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Abstract

Introduction: Different therapies can improve clinical and motor symptoms of multiple sclerosis (MS) similarly but studies comparing the effects of different exercise therapies on clinical and motor outcomes are scant. We compared the effects of exergaming (EXE), balance (BAL), cycling (CYC), proprioceptive neuromuscular facilitation (PNF), and a standard care wait-listed control group (CON) on clinical and motor symptoms and quality of life (QoL) in people with MS (PwMS). **Methods:** PwMS (n=68, 90% females; age: 47.0y, Expanded Disability Status Scale: 5 to 6) were randomized to 5 groups. Before and after the interventions (5x/week for 5 weeks) PwMS were tested for: MS-related clinical and motor symptoms (Multiple Sclerosis Impact Scale-29; MSIS-29, primary outcome), QoL (EQ-5D), symptoms of depression, gait and balance ability (Tinetti Assessment Tool, TAT), static and dynamic balance and fall risk (Berg Balance Scale (BBS), walking capacity (six-minute walk test, 6MWT), and standing posturography on a force platform. **Results:** EXE, BAL, and CYC improved MSIS-29 scores similarly. EXE and CYC improved QoL and walking capacity similarly but more than BAL. Only EXE improved gait and balance scores (TAT). EXE and BAL improved fall risk and standing balance similarly but more than CYC. PNF and CON revealed no changes. EQ-5D moderated the exercise effects on MSIS-29 scores only in EXE. Changes in QoL and changes in MSIS-29 scores correlated R^2=0.73 only in EXE. **Conclusion:** In conclusion, BAL and CYC but EXE in particular, but not PNF, can improve clinical and motor symptoms and QoL in PwMS (EDSS: 5 to 6), expanding the evidence-based exercise options to reduce mobility limitations in PwMS.

Key words: exercise specificity, sensorimotor training, posture

Introduction

Multiple sclerosis (MS) is an immune system-mediated demyelinating disease, resulting in physical, cognitive, and depressive symptoms in twice as many women than men aged 20-50 years (1). Because the cause of MS is unknown, people with MS (PwMS) take drugs and receive therapies in an effort to reduce symptoms, improve function, and prevent new attacks. Medications can be effective to treat MS, but side effects and patients' poor tolerance make complementary and alternative therapies important. Exercise therapy plays a role in moderating and managing spasticity, gait and balance impairments, fatigue, and bowel dysfunction especially in more ill relapsing remitting and progressive PwMS (Expanded Disability Status Scale (EDSS) score >6) (1-3).

Albeit most acutely needed (4-6), studies examining the comparative effectiveness of exercise therapies are scant. A comparison of aerobic plus resistance vs. aerobic-only training revealed, against expectations, no superior effects on leg and shoulder strength, quality of life (QoL), and fatigue in PwMS (EDSS score ≤6) (7). Conventional balance training (BAL), exergaming (EXE) on an unstable platform, and single-task exercises on an unstable platform similarly improved balance and gait scores with some specificity favoring dual-task performance after dual-task EXE (8). Likewise, progressive resistance training on a bicycle ergometer plus balance exercise compared with a home-based lower-limb strengthening and balance exercise improved measures of mobility, falls efficacy, fatigue and depression similarly but more than control (9). Three diverse exercise interventions improved performance scores to a similar extent, suggesting a generic exercise effect in PwMS (10). Female PwMS treated with standard immune regulatory medication, yoga and aqua therapy (11) but not endurance and coordinative exercising (12)

produced comparable positive effects on, fatigue, depression, and paresthesia. While in most of these studies exercise intensity was not controlled, a comparison of cycling (CYC) at three intensities revealed no dose effects on QoL, gait performance, and leg power (13). The generic exercise effects on outcomes in PwMS may in part be related to response heterogeneity (14).

Different therapies can improve clinical and motor symptoms of MS similarly but for different reasons. While EXE is a conceptually favored therapy for clinical and motor symptoms of MS (15) due to its potential to improve muscular and cardiovascular fitness, balance while standing and walking, and inter-limb and visuomotor coordination, such favorable effects can be highly variable and even absent, requiring further studies (5,14). Comparative effectiveness of different exercise therapies may be related to a common factor such as intensity controlled through cardiovascular load (16-18). However, such studies are scant. In addition to intense exercise, therapists have been using Bobath-guided proprioceptive neuromuscular facilitation (PNF) for reducing spasticity and pain and increasing muscle strength and range of motion in PwMS. However, PNF's effectiveness, as a modality with low cardiovascular load, in general and in comparison with other exercise treatment in particular has been rarely studied (19,20). The purpose of the present study was to compare the effects of EXE, BAL, and CYC at the same cardiovascular and perceived load with PNF as an active control and with a no-intervention control (CON) on clinical and motor symptoms and QoL in PwMS. Based on the literature, we hypothesized no differences in the effects between the EXE, BAL, and CYC relative to PNF and CON on the primary and secondary outcomes.

Methods

Design and participants. This is an assessor-blinded, four-intervention, comparative effectiveness, pre-post randomized clinical trial. Family physicians referred PwMS to the hospital neurologist to confirm the diagnosis of MS, screen PwMS for eligibility, and rate MS severity by EDSS. Using consecutive sampling from the hospital's database, the neurologist identified 82 PwMS who, based on medical records, appeared to be suitable for the study. The neurologist himself or his designee contacted patients by phone or mail. All patients first signed an informed consent (IKEB008/2017) and then participated in a screening session, which included a cognitive test administered by a neuropsychologist. 70 PwMS met inclusion criteria. A physical therapist not involved in the trial performed the concealed randomization of these 70 PwMS: He drew a colored ribbon from a covered box and attached one ribbon to each patient folder. The flowchart describes the five groups: high-intensity EXE (n=14, 12F), high-intensity BAL (n=14, 12F), high-intensity CYC (n=14, 13F), active PNF control (n=14, 13F), and a standard care, wait-listed, no-intervention control group (CON, n=12, 11F) (Supplemental Digital Content 1, http://links.lww.com/MSS/B856).

Inclusion criteria were: male or female gender, age ≥ 30, EDSS score of 4 to 6, a relapse frequency ≤ 1 per year over the past fiver years to minimize a change in medication, and Mini-Mental State Examination score ≥ 24. Exclusion criteria were: steroid therapy currently or during the past month, acute exacerbation of MS within 3 months of starting the program, radiological change in disease progression over the past two years, a substantial change in medication over the past year, use of a cane or walker, depression (Beck Depression Inventory, BDI, score > 40), a serious unstable medical condition, severe cardiac disease (i.e., congestive heart failure,

ischemic disease, pacemaker, orthostatic hypotension), uncontrolled diabetes, history of stroke, traumatic brain injury, an epileptic seizure within a year, or current participation in a self-directed or formal group exercise program.

Before the trial all PwMS and during the trial CON only were enrolled in standard physical therapy provided by government insurance. PwMS other than those in CON stopped this care but CON continued to receive standard care. PwMS gave written informed consent and the Institutional Research Ethics Committee approved the registered (NCT03424538) study protocol.

Outcomes. Changes in the scores or performance in the primary and secondary outcomes were measured before and after the interventions by the same examiners who were blinded to intervention allocation. The testing order was standardized among PwMS and testing sessions. Pretests and posttests were performed within 1 week of the interventions with at least a 48-h gap between pre-testing and Session 1 and between Session 25 and post-testing.

Primary outcome was the Multiple Sclerosis Impact Scale (MSIS-29), a valid and reliable measure of physical and psychological functions and it is responsive to interventions in PwMS (21,22).

Secondary outcomes addressed life domains. The EQ-5D reliably measures health-related QoL in PwMS (23). Depression was measured by BDI, a reliable tool in clinical populations (24). The Tinetti Assessment Tool is a valid and reliable (intraclass correlation $R>0.80$) test of gait and balance in PwMS (25). Balance and coordination were measured with the Berg Balance Scale

(BBS), a valid and reliable (R=0.80) measure of fall risk (26). The six-minute walk (6MWT) test is a valid and reliable (R=0.95) index of walking capacity and fatigue in MS (27). Postural stability was measured by COP path length in standing on a force platform (Posture Evaluation Platform; Med-Eval Co., Budapest, Hungary) in a wide and narrow stance with eyes open or closed for 20 s after 1 familiarization trial in each condition, a reliable outcome measure of static postural stability in PwMS (28). Ten minutes before the start of warm-up and 10 minutes after the end of cool-down, in all PwMS but CON resting blood pressure (BP) and hear rate (HR) was measured in sitting for one minute (Omron M7 Intelli IT, OMRON Healthcare UK Ltd., Milton Keynes, United Kingdom). HR during the exercise was measured with a watch and the session average and maximal value recorded (Polar model RS800CX; Polar Electro Co. Ltd., Kempele, Finland).

