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ORIGINAL RESEARCH

High Frequency and Intensity Rehabilitation in 641 Subacute Ischemic Stroke Patients

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Abstract

Objectives: To determine the effects of exergaming on quality of life (QoL), motor, and clinical symptoms in subacute stroke patients.

Design: A pseudorandomized controlled trial, using a before-after test design.

Setting: University hospital.

Participants: Subacute, ischemic stroke outpatients (N=3857), 680 of whom were randomized and 641 completed the study.

Interventions: We determined the effects of 5 times a week twice daily (EX2; 50 sessions; n=286) and once daily (EX1; 25 sessions; n=272) exergaming and low-intensity standard care (control [CON]; 25 sessions; n=83) on clinical, mobility, blood pressure (BP), and QoL outcomes.

Main Outcome Measures: The primary outcome was Modified Rankin Scale. Secondary outcomes were activities of daily living, 5 aspects of health-related QoL, Beck Depression Inventory, 6-minute walk test (6MWT), Berg Balance Scale (BBS), and static balance (center of pressure).

Results: During exercise, the peak heart rate was 134, 134, and 126 beats per minute in the EX2, EX1, and CON groups, respectively. mRS improved similarly in the EX2 (−1.8; effect size, d=−4.0) and EX1 (−1.4; d=−2.6) groups, but more than in the CON group (−0.7; d=−0.6). QoL, Barthel Index, BBS, 6MWT, and standing posturography improved more in the EX2 group and the same in the EX1 and CON groups. Systolic and diastolic resting BP decreased more in the EX2 and EX1 groups than in the CON group. The intervention effects did not differ between men (n=349) and women (n=292).

Conclusions: Twice daily compared with once daily high-intensity exergaming or once daily lower intensity standard care produced superior effects on clinical and motor symptoms, BP, and QoL in male and female subacute ischemic stroke participants.

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Although stroke incidence and mortality in western European countries have been declining in recent years, these rates are still increasing central-eastern Europe.[1] In 2009, the incidence of stroke was 43.3 per 10,000 people in Hungary, which was twice the rate in Italy and Finland. This high incidence results in 10% of all deaths and high disability-adjusted life-years scores.[2] Even though policymakers recognize the importance of prevention in developing countries, most of these efforts are ineffective, leaving people with stroke (PwS) with the next best option: reducing symptoms and risks for recurrent strokes.

Recommendations for subacute stroke participants' exercise rehabilitation advise therapists toward moderate intensity exercise.[3,4] Recent trends, however, emphasize exercise intensity

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in the rehabilitation of a number of patient groups, including Parkinson disease (PD),[5,6] multiple sclerosis,[7] spinal cord injury,[8] and stroke,[9,10] as well as after ischemic heart attacks.[11] Heart rates (HR) greater than 60% of the age-predicted maximum and rates of perceived exertion (RPE) higher than 15/20 denote high exercise intensity. Another marker of high exercise intensity is frequency (ie, consecutive daily sessions or even multiple sessions within a day).[12] This latter paradigm has not been systematically tested in the rehabilitation of PwS. There is also considerable debate whether exercise specific or not specific to mobility impairments should be used in the rehabilitation of subacute stroke participants and to what extent technology should be incorporated.[3,13-17] Indeed, implicitly learning and relearning stepping and balance sequences in a technology-aided gaming environment seems to accelerate neurologic patients' exercise-based rehabilitation[17-20] with the effects lasting for months in PD patients.[21]

Sex differences in the responsiveness to exercise rehabilitation in subacute stroke participants are an understudied area owing to small sample sizes and differences in hormonal profiles, age, and mortality between male and female PwS.[22,23] The effectiveness of physical exercise in reducing risks for first and recurring strokes is higher in men than women, and the responsiveness to exercise for improving clinical functions after a stroke tends to be higher for men than women.[24,25]

