow-up, compared with PMR. The current study extends their findings, showing significantly higher SF-36 mental health in the IEME + HIIT group at 4-month follow-up. In addition, the IEME + HIIT group had lower anxiety (HADS) at 4-month follow-up. The present study also demonstrated a benefit of IEME + HIIT compared with PMR + MCT for self-efficacy (SEPECSA), similar to Hersche et al. (2019b). Missing significant group × time interaction effects and between-group differences on fatigue are also in line with Hersche et al. (2019b). In addition, another recently published study by Englund et al. (2022), that investigated the effects of a 12-week high-intensity resistance training (HIRT) in fatigued pwMS, found significant improvements in fatigue over time that did not differ between the two groups, performing HIRT either once or twice weekly.

Missing significant group × time interaction effects on $\dot{V}O_{2peak}$ are in contrast to previous studies comparing the effects of HIIT with MCT (Schlagheck et al., 2021; Zimmer et al., 2018). This may be due to the MCT participants training at higher intensities than prescribed, which may have reduced the training intensity difference between MCT (mean training intensity 79.48% HR_{peak}) and HIIT (mean training intensity 102.64% HR_{peak}). Nevertheless, the IEME + HIIT group showed significantly higher $\dot{V}O_{2peak}$ scores after the 3-week intervention compared with the PMR + MCT group.

This is the first study of a combination of IEME + HIIT for pwMS on HRQoL as the primary outcome. Further strengths of this study are the 6-month follow-up, restriction of inclusion to fatigued pwMS, the high compliance with the interventions and the high follow-up response rates. Study limitations are, firstly, that it is not clear to what extent the different approaches (education and exercise) contribute to the outcomes. However, IEME and HIIT were thought to complement each other, as IEME supports pwMS to implement and continue self-guided HIIT at home, thus fostering sustainability and/or augmentation of the positive HIIT effects. Secondly, study treatments were delivered in addition to the multidisciplinary inpatient rehabilitation programme. The increasing knowledge about the effectiveness of energy management programmes and exercise (including HIIT) amongst therapists and pwMS in recent years could have contributed to a convergence of the