Interventions

The interventions aimed to improve clinical and motor symptoms of MS, QoL, postural stability, and mobility. In a preliminary session, participants were familiarized with the tests and the exercises. We made every effort to eliminate contamination between groups. EXE wave was done first in one wave to record HR during exercise that could be set as target for BAL and CYC subsequently as 80% of age predicted peak HR, a zone of 110 to 170 beats/min. These values were paired with a low and high auditory warning beep. About 4-6 patients exercised in one of three gyms concurrently. After EXE finished the intervention, 4-6 patients in CYC, BAL, and PNF, respectively, exercised at the same time in different rooms. We had three, 25-day waves for CYC, BAL, and PNF. A given patient exercised at the same time of the day.

The interventions consisted 25, 1-h sessions over five weeks conducted in the hospital's outpatient physical therapy gyms. Up to three physical therapists, who were trained and supervised by the principal investigator and who did not perform the assessments, delivered the interventions for groups of 4 to 8 individuals at the same of time of the day. After each session, PwMS recorded their observations concerning their symptoms and therapists checked these diaries daily.

Supplemental Digital Content 2, http://links.lww.com/MSS/B857, provides details of the 10-min warm-up, the 40-min interventions, and the 10-min cool down. EXE received sensorimotor and visuomotor agility training using each of the three modules of the Xbox 360 core system (Kinect Adventures video game; Microsoft Co., Redwood, WA, USA). BAL-training consisted of dynamic and static balance and stepping exercises performed in multiple directions. CYC training was a 'spinning class'. A PNF-trained physical therapist delivered the PNF intervention. PwMS in the wait-listed CON group were instructed to continue with standard physical therapy and habitual activity. They were offered enrollment into supervised exercise after the study. All PwMS, including CON, were asked not to change their diet, medication (including vitamin D dose), or exercise habits for the duration of this study.

Statistical analyses

Using G*Power (G*Power®, Version 3.1.9.2.) (29), we estimated the number of participants needed for a significant Group (EXE, CYC, PNF, CON) by Time (pre, post) interaction for the primary outcome. A priori power analysis revealed that enrolling 12 PwMS per group with a 10-point (30) improvement in MSIS-29 relative to no change in CON would produce a medium

effect of 0.5 (alpha: 0.05, power: 1-beta (power) of 0.8). We randomized n=70 PwMS in anticipation of drop out due to illness, adherence, and disease exacerbation.

Data are expressed as mean±SD. Continuous variables were normally distributed based on the Shapiro–Wilk test. We compared the five groups at baseline using a one-way ANOVA or a Kruskal-Wallis test. We compared the gain score for continuous variables between the five groups using a one-way ANOVAs or a Kruskal-Wallis text for categorical data. A significant effect, characterized by $p\eta^2$ effect size (ES), was interpreted as a group by time interaction and was followed by a Tukey's posthoc or a Mann-Whitney test to determine the means that were different. Cutoffs for $p\eta^2$ are ≥0.01 (small), ≥ 0.06 (medium), and ≥0.14 (large) (31). We further quantified the within group changes by Cohen's ESs (small: 0.20; moderate: 0.50;large: 0.80). The Holm method was used to correct for family-wise error. We determined the relationship between changes in selected variables using Pearson product moment correlations. Conditional process mediation (Process macro; 5000 bootstrap samples, bias-corrected confidence intervals) determined if changes in variables mediated the effects of EXE, BAL, CYC, and PNF vs. CON on MSIS-29. The level of significance was set at $p<0.05$. All analyses were done in SPSS (SPSS® 22.0, IBM Corporation, Armonk NY, USA).

Results

Participants' characteristics in the five groups were similar at baseline (Tables 1, 2). Relapsing-Remitting and Primary Progressive Multiple Sclerosis was the diagnosis in 62% and 38% of the 68 PwMS (90% female) aged 47y with a low, 20.0 $kg \cdot m^{-2}$, body mass index. A given patient

took only one of three drugs for MS. No patient had more than two of the 12 co-morbidities of which thyroid dysfunction was the highest at 29%.

Supplemental Digital Content 3, http://links.lww.com/MSS/B858, shows that HR, SBP, and DBP measured at rest 10 minutes before the start and 10 min after the end of each session was similar in the four interventions groups and neither intervention modified these values over 25 sessions (all $p>0.05$). HR during exercise was similar in EXE (120.5 ±5.01 beats/min) and CYC (119.5 ±4.93) but lower ($p< 0.05$) in BAL (115.1 ±6.54) and lowest ($p<0.05$ vs. other three groups) in PNF (99.5 ±6.94) (Group main effect: $F=420.8$, $p=0.001$, $p\eta^2 =0.960$). Peak HR during exercise was similar in EXE (136.1 ±6.63 beats/min) and CYC (131.5 ±6.52) but lower ($p<0.05$) in BAL 124.8 (±5.89) and lowest ($p<0.05$ vs. other 3 groups) in PNF (111.4 ±7.15) (Group main effect: $F=486.6$; $p=0.001$; $p\eta^2 =0.966$). These peak HR values corresponded to 78.6% (EXE), 72.2% (BAL), 76.0% (CYC), and 64.4% (PNF) of age predicted peak HR. RPE recorded during exercise (10-point scale) was different between all groups ($p<0.05$) and was the highest in EXE (7.9 ±0.75), followed by CYC (6.9 ±1.02), BAL (5.2 ±0.70), and PNF (2.8 ±0.56) ($F=233.1$, $p=0.001$; $p\eta^2 =0.931$).

Table 3 shows the intervention data. Improvements in MSIS-29 scores, the primary outcome were not different between EXE (-10%), BAL (-6%), and CYC (-6%) (all $p<0.05$). These changes were greater than the -2% and 1% change in PNF and CON (both $p>0.05$). Improvements in EQ5-Sum did not differ between EXE (-16%) and CYC (-10.2%, both $p<0.05$). These changes were greater than the 0.1 to -4.0% change in BAL, PNF, and CON (all $p>0.05$). Only EXE improved TAT by 21% ($p<0.05$). Improvements in BBS did not differ between EXE

(30%) and BAL (19%, both $p<0.05$) and exceeded the changes in the other three groups. Improvements in walking capacity (6MWT) did not differ between EXE (26%) and CYC (15%, both $p<0.05$). These changes were greater than the 4 to 10% change in BAL, PNF, and CON (all $p>0.05$). EXE and BAL reduced COP path measured in wide stance eyes open by 32 and 18% (both $p<0.05$). These changes were greater than the ~-11% change in the other three groups (all $p>0.05$). The interventions did not improve or the post-hoc analyses did not survive the Holm adjustment for multiple comparisons for EQ5-VAS, BDI, and three static standing balance outcomes (WEC, NEO, NEC, Table 3). Figure 1 shows the distribution of individual changes in the scores of primary and selected secondary outcomes.

Moderation analysis revealed that EQ5D-SUM moderated the exercise effects on MSIS-29 only in EXE ($p=0.002$) but no other variables moderated directly or indirectly the exercise effects in MSIS-29 (all $p>0.05$). Changes in EQ5D-SUM and changes in MSIS-29 correlated $R^2=0.73$ ($p<0.001$, Figure 2) only in EXE and relationships between changes in other variables did not reach significance.

Discussion

We compared the effects of 25 sessions of EXE, BAL, and CYC at the same cardiovascular and perceived load with PNF and CON on QoL and clinical and motor symptoms in PwMS. In a partial agreement with the hypothesis, EXE, BAL, and CYC but not PNF and CON were selectively effective and improved clinical and motor symptoms and QoL in PwMS.