The purpose of the present pseudorandomized controlled trial was to determine and compare the effects of an unusually high intensity and frequency exergaming mobility rehabilitation program on the clinical symptoms, blood pressure (BP), mobility, and quality of life (QoL) of subacute stroke participants. Intensity was set by HR, RPE, and within-day session frequency. One group attended the program twice daily for a total of 50 high-intensity exergaming sessions (EX2). A second group attended 1 high-intensity exergaming session per day for a total of 25 visits (EX1). A third group received low-intensity standard care in 25 sessions, serving as a control group (CON). We hypothesized that all programs would be effective. However, based on favorable experience with other patient groups in terms of responsiveness and adherence,[5,13,14,21,26-28] we expected a hierarchical response pattern according to exercise intensity and frequency.

List of abbreviations:

6MWT	**6-minute walk test**
ADL	**activities of daily living**
BBS	**Berg Balance Scale**
BI	**Barthel Index**
BP	**blood pressure**
CON	**control group**
COP	**center of pressure**
EQ5-VAS	**100 mm visual analog measure of health-related quality of life**
EX1	**1 exergaming session daily**
EX2	**2 exergaming sessions daily**
HR	**heart rate**
mRS	**modified Rankin Scale**
PD	**Parkinson disease**
PwS	**people with stroke**
$p\eta^2$	**partial eta squared**
QoL	**quality of life**
rBP	**resting blood pressure**
rHR	**resting heart rate**
RPE	**rate of perceived exertion**
rSBP	**resting systolic blood pressure**

Methods

Design and participants

This study was conducted as an assessor-blinded, pre-post, pseudorandomized controlled trial. Using a consecutive selection from the hospital's medical records, a neurologist identified and examined participants for admission to the study conducted during the period from September 2014 to September 2018.

Patients admitted to the emergency department with a suspected stroke underwent a neurologic exam, which included the National Institutes of Health Stroke Scale. This examination helped to determine the level of impairment in mobility and sensory function (range, 6-21; median, 16).

All participants were outpatients. Inclusion criteria were first-ever ischemic stroke diagnosed by a neurologist based on computed tomography or magnetic resonance imaging scans, time after stroke of 2 to 4 weeks, mobility and postural limitation determined by neurologic exam, and a modified Rankin Scale (mRS) score of 2 or higher. Exclusion criteria included a history of multiple strokes, systolic resting blood pressure (rSBP) less than 120 or greater than 160 mmHg, orthostatic hypotension, carotid artery stenosis, severe heart disease, hemophilia, traumatic brain injury, seizure disorder, uncontrolled diabetes, abnormal electroencephalography; Mini Mental State Examination score less than 22, an abnormal blood panel, use of sedatives, irregular medication schedule, serious aphasia (Western Aphasia Battery, ≤25), serious visual or hearing impairments, serious sensory dysfunction, serious orthopedic problems, neurologic conditions affecting motor function (PD, multiple sclerosis, multiple system atrophy, Guillain−Barré syndrome), alcoholism, recreational drug use, smoking after stroke diagnosis, inability to walk a minimum of 100 meters with or without a walking aid in 6 minutes, Berg Balance Scale (BBS) score of 32 or less, Barthel Index (BI) score of 70 or less, inability to understand verbal instructions or prompts from a television screen, or current participation in a self-directed or formal group exercise program other than standard physical therapy.

Figure 1 shows the flow of participants. Those who did not consent to be randomly assigned to exergaming were assigned to the CON group. These individuals were motivated for and interested in receiving rehabilitation but were unwilling to be randomized. The remaining participants were randomized to 1 session per day (EX1) or 2 sessions per day (EX2) of high-intensity exergaming. A physical therapist not involved in the trial performed the concealed randomization by drawing a colored ribbon from a covered box and attached 1 ribbon to each patient folder. Before the start of the study, all participants were enrolled in standard physical therapy provided by government insurance. Those assigned to the EX1 and EX2 groups stopped this care, and those in the CON group continued to receive this care. Participants gave written informed consent and the Institutional Research Ethics Committee approved the study protocol (NCT03736200).