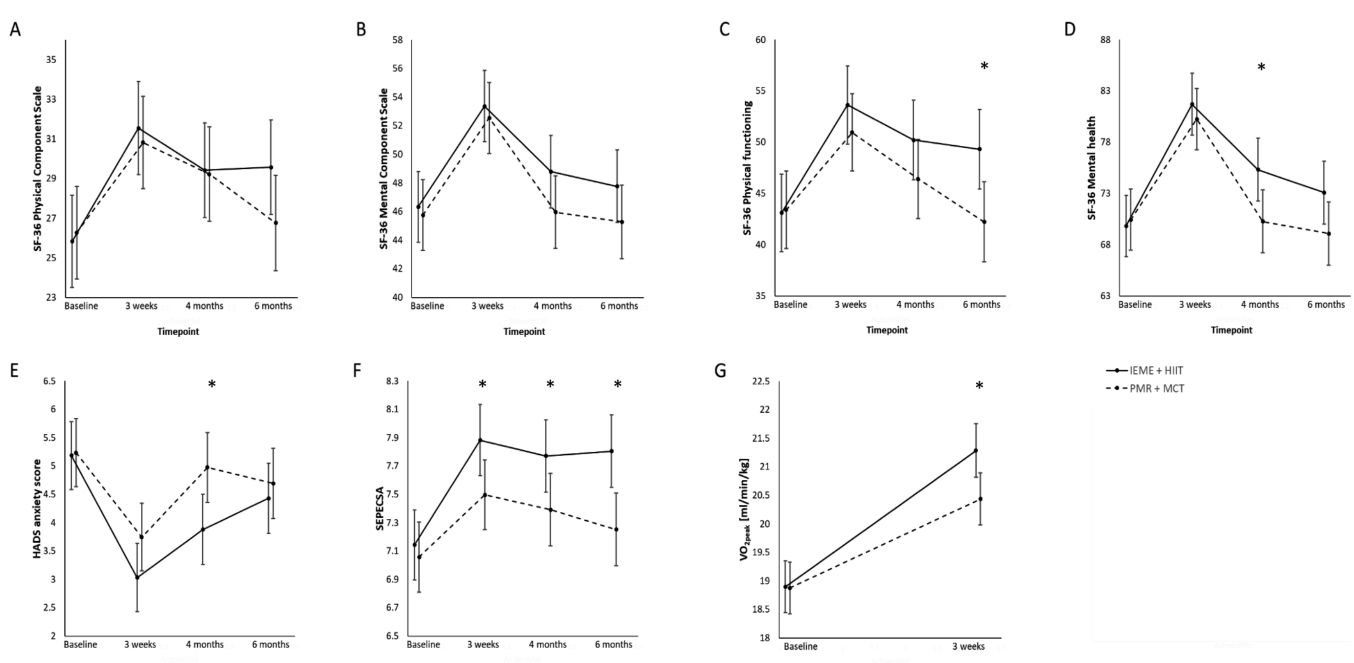

Fig. 2. Kinetics of SF-36 outcomes (A-D), HADS anxiety score (E), SEPECSA (F) and $\dot{V}O_{2peak}$ (G) between IEME + HIIT and PMR + MCT.
Data are shown as baseline-adjusted outcome kinetics (estimated marginal means with 95% confidence interval (95% CI)) separated by intervention groups. *Significant difference between the groups in the pairwise comparisons of the group × time interaction. IEME: inpatient energy management education; HIIT: high-intensity interval training; PMR: progressive muscle relaxation; MCT: moderate continuous training; SF-36: Medical Outcome Study 36-item Short Form Health Survey; HADS: Hospital Anxiety and Depression Scale; SEPECSA: Self-Efficacy for Performing Energy Conservation Strategies Assessment; $\dot{V}O_{2peak}$: peak oxygen consumption.

effects of the two groups, as elements of IEME and/or HIIT may have been incorporated in individual sessions. Finally, adherence to the learned energy conservation strategies or PMR exercises and continuation of exercise at home were not monitored. Hence, occurrence and extent of potential long-term changes in the habits of the participants remain unclear.

No significant between-group differences in the primary outcome HRQoL (SF-36 PCS and MCS) were observed. In contrast, there were significant between-group differences in favour of IEME + HIIT in physical functioning and mental health (SF-36 subscales), anxiety (HADS), and cardiorespiratory fitness ($\dot{V}O_{2peak}$) at different measurement time-points. The significantly higher scores in self-efficacy (SEPECSA) in the IEME + HIIT group after the 3-week intervention and at 4- and 6-month follow-up may be particularly relevant for managing treatment-resistant fatigue in daily life. In clinical practice, treatment choices must take into account these findings. However, the results of the secondary outcomes should be interpreted in light of the fact that this study was unable to show significant differences between groups in overall temporal evolution, as can be seen from the absence of significant group × time interaction effects. Thus, these results need to be verified in future studies. Additionally, future research should clarify the optimal way to combine energy management and HIIT to provide a sustainable multidisciplinary rehabilitative intervention for improving HRQoL in fatigued pwMS. Increased use of digital approaches and technologies, more frequent inpatient rehabilitation stays, and continuation of intensive multidisciplinary programmes in the outpatient setting could help improve the sustainability of intervention effects.

5. Conclusion

IEME + HIIT was not superior to PMR + MCT regarding the effects on HRQoL (SF-36 PCS and MCS) at 6-month follow-up in pwMS. However, there were significant between-group differences in favour of IEME + HIIT in physical functioning and mental health (SF-36 subscales), anxiety (HADS), cardiorespiratory fitness ($\dot{V}O_{2peak}$) and self-efficacy (SEPECSA) at different measurement time-points that need to be considered in clinical practice. Further research is needed on combined approaches that increase HRQoL during the 3-week inpatient rehabilitation stay and are capable to sustain HRQoL improvement beyond inpatient rehabilitation in fatigued pwMS.

Data availability

The data presented in this study are available on reasonable request from the corresponding author.

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CRediT authorship contribution statement

Nadine Patt: Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Marie Kupjetz:** Investigation, Data curation, Writing – review & editing, Project administration. **Jan Kool:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Ruth Hersche:** Conceptualization, Methodology, Writing – review & editing. **Max Oberste:** Formal analysis, Writing – review & editing, Visualization. **Niklas Joisten:** Methodology, Writing – review & editing. **Roman Gonzenbach:** Resources, Writing – review & editing. **Claudio Renato Nigg:** Writing – review & editing, Supervision. **Philipp Zimmer:** Conceptualization, Methodology, Writing – review & editing. **Jens Bansi:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104929.

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