EXE improved the scores in MSIS-29, the primary outcome nearly 3 points more than the 8-point clinically meaningful minimal change (Table 3) (30). An effective intervention is expected to improve MSIS-29 by 8 points in 80% of MS patients with an EDSS score of 5.2 (Table 1). Indeed, 11 of the 14 PwMS in EXE improved by 7 or more points (Fig. 1). BAL and CYC also each improved MSIS-29 scores by ~6 points, more than the control groups. These data suggest that EXE in particular reduced the perceived effort PwMS experienced to walk, balance, and manipulate objects and the sense of clumsiness, stiff, the presence of spasms, tremor, and limb heaviness, making participants feel less tired, anxious, and dependent on others. By setting MSIS-29 score as the primary outcome, we followed recommendations for using a clearly defined clinical primary outcome in PwMS (6). Only a few studies have assessed the effects of exercise training on MSIS-29 (6). Physical therapy, yoga, and fitness exercise training in a community setting improved sub-scales of MSIS-29 relative to controls (32) and home-based EXE with the Nintendo Wii Balance Board System improved MSIS-29 by 12%, similar to the 10% in the present study (Table 3, Fig. 1) (33). However, other exergaming or innovative balance and gait interventions did not measure clinical outcomes, making comparisons between the present and previous data difficult (4,5,11-14,34). While PNF has been advocated to ameliorate clinical symptoms in particularly spasticity and pain through reflex mechanisms in PwMS (19,20), the current data suggest no such beneficial effects (Table 3).

Mediation and regression analyses revealed that changes in QoL mediated and predicted improvements in MSIS-29 only in EXE (Figure 2). This observation is in line with studies reporting favorable effects by a variety of exercise interventions on QoL in PwMS (2,4,5,34), superseding previous conclusions of nil exercise effects on QoL in PwMA (6,35). Unlike MSIS-

29, the EQ5-SUM measures non-disease specific domains of life, including mobility, self care, usual activities, general pain/discomfort, and anxiety/depression. EXE was thus effective in improving perception of general and also disease-related QoL. These data are important, as it provides further support for PwMS becoming engaged not only in exercise in general but in high-intensity exercise in particular (18). Indeed, high-intensity and -frequency exercise training has become a concept-based choice in a number of patient groups (36-38) and mobility-limited older adults (39), including PwMS (16-18,40), suggesting that cardiovascular and neuromuscular loading up to a high level does not exacerbate disease symptoms. Based on exercise diaries, we indeed observed no adverse reactions, encountered no dropouts, and each PwMS attended every session, resulting in 100% adherence. The encouraging news is that exercise does not need to be necessarily of high intensity because a number of lowe(er) intensity interventions have meaningfully improved specific outcomes (6,11,12,35).

The improved perception of QoL may be related to exercise-induced increases in fitness, mobility, and balance. A variety of exercise routines can improve maximal oxygen uptake, a measure of fitness, up to 22% in PwMS (41). EXE and CYC were the most effective to improve walking capacity by 32 to 57m, contrasting with 6-19m changes in BAL, PNF, and CON (Table 3). Coupled with the superior increases in mobility and balance in EXE compared with BAL and CYC (Table 3), the emerging picture is that EXE can simultaneously address multi-faceted dysfunctions in PwMS, including balance, fall risk, postural control, and fitness (5). In particular, the 6MWT performance tends correlate with fitness measured by VO2max in Parkinson's patients (42). Based on normative data (~380m) (43) for patients with an EDSS of 5.2 (Table 1), our participants had severe mobility disability indexed by the 6MWT (~240m) but this distance

was longer than the ~115m in more disabled MS patients (44). The increase of 57.4m in 6MWT (Table 3) far exceeds the 22m minimally important change (45) and the 13m change reported previously (44), suggesting substantial increases in walking ability and mobility following EXE (and CYC) but not BAL or PNF. The changes in BBS, TAT and COP tended to agree with the direction and magnitude of changes reported previously but initial levels and disease severity differed from our values and varied also between studies (2,44,46). These changes altogether suggest that EXE was selectively effective in improving mobility and postural control and that PNF, at least the way we administered it here, has low effectiveness.

One limitation of this study is the brevity of the program. A lack of follow-up is another limitation because exercise effects are often not sustained in PwMS (6,44) and we cannot tell if any of the interventions would have slowed disease progression. It is unclear for how long such a high-intensity and frequency of exercise is necessary and sustainable in PwMS. We did not measure changes in cognition. We also did not have members of CON visit the facility 25 times, which would have been necessary to determine the net effects of the interventions beyond the effects produced by the social element of the visits. We cannot resolve the inconsistency in our data that while symptoms of depression improved when measured as an element of MSIS-29 and EQ5, depression symptoms did not improve when measured by DBI (Table 3), contrasting with previous data (12). The specificity of these intervention effects to clinical symptoms are unclear because several high-intensity programs used different exercises, which were also effective even in a home environment, requiring less equipment and supervision than what we used (34). Patients could have modified their physical activity and diet during the study period affecting the results but we did not quantify these factors. Indeed, 6MWT performance accounts for 45% of

the variance in mean steps/day and ~10m increases in 6MWT performance can sum to an increase in daily step count by over 2,000 steps in the community (47). While in this randomized comparative effectiveness trial the assessors were blinded to patients' group assignment, there could still be a bias in the assessments because we did not assess if the masking was successfully maintained. Without neural, biomechanical or behavioral markers, we were unable to determine the mechanisms through which the interventions produced the favorable mobility and clinical effects.

In conclusion, this assessor-blinded randomized clinical trial compared four exercise interventions showing that BAL and CYC, but EXE in particular, but not PNF can improve clinical and motor symptoms and QoL in PwMS (EDSS: 5 to 6), expanding the evidence-based exercise options to reduce mobility limitations in PwMS.

Acknowledgments

This study received no funding. The authors declare no conflict of interest. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The present study does not constitute an endorsement by the American College of Sports Medicine.

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Figure captions

Figure 1. Individual changes in: A. Multiple Sclerosis Impact Scale; B. Sum of the EuroQol questionnaire sub-scales (EQ5-Sum); C: Distance walked during six minuets (6MWT), and D: in the path of the center of pressure (COP) while standing in a wide stance with eyes open. Each line represents one participant in the exergaming (EXE) group. While EXE improved ($p<0.05$) in all four variables (filled symbol, group means), the proprioceptive facilitation active (PNF, filled gray symbol) and the no-intervention control (CON, unfilled symbol) groups did not change. For sake of clarity, the data for the balance training and cycling groups, which improved less than EXE, are not shown and for the PNF and CON groups only the post intervention means are displayed.

Figure 2. Relationship between percent changes in Multiple Sclerosis Impact Scale (MSIS-29) and percent changes in the sum of the EuroQol questionnaire sub-scales (EQ5-SUM). The equation of $y=0.39x-1.9$ and $R^2=0.73$ characterize the relationship in the exergaming (EXE) only group ($n=14$, $p<0.001$).