Outcomes

Primary and secondary outcomes were measured before and after the interventions by the same certified physical therapists who were blinded to intervention allocation and were trained by the primary investigator. The testing order was standardized among participants and testing sessions. Pre- and posttests were performed within 1 week of the intervention. Patients were instructed

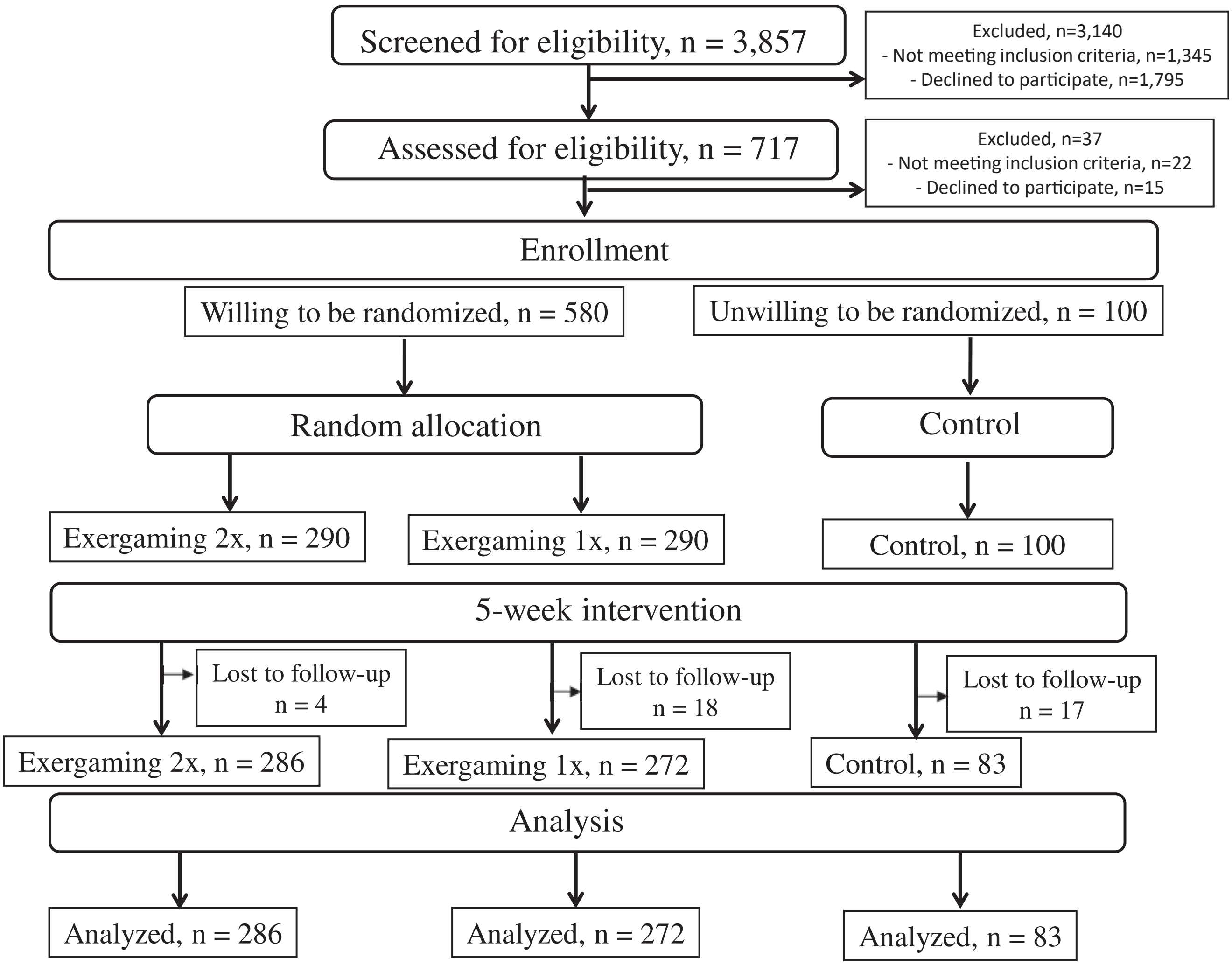

Fig 1 Flow of participants.