Figure 1

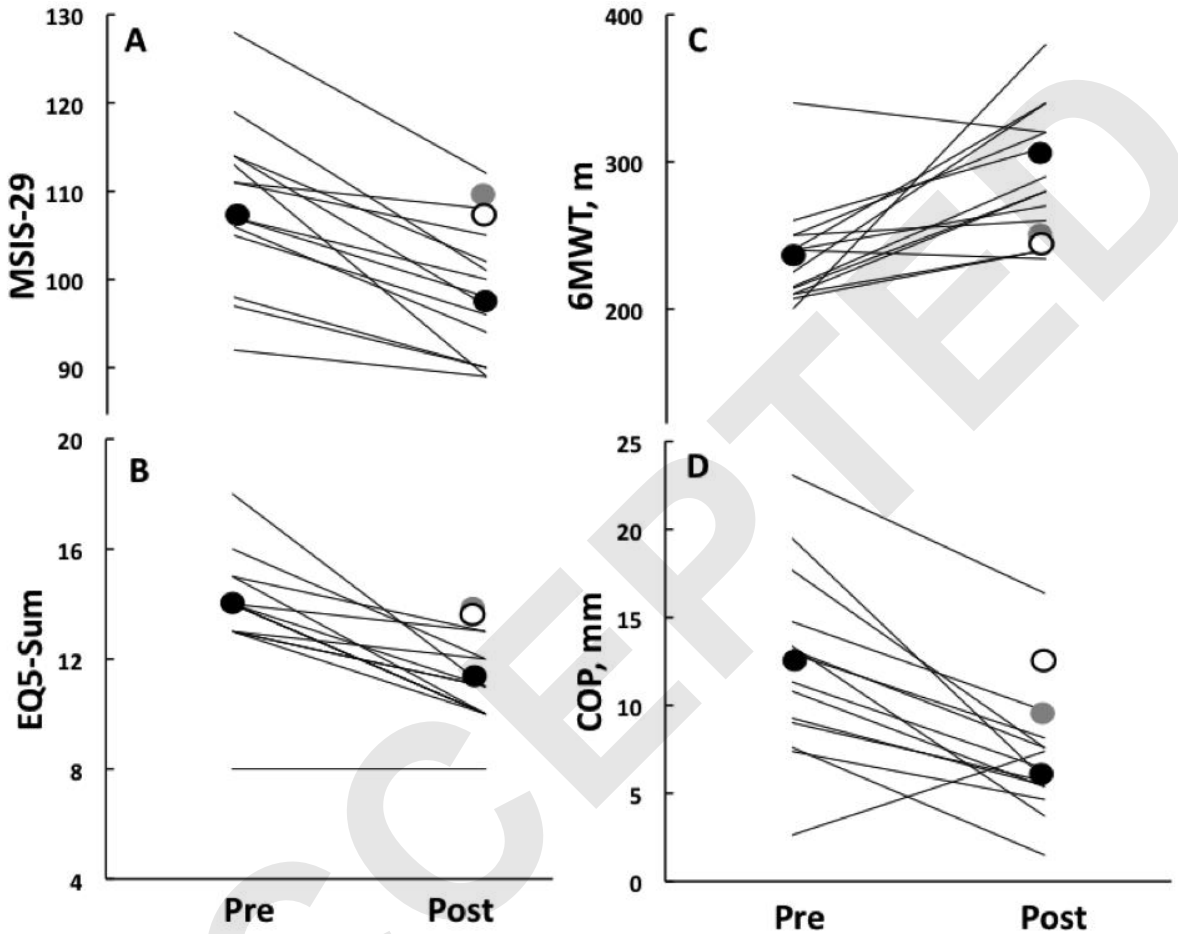

Figure 2

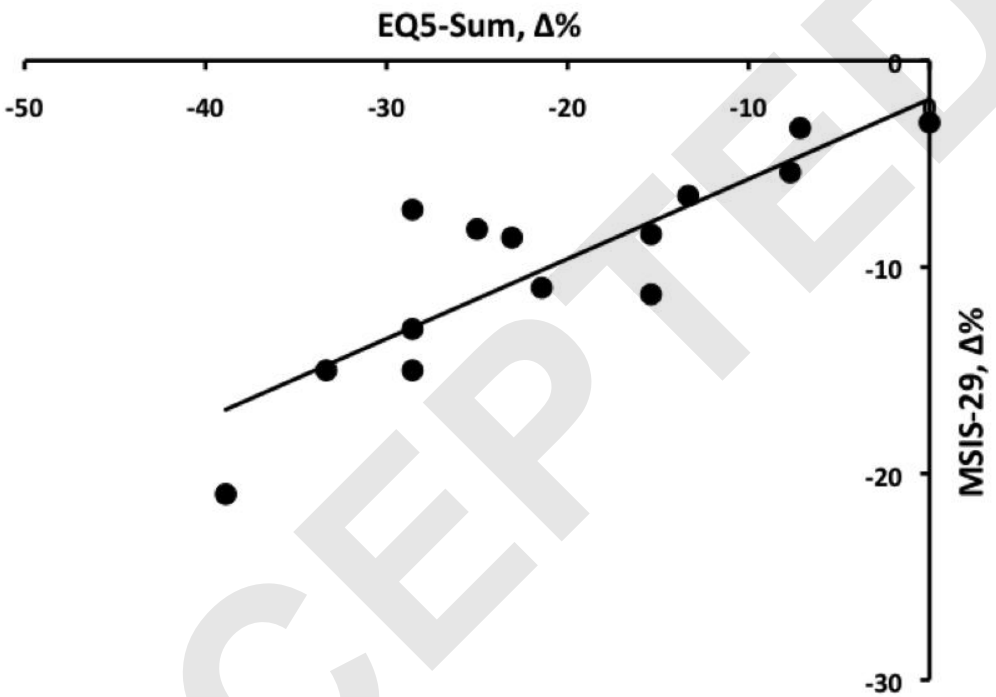

Table 1. Demographic and clinical characteristics at baseline.

	EXE	BAL	CYC	PNF	CON	All
n (RRMS, PRMS)	14 (7,7)	14 (9,5)	14 (9,5)	14 (9,5)	12 (8,4)	68 (42,26)
Females, %	86	86	93	93	92	90
RRMS, n (%)	7 (50)	9 (64)	9 (64)	9 (64)	8 (66)	42 (62)
PRMS, n (%)	7 (50)	5 (36)	5 (36)	5 (36)	4 (34)	26 (38)
EDSS, median	5.0	5.0	5.0	5.0	5.0	5.0
EDSS, range	5-6	5-6	5-6	5-6	5-6	5-6
MSIS-29	108.7	109.1	106.0	110.7	109.8	108.8
	9.29	8.60	10.35	9.76	10.67	9.57
MS duration, y	12.1	13.6	13.2	12.7	14.0	13.1
	2.68	4.07	4.42	4.25	4.11	3.89
Age, y	48.2	46.9	48.1	46.9	44.4	47.0
	5.48	6.46	5.65	5.57	6.76	5.95
Height, cm	171.6	170.1	169.5	168.7	173.5	170.6
	5.94	2.80	4.67	5.36	6.27	5.23
Mass, kg	59.7	59.8	55.6	58.4	57.9	58.3
	9.72	9.67	5.27	8.54	7.77	8.27
BMI, $kg \cdot m^{-2}$	20.2	20.7	19.4	20.5	19.2	20.0
	2.77	3.57	1.72	2.44	1.87	2.57
MMSE	27.2	26.9	27.2	26.7	26.8	27.0
	1.05	1.23	1.05	1.54	1.11	1.20
Smoking, n (%)	3 (21)	7 (50)	4 (29)	6 (43)	3 (25)	23 (34)
Alcohol, 1-3 drinks/day, n (%)	7 (50)	10 (71)	6 (43)	6 (43)	6 (50)	35 (51)
Co-morbidities, n						
Thyroid dysfunction	4	4	3	3	5	19
Hypertension	4	5	4	2	0	15
Depression	2	1	5	1	3	12
Gastric inflammation	1	2	1	3	2	9
Rheumatoid arthritis	2	1	2	1	1	7
Epilepsy	0	0	2	2	2	6
Cardiac ischemia	2	1	1	1	0	5
Fibromyalgia	0	1	1	1	2	5
Anxiety	1	1	0	1	1	4
Vertebral hernia	0	1	1	2	0	4
Bipolar disorder	0	1	0	1	1	3
Diabetes	1	0	0	0	0	1
Drugs, n						
Copaxone (Glatiramer acetate)	5	7	5	8	5	30
Tecfidera (Dimethyl fumarate)	5	3	6	4	2	20
Tysabri (Natalizumab)	4	4	3	2	5	18
Vitamin D, n (%)	11 (79)	12 (86)	11 (79)	10 (71)	11 (92)	68 (81)
IU/day	1519	1262	1286	1357	688	1221
IU/day, median	857	929	1000	1143	857	857

Values are mean ±SD or as noted
EXE, exergaming exercise group
BAL, balance training group
CYC, cycling training group
PNF, proprioceptive neuromuscular facilitation active control group
CON, no-intervention control group
RRMS, Relapsing-Remitting Multiple Sclerosis
PRMS, Primary Progressive Multiple Sclerosis
EDSS, Expanded Disability Status Scale
MSIS-29, Multiple Sclerosis Impact Scale
BMI, body mass index
IU, international unit

Table 2. Secondary outcomes at baseline.

		EXE	BAL	CYC	PNF	CON	F*	p
EQ5-VAS, mm	Mean	62.1	64.3	61.4	62.9	64.2	0.5	0.717
	±SD	6.99	6.46	6.63	6.11	5.15		
EQ5-Sum score	Mean	13.9	13.6	13.4	13.9	13.3	0.3	0.829
	±SD	2.18	0.93	1.83	1.44	0.89		
BDI	Mean	12.6	11.6	13.6	12.3	14.3	1.6	0.185
	±SD	3.23	2.56	3.43	2.55	3.22		
TAT	Mean	15.9	16.4	15.7	16.4	16.7	0.8	0.525
	±SD	1.86	1.22	1.98	1.22	1.61		
BBS	Mean	21.7	21.9	20.7	21.1	22.5	0.6	0.674
	±SD	3.56	2.32	3.79	1.51	4.38		
6MWT, m	Mean	235.8	230.4	245.7	244.3	243.3	0.4	0.834
	±SD	35.48	30.03	41.08	52.98	39.56		
COP, cm								
WEO	Mean	12.3	13.0	11.8	11.4	13.0	0.4	0.817
	±SD	5.32	4.15	3.81	3.22	4.51		
WEC	Mean	8.6	9.3	7.8	8.7	8.9	0.5	0.747
	±SD	3.61	2.98	2.70	2.23	3.60		
NEO	Mean	11.6	11.8	11.6	9.2	10.3	0.4	0.828
	±SD	8.18	8.18	3.86	6.23	7.53		
NEC	Mean	12.0	11.7	11.4	10.4	10.1	0.6	0.691
	±SD	3.86	3.31	5.03	3.01	3.79		

EXE, exergaming exercise group
BAL, balance training group
CYC, cycling training group
PNF, proprioceptive neuromuscular facilitation active control group
CON, no-intervention control group
EQ-5D, EuroQol five dimensions questionnaire, VAS: visual analog scale
BDI, Beck depression inventory (0-13: minimal; 14-19: mild; 20-28: moderate; 29-63: severe)
TAT, Tinetti Assessment Tool, maximal score 28, ≤ 19 high fall risk
BBS, Berg balance scale. Fall risk: 0-20: high; 21-40: medium; 41-56: low
6MWT, six-minute walk test, higher values denote better walking capacity, fitness
COP, center of pressure measured in quiet standing for 20 s
WEO, wide stance eyes open
WEC, wide stance eyes closed
NEO, narrow stance eyes open
NEC, narrow stance eyes closed
* F and p values for one way ANOVA

Table 3. Change scores after interventions.

Variable		EXE, n =14	BAL, n=14	CYC, n=14	PNF, n=14	CON, n=12	$F_{4,63}$	p	$p\eta^2$
MSIS-29*	Mean	-10.8	-6.3	-6.3	-1.9	1.0	9.4	**0.001**	0.375
	±SD	6.09	4.36	8.07	2.80	3.46			
	ES	-1.12	-0.66	-0.54	-0.20	0.01			
EQ5-VAS, mm	Mean	7.1	0.0	5.7	0.7	-0.8	3.9**	**0.006**	0.202
	±SD	6.11	6.79	7.56	7.30	5.15			
	ES	0.73	0.09	0.66	0.12	-0.07			
EQ5-Sum score	Mean	-2.3	-0.6	-1.4	-0.5	0.0	5.9	**0.001**	0.276
	±SD	1.44	1.15	1.70	1.16	1.13			
	ES	-0.97	-0.62	-0.53	-0.35	0.02			
BDI	Mean	-0.2	0.1	-1.0	-0.6	-0.4	0.4	0.824	0.023
	±SD	2.67	1.86	2.75	1.87	2.94			
	ES	-0.02	0.00	-0.13	-0.07	-0.02			
TAT	Mean	3.1	1.7	2.1	1.1	0.3	3.4	**0.013**	0.179
	±SD	2.71	1.90	2.85	1.49	0.97			
	ES	1.14	0.22	0.49	0.31	0.13			
BBS	Mean	6.1	3.9	2.5	1.6	-0.2	8.3	**0.001**	0.345
	±SD	3.52	2.25	2.62	3.52	2.62			
	ES	1.53	2.31	0.52	0.11	-0.17			
6MWT, m	Mean	57.4	19.2	32.1	5.5	6.3	3.3	**0.015**	0.175
	±SD	52.09	35.40	44.58	34.64	49.27			
	ES	1.20	0.82	0.59	0.22	0.04			
WEO, cm	Mean	-5.5	-2.4	-1.7	-1.8	0.4	4.1	**0.005**	0.208
	±SD	4.20	3.62	3.64	3.99	3.34			
	ES	-1.23	-0.69	-0.24	-0.12	0.09			
WEC, cm	Mean	-2.0	-1.5	-0.9	-0.8	-1.0	0.4	0.830	0.023
	±SD	3.51	3.14	3.63	3.01	3.55			
	ES	-0.14	-0.10	-0.08	-0.09	-0.07			
NEO, cm	Mean	-3.9	-2.1	-2.2	-0.9	-0.5	0.5	0.755	0.029
	±SD	7.41	7.95	5.63	5.83	8.18			
	ES	-0.44	-0.28	-0.31	-0.12	-0.08			
NEC, cm	Mean	-2.9	-1.6	-1.7	-0.9	0.5	0.4	0.506	0.051
	±SD	5.20	4.85	4.90	4.04	5.22			
	ES	-0.26	-0.15	-0.13	-0.09	0.07			

Values are after minus before intervention in absolute units
The text accompanying the Table in the 'Results' details the post-hoc analyses
EXE, exergaming exercise group
BAL, balance training group
CYC, cycling training group
PNF, proprioceptive neuromuscular facilitation active control group
CON, no-intervention control group
MSIS-29, Multiple Sclerosis Impact Scale
EQ-5D, EuroQol five dimensions questionnaire, VAS: visual analog scale
BDI, Beck depression inventory (0-13: minimal; 14-19: mild; 20-28: moderate; 29-63: severe)
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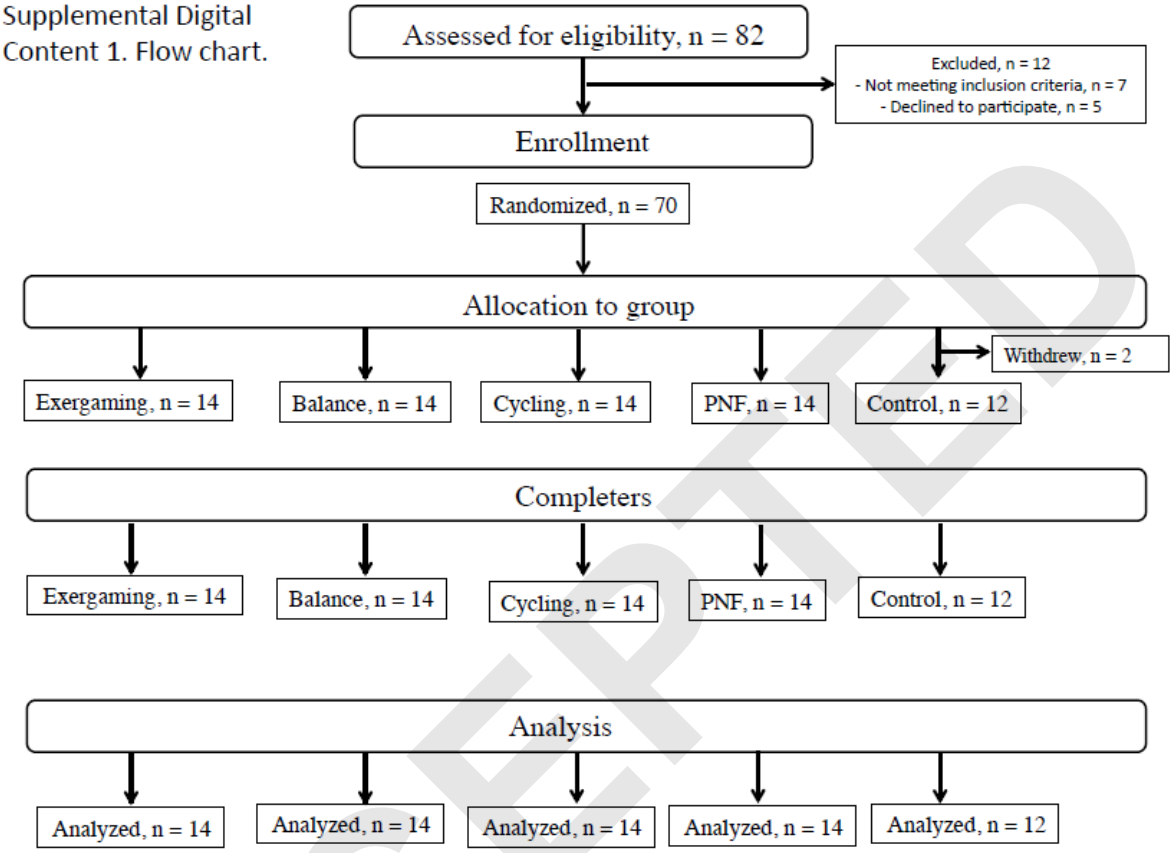
6MWT, six-minute walk test, higher values denote better walking capacity, fitness
COP, center of pressure measured in quiet standing for 20 s
WEO, wide stance eyes open
WEC, wide stance eyes closed

NEO, narrow stance eyes open
NEC, narrow stance eyes closed
F, one-way analysis of variance
p, probability < 0.05 denotes a Group by Time interaction based on the change scores
pη2, Small effect size: 0.02 to 0.12; Medium: 0.13 to 0.25; Large ≥ 0.26
ES, Cohen's effect size. Small: ≤0.20; Moderate 0.21 to 0.50; Large: ≥0.80
*, primary outcome
** Did not survive Holm adjustment for multiple comparisons

Supplemental Digital Content 1. Flow chart.