not to drink caffeinated drinks 2 hours before measurements or exercise. The primary outcome was mRS, which measures independence in activities of daily living (ADL) and discriminates among less severe levels of disability. mRS is a reliable and valid measure and is sensitive to change over time. A change of 1 unit in mRS is considered clinically meaningful.[29-31]

Secondary outcomes addressed life domains. These tests are reliable, valid, and are sensitive to change over time in PwS. The BI measures ADL performance. The EuroQol questionnaire measures 5 aspects of health-related QoL. The Beck Depression Inventory measures depression. The BBS measures fall risk. The 6-minute walk test (6MWT) measures fitness and walking capacity. Therapists equipped with a stopwatch administered this test in a 50-meter hallway that had wide tape marks on the floor every 10 meters and short, thin tape marks every 2 meters, within which the distance walked was measured by a measuring tape to the nearest cm when patients stopped at 6 minutes. Patients were not verbally encouraged during the test because, in our experience, some patients respond negatively to the stress associated with the performance demand by freezing and becoming confused. The instructions given were: "Walk as far as you safely can for 6 minutes. Stop only when instructed at 6 minutes." There were no falls or medical emergencies during this test. Static balance was measured by the center of pressure (COP) path in standing on a force platform[a] in the following order and conditions: (1) wide stance eyes open, (2) wide stance eyes closed, (3) narrow stance eyes open, and (4) narrow stance eyes closed for 20 seconds, with 1 trial each. Resting HR (rHR)[b] and resting BP[c] were measured sitting 10 minutes before and after each session, and peak HR was measured during each exercise session. In the first visit, participants became familiar with exergaming by watching and performing modules and completed questionnaires. The second visit included the measurements of body height and mass, COP, and 6MWT.

Interventions

The EX2 group exercised twice daily at 8:00 to 9.00 and 14:00 to 15:00. The 1-hour sessions comprised 5 minutes of warm-up, 25 minutes of exergaming, 25 minutes of agility training, and 5 minutes of cool-down. The intervention consisted of 5 consecutive sessions per week for 5 consecutive weeks (ie, 50 sessions for EX2 and 25 sessions for EX1) in the hospital's outpatient physical therapy gym. In the EX2 and EX1 groups, exercise intensity was set in each session to an RPE of 14 to 16 of 20. RPE was also recorded in the CON group. The EX1 and EX2 groups performed the same program except that the EX2 group performed it twice per day.

Two physical therapists, who did not perform the assessments, delivered the interventions for groups of 6 to 8 participants who exercised barefoot on soft gym mats. Warm-up included spinal mobilization, stabilizing exercises, stepping patterns, and gait variations. Exergaming used 3 modules of the Xbox 360 core system.[d] Reflex Ridge[d] prompts users to reflexively respond to visual stimuli. Space Pop[d] prompts performers to reach targets with the extremities and the entire body to improve spatial orientation. Just Dance[e] prompts users to generate and combine movement sequences, illustrated previously by video clips.[5] The agility component included the manipulation and transport of handheld sensory tools, weighted bars, fitness balls, and pilates equipment. These routines require attention, executive function, and high speed of cognitive processing of oncoming visual and auditory cues, affording a high cognitive load. The program also provides a strong neuromuscular stimulus owing to an ever-changing sensory environment (soft/hard surfaces, weighted/unweighted implements, slow/fast movement execution, reactive/