Supplemental Digital Content 2. Description of the interventions.

Warm-up, 10 minutes

Except for CON, all PwMS warmed up for 10 minutes by performing spinal mobilization, stabilizing exercises, stepping patterns, and gait variations. These routines innvolved the manipulation and transport of sensory tools, weighted bars, and fitness balls and pilates equipment. For all PwMS but in CON, the 10 minute-long cool down comprised walking and breathing exercises. Ten minutes before the start of warm-up and 10 minutes after the end of cool-down, in all PwMS but in CON resting HR and BP were measured in sitting.

Interventions, 40 minutes

Exergaming (EXE) - These exercise are designed to improve whole body and limb movement coordination, postural control, and speed and accuracy of movement responses to auditory and visual cues, illustrated by video clips (1). PwMS exercised on soft mats barefoot or in socks. Reflex Ridge prompts users to reflexively, rapidly, and accurately respond to discrete visual cues and virtual targets while keeping score of targets hit. Space Pop improves bodily and limb spatial orientation by prompting performers to reach virtual targets with the extremities and the entire body and continuously, rapidly, and accurately avoid oncoming virtual targets appearing on the projection screen within a 6-m2 area while keeping score of targets hit. Just Dance prompts users to generate and combine movements into complex sequences, imitate peer's rhythmic movements, follow musical rhythmical cues, execute asymmetrical movements, and stop and start limb and trunk movements in a predictable and unpredictable manner.

Balance training (BAL) - Exercises, performed also on soft surfaces barefoot or in socks, barefoot included: Standing and sitting on unstable surfaces while manipulating hand-held sticks with ball-shaped weights added to each end; making very small and very large steps on unstable surfaces; making exaggerated and narrow arm, shoulder movements on unstable surfaces and while sitting, walking, and running; precision stepping into the targets circles laid out on unstable surfaces; stepping up onto exercise blocks of varying stiffness and height; walking through agility ladder with and without trunk and entire body rotation; walking forward, sideways, and backwards while stepping over 5-20-cm-high hurdles; walking progression forward, sideways, and backwards with step combinations; standing balancing on Togu Dynair balance objects and inflated BOSU balance balls, and walking, standing, and balancing exercises with (weighted) medicine balls. In EXE and BAL participants were motivated to remain within the target HR zone, checked by coaches at end of each exercise sequence, by adjusting exercise intensity.

Cycling training (CYC) - PwMS rode a bicycle ergometer and followed therapists' instructions to be within the target HR zone. CYC did not receive visual feedback but listened to music. Exercise was administered in 5-minutes-long bouts, interspersed with 1 minute of freewheeling. The purpose of CYC was to improve cardiovascular fitness and minimize exercise stimulus for walking and turning skills, and walking balance.

Proprioceptive neuromuscular facilitation (PNF) - Part A) 10 minutes of warm-up as described for EXE; Part B) 10 minutes of PNF using dynamic and stabilizing reversals and rhythmic stabilization in sitting and lying. Dynamic reversals use isotonic contractions of the

target agonists followed by contraction of the antagonists against resistance. Static reversals alternate isotonic contractions of the agonists followed by contraction of the antagonists against resistance over a small joint range of motion. Stabilizing reversals alternate isometric contractions of the agonists followed by the contraction of the antagonists against resistance in a fixed joint position. Stretches were amplified by the use of hand-held implements while standing on Togu Dynair Pillows or soft gym mats. These exercises improve muscle strength, the coordination between agonist and antagonist muscles, joint range of motion, and reduce fatigue (2). Part C) 20 minutes of PNF using the Contract-Relax (CR) method to increase passive range of motion and the Hold-Relax (HR) method to increase passive range of motion reduce pain. In CR, PwMS a resisted isotonic contraction of the restricting muscles (antagonists) followed by relaxation and movement into the increased range. In HR, PwMS performed a resisted isometric contraction of the antagonistic muscles (shortened muscles) followed by relaxation. Both HR and CR targeted the muscles of the upper and lower extremities. 4) The 5 minute-long cool down comprised walking and breathing exercises.

Cool down, 10 minutes

This segment included slow walking, breathing, meditation, and mild stretches in standing sitting, and lying positions.

References

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Supplemental Digital Content 3. Heart rate, blood pressure, and rate of perceived exertion data

	Resting heart rate (beats/min) before each session							
	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	85.57	4.1	83.36	5.4	84.5	4.4	84.57	5.9
2	81.36	3.5	82.57	3.1	83.64	3.8	82.93	3.0
3	81.43	5.0	81.29	3.4	82.43	3.5	81.43	3.8
4	85.14	4.5	84.86	4.3	81.79	4.2	84.57	4.1
5	84.57	3.8	84.07	4.8	82.5	5.0	83.79	5.7
6	85.36	4.9	86.71	4.3	85.36	5.3	84.86	4.8
7	82.5	5.3	85.14	2.7	83.71	5.2	83.79	3.3
8	84.86	4.5	85.93	5.4	86.14	3.1	84.43	6.0
9	84.29	3.2	84.64	5.3	84.79	4.3	84.5	6.1
10	83.21	3.9	82.71	4.0	84.29	3.1	83.29	3.5
11	83.36	4.3	83.93	4.5	81.5	4.5	84.5	5.8
12	83.07	3.6	82.79	5.1	84.36	3.6	83.93	5.9
13	82.07	5.6	83.14	5.6	80.21	5.4	81.57	4.9
14	82.07	5.7	82.64	4.0	84	2.9	83.43	2.7
15	84.36	3.2	84.5	5.3	85.29	4.6	84.5	6.1
16	83.07	4.3	83.5	6.0	79.64	3.6	84.14	5.9
17	80.36	6.2	81.29	6.4	83.14	3.8	83	4.5
18	81.43	3.9	81.07	4.4	82.36	4.9	78.14	5.1
19	84.5	4.3	84.43	6.1	84.43	4.2	84.5	6.1
20	83.64	4.6	84.29	5.4	84	4.3	84.5	6.1
21	83.57	5.4	83.79	3.1	82.71	4.2	83	4.5
22	79.43	6.2	81.07	6.0	80.71	5.1	82.71	4.6
23	82.29	5.1	82.79	4.9	83.71	5.4	80.29	5.6
24	83.14	2.7	83.57	4.2	83.29	4.9	84.57	3.0
25	83.64	6.1	82.79	3.5	83.86	2.8	85.64	4.2
Mean	83.13		83.47		83.29		83.46	
±SD*	4.753		4.839		4.45		5.063	

* Computed based on individual values

	Resting heart rate (beats/min) after each session							
	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	87.9	2.8	84.4	4.0	84.4	4.8	83.6	6.1
2	88.4	3.7	83.9	3.5	84.1	4.3	84.5	6.1
3	91.9	3.1	83.2	4.6	83.7	5.1	83.3	3.5
4	88.1	4.5	83.6	2.4	81.3	5.9	84.5	5.8
5	83.4	3.7	85.2	3.6	84.2	3.7	83.9	5.9
6	85.8	5.8	85.5	6.1	82.8	6.0	82.4	5.2
7	81.9	4.1	82.7	4.6	83.1	3.7	83.4	2.7
8	84.9	3.6	84.6	3.8	84.6	4.1	84.5	6.1
9	83.1	4.2	84.1	2.6	80.5	4.2	84.1	5.9
10	80.3	6.1	80.4	5.7	83.1	5.5	83.0	4.5
11	82.2	3.7	82.4	5.1	82.1	5.0	78.1	5.1
12	82.4	2.8	84.2	3.1	84.6	4.1	84.5	6.1
13	82.6	5.1	81.9	4.9	84.0	4.5	84.5	6.1
14	85.4	4.4	81.9	5.4	84.2	3.0	83.3	3.5
15	83.6	4.4	83.4	3.9	81.3	5.9	84.9	5.8
16	83.1	3.6	84.6	3.5	85.0	5.5	86.1	5.5
17	82.9	3.8	82.8	4.7	84.2	3.0	83.3	3.5
18	83.9	3.9	83.0	2.5	81.8	4.6	84.5	5.8
19	84.1	3.8	85.4	3.3	84.6	4.0	83.9	5.9
20	82.9	3.8	83.2	4.8	83.6	3.3	84.3	5.5
21	83.5	3.2	83.6	5.6	84.0	5.1	83.9	3.5
22	82.8	4.5	84.9	4.4	83.4	3.0	82.2	4.0
23	82.8	4.9	85.3	3.4	84.1	4.3	83.2	4.8
24	83.6	2.7	82.6	5.2	82.9	5.3	83.8	5.5
25	83.3	4.9	85.1	4.8	83.1	4.8	82.6	4.6
Mean	84.18		83.68		83.38		83.61	
±SD*	4.687		4.381		4.592		5.192	

* Computed based on individual values

	Resting systolic blood pressure (mm Hg) before each session							
	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	126.6	6.9	125.8	6.7	123.6	8.4	128.1	6.1
2	122.5	4.6	122.9	6.4	123.1	7.9	126.9	8.6
3	127.3	3.1	127.1	3.1	122.5	8.2	127.1	3.0
4	126.3	6.9	127.4	7.8	124.4	6.7	127.4	5.3
5	124.6	8.9	124.8	8.6	125.4	7.7	127.0	4.3
6	127.2	7.1	127.4	6.3	124.6	6.5	127.3	5.3
7	126.7	5.2	125.9	4.6	124.1	4.5	126.1	5.3
8	121.9	4.1	124.8	6.4	124.3	4.9	125.1	4.8
9	122.8	5.0	124.2	4.1	128.2	5.4	126.7	4.5
10	123.8	4.2	125.1	4.5	123.7	4.1	123.8	4.5
11	124.1	6.5	125.4	6.2	121.8	4.4	121.4	6.1
12	123.6	4.5	124.4	4.4	122.7	5.8	122.8	4.4
13	121.5	4.3	122.1	3.3	122.2	4.9	119.9	4.7
14	124.9	5.0	122.5	6.1	122.6	4.2	124.6	8.0
15	129.7	4.7	125.4	5.0	125.3	3.8	122.3	5.7
16	123.1	4.8	122.1	6.8	124.5	4.9	121.9	6.6
17	121.6	4.2	121.2	3.4	123.9	6.3	121.0	3.5
18	125.8	5.1	126.6	5.4	123.7	6.1	127.4	5.1
19	125.9	4.8	125.3	4.8	121.9	4.1	124.0	5.7
20	129.6	5.9	131.6	6.0	124.4	3.8	131.2	5.9
21	125.7	6.5	126.9	6.0	125.1	6.9	128.1	6.1
22	123.1	4.9	120.9	3.4	122.9	7.0	125.6	7.8
23	119.7	4.6	121.8	6.6	123.4	4.9	122.6	5.0

	Resting systolic blood pressure (mm Hg) after each sessi							
	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	135.4	7.1	124.1	6.1	128.5	6.5	126.6	4.3
2	133.7	4.8	124.7	5.4	125.1	6.1	125.8	2.2
3	134.1	4.5	124.2	5.2	123.6	4.1	124.6	4.8
4	133.4	4.4	123.5	4.8	121.2	5.4	121.4	6.1
5	127.6	5.6	123.2	4.8	123.5	5.4	122.8	4.4
6	129.2	8.9	124.6	7.3	124.6	4.6	125.9	5.0
7	124.6	5.1	124.8	5.6	123.7	4.2	124.6	8.0
8	127.9	4.4	126.4	4.4	124.7	3.9	122.3	5.7
9	124.0	5.4	121.6	4.6	124.4	5.5	121.9	6.6
10	121.1	4.6	122.1	5.3	122.4	5.8	121.0	3.5
11	126.9	5.5	125.1	4.3	122.2	5.6	126.1	3.6
12	124.9	4.3	126.2	4.6	121.9	4.8	124.0	5.7
13	129.9	5.4	127.2	5.4	126.1	4.1	131.2	5.9
14	128.1	6.2	124.8	5.4	123.5	4.2	123.8	4.5
15	124.3	6.4	121.7	3.5	121.4	4.0	121.4	6.1
16	122.3	4.9	122.4	4.7	121.9	4.3	122.6	5.6
17	122.2	5.2	122.9	6.4	123.9	4.2	121.9	4.5
18	128.7	8.6	121.9	3.9	122.0	4.3	121.4	6.1
19	128.1	6.0	124.1	4.4	123.1	5.3	122.8	4.4
20	123.9	4.1	124.5	5.3	123.6	4.0	123.8	4.5
21	121.6	4.4	126.0	6.1	125.1	2.9	123.3	4.3
22	129.9	6.4	122.2	4.0	127.1	4.5	122.2	7.3
23	127.4	4.4	126.4	6.1	128.0	5.2	123.2	8.6

24	125.6	7.5	125.1	8.5	127.4	4.9	121.6	4.4
25	125.0	7.5	121.4	6.4	124.6	4.1	126.6	5.3
Mean	124.7		124.7		124.0		125.1	
±SD*	5.961		6.133		5.789		6.058	

* Computed based on individual values

24	123.9	4.0	124.9	4.5	125.4	4.1	121.9	5.8
25	122.4	4.5	126.1	5.5	124.4	6.9	121.8	5.6
Mean	127.0		124.2		124.1		123.5	
±SD*	6.726		5.247		5.087		5.763	

* Computed based on individual values

Resting diastolic blood pressure (mm Hg) before each session

	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	83.9	4.1	85.1	4.2	86.8	3.5	83.9	4.0
2	83.6	4.5	84.0	3.8	81.9	3.9	83.0	3.4
3	81.9	2.3	84.7	4.3	85.9	5.6	85.2	4.2
4	86.0	4.0	84.4	3.0	85.6	4.8	86.2	4.3
5	85.6	5.7	85.8	4.8	84.3	3.7	82.9	4.2
6	84.4	4.9	85.7	4.3	83.1	4.5	83.4	5.0
7	82.6	3.7	84.7	3.7	82.9	4.1	82.4	2.8
8	84.6	4.5	83.1	5.0	82.3	3.2	83.1	3.8
9	81.5	2.5	82.0	4.2	82.9	4.6	81.7	4.4
10	84.0	3.2	84.4	5.6	83.1	4.0	83.9	5.9
11	85.1	5.2	84.0	6.1	83.1	3.4	84.1	5.7
12	83.5	4.3	82.2	5.2	82.0	2.7	81.8	4.4
13	83.4	3.8	83.6	3.4	83.3	2.9	84.4	3.5
14	82.8	5.8	83.8	3.1	84.0	4.4	83.9	4.4
15	82.7	4.1	81.9	4.1	82.6	5.1	81.7	4.4
16	81.6	3.1	81.4	4.3	82.5	4.8	81.7	4.4
17	84.3	4.1	83.2	3.4	81.9	4.2	82.8	3.0
18	83.1	4.3	84.1	5.0	83.0	4.4	83.9	4.7
19	82.4	4.4	82.5	5.6	81.4	5.3	81.7	4.4
20	81.8	2.5	82.2	4.5	84.0	4.2	81.7	4.4
21	83.9	4.2	84.5	4.1	84.4	4.1	83.9	4.0
22	82.9	3.8	82.9	4.0	82.1	3.1	82.9	3.3
23	84.0	3.8	84.4	3.7	82.9	3.0	84.0	3.0
24	83.6	4.4	82.4	3.3	83.1	4.7	84.3	4.4
25	82.1	4.8	86.1	5.2	82.2	3.0	82.1	4.7
Mean	83.41		83.71		83.24		83.22	
±SD*	4.20		4.429		4.192		4.27	

* Computed based on individual values

Resting diastolic blood pressure (mm Hg) after each sessi

	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	91.9	7.2	84.5	5.2	85.6	5.5	83.1	3.8
2	93.1	4.9	83.8	4.5	82.5	5.6	81.7	4.4
3	92.6	6.4	84.1	4.1	82.9	4.1	83.9	5.9
4	89.6	4.9	84.8	6.1	82.4	3.7	84.1	5.7
5	87.3	3.2	84.1	3.6	81.5	4.0	81.8	4.4
6	86.1	6.0	82.1	3.9	83.6	3.2	84.4	3.5
7	83.7	5.3	82.6	5.3	84.9	4.0	83.9	4.4
8	81.9	2.5	82.9	3.1	83.9	5.1	81.7	4.4
9	81.8	3.0	82.1	2.9	82.8	4.7	81.7	4.4
10	83.3	2.7	81.9	4.9	82.0	3.1	82.8	3.0
11	83.3	4.1	83.8	2.8	83.9	2.9	83.9	4.7
12	82.9	3.7	83.4	4.4	82.1	4.6	81.7	4.4
13	81.9	2.6	83.0	3.1	83.1	5.1	81.7	4.4
14	85.4	4.0	84.0	4.0	83.7	3.9	83.9	5.9
15	84.6	5.2	84.4	5.5	82.4	3.7	84.1	5.7
16	82.9	3.9	82.1	4.3	81.4	2.7	81.8	4.4
17	84.1	3.2	84.4	3.9	83.9	5.0	83.9	5.9
18	85.2	5.7	84.9	4.4	83.4	4.7	84.1	5.7
19	83.4	3.7	83.3	2.6	82.2	2.9	81.8	4.4
20	84.4	3.5	85.3	4.8	83.1	4.1	83.9	5.9
21	84.2	5.8	83.6	3.1	82.1	5.6	83.8	4.1
22	84.2	4.8	85.1	4.1	83.9	5.8	83.6	3.2
23	83.9	3.7	86.0	4.3	85.1	4.8	85.3	3.3
24	83.8	3.7	83.2	4.9	82.9	4.9	83.9	3.6
25	82.8	5.6	83.4	5.4	82.0	5.7	83.7	3.8
Mean	85.13		83.72		83.1		83.2	
±SD*	5.441		4.282		4.449		4.591	

* Computed based on individual values

Average heart rate during each session

	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	123.9	5.1	111.7	6.7	120.2	5.0	94.4	9.1
2	120.1	5.0	114.9	8.1	119.1	5.4	95.6	4.4
3	122.3	6.8	115.1	5.9	122.9	6.2	98.7	4.4
4	121.1	6.3	112.3	6.8	119.9	4.8	96.6	3.5
5	121.4	6.2	113.1	7.2	120.9	6.1	95.9	6.1
6	121.1	5.4	114.5	7.2	121.0	4.5	92.9	7.4
7	121.6	4.8	116.6	4.5	120.5	3.4	95.8	9.1
8	120.2	5.8	112.1	6.3	117.7	4.3	98.1	8.0
9	121.1	5.6	113.2	8.3	118.4	6.2	101.7	4.8
10	119.8	5.2	117.4	4.6	120.9	4.1	100.4	6.5
11	118.6	3.2	113.8	7.6	119.1	4.3	101.5	3.9
12	120.8	3.9	119.2	5.4	119.4	3.6	98.9	4.4
13	119.6	4.3	115.8	6.3	119.1	4.7	93.6	10.2
14	117.4	3.3	115.1	5.6	115.6	5.0	100.1	5.6
15	119.6	3.7	116.9	5.1	117.4	4.6	102.0	5.1
16	119.6	4.3	114.6	7.0	119.4	4.1	104.1	6.5
17	119.6	4.0	115.0	6.8	118.4	4.3	97.4	3.7

Maximal heart rate during each session

	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	139.7	7.1	125.5	5.5	132.9	8.4	113.4	6.4
2	133.7	6.4	117.4	4.2	132.1	10.8	113.3	5.6
3	134.5	6.5	124.4	7.6	131.7	6.0	114.0	5.4
4	131.6	5.3	124.2	6.4	131.1	4.7	107.8	5.7
5	137.1	7.4	125.8	6.6	132.9	6.0	109.4	6.9
6	135.4	5.6	125.5	5.2	130.6	6.5	110.6	7.7
7	137.1	7.0	120.9	4.3	132.1	5.3	108.5	7.1
8	133.9	5.0	122.4	4.8	131.4	4.5	108.6	6.4
9	136.1	5.3	125.9	4.9	131.2	6.0	110.0	6.6
10	138.0	7.4	124.4	6.4	131.3	8.1	109.3	6.5
11	135.4	7.5	124.6	3.9	130.9	7.1	111.1	8.8
12	138.8	7.4	123.8	5.5	131.8	8.6	112.7	7.8
13	134.6	5.8	124.1	5.8	131.9	8.7	111.3	9.6
14	135.4	6.5	123.7	3.2	133.4	5.5	112.0	6.7
15	136.8	5.9	125.7	4.8	129.7	5.3	114.4	6.9
16	137.6	5.6	126.6	7.5	131.8	5.5	115.5	5.3
17	135.6	6.4	125.2	5.7	130.9	5.6	109.9	8.3

18	120.6	4.4	114.9	7.0	118.6	3.4	101.6	2.9
19	120.7	2.7	117.4	4.7	118.9	2.8	102.7	3.9
20	123.4	8.7	118.8	6.0	122.0	10.7	101.3	3.7
21	120.5	2.7	114.7	7.1	119.8	4.6	104.4	5.6
22	120.5	5.1	113.5	6.5	120.8	4.5	102.6	9.7
23	118.1	5.2	115.4	5.4	119.3	3.0	103.9	4.5
24	119.6	3.9	115.4	7.8	118.9	2.6	100.5	10.4
25	120.8	4.2	116.9	5.9	119.1	3.2	102.2	3.3
Mean	120.5		115.1		119.5		99.48	
±SD*	5.013		6.535		4.939		6.935	

* Computed based on individual values

18	134.6	5.7	128.9	6.9	129.6	6.5	110.4	5.6
19	136.9	6.0	127.3	6.2	130.6	5.8	110.7	6.2
20	138.9	5.2	124.4	5.4	131.5	5.4	110.9	8.3
21	134.7	6.3	126.1	6.0	134.6	6.9	110.4	5.7
22	137.5	10.4	126.2	4.7	130.8	6.2	115.2	6.2
23	135.2	7.6	126.2	5.8	129.6	6.8	111.9	4.7
24	136.9	8.2	125.9	5.6	130.4	6.5	113.1	11.2
25	135.3	5.2	125.7	6.5	131.9	5.4	110.7	8.2
Mean	136.1		124.8		131.5		111.4	
±SD*	6.63		5.891		6.521		7.149	

* Computed based on individual values

Rate of perceived exertion during each session

	EXE		BAL		CYC		PNF	
Sessi	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1	8.2	0.6	5.1	0.7	6.9	1.0	3.0	0.7
2	8.1	0.6	5.1	0.7	6.6	0.8	2.8	0.6
3	7.8	0.9	5.1	0.6	6.8	1.2	2.6	0.5
4	8.1	0.7	5.0	0.8	6.9	1.3	2.8	0.6
5	7.9	0.5	5.3	0.6	6.9	1.1	2.7	0.6
6	7.9	0.7	5.1	0.7	6.7	0.9	3.0	0.6
7	7.7	0.7	5.1	0.8	6.8	1.1	2.8	0.6
8	8.0	0.8	5.1	0.7	6.9	1.0	2.9	0.5
9	7.9	0.9	5.1	0.7	6.8	1.2	2.9	0.7
10	7.8	0.7	5.3	0.7	6.9	1.1	2.7	0.6
11	7.6	0.8	5.1	0.8	7.3	0.9	2.9	0.5
12	8.0	0.7	5.2	0.7	6.8	1.1	2.9	0.6
13	8.1	0.7	5.0	0.8	6.9	1.1	2.7	0.6
14	7.9	0.8	5.4	0.6	6.9	0.9	2.8	0.4
15	8.1	1.0	5.3	0.6	7.1	1.1	2.6	0.5
16	7.9	0.7	5.4	0.6	7.0	1.1	2.8	0.4
17	8.1	0.6	5.3	0.8	6.7	1.1	2.6	0.6
18	7.8	1.0	5.2	0.8	7.1	1.0	2.8	0.7
19	7.8	0.7	5.4	0.8	6.9	1.1	2.9	0.5
20	7.9	0.8	5.5	0.7	7.0	1.0	2.7	0.5
21	7.7	0.9	5.3	0.6	6.9	0.9	3.1	0.4
22	8.3	0.5	5.5	0.5	6.9	1.1	2.8	0.4
23	8.1	0.9	5.4	0.9	6.8	1.1	3.0	0.7
24	8.1	0.7	5.4	0.7	7.0	1.0	2.9	0.6
25	7.9	0.9	5.1	0.7	6.8	1.1	2.9	0.5
Mean	7.9		5.2		6.9		2.8	
±SD*	0.751		0.70		1.022		0.561	

* Computed based on individual values

Borg scale of 0 to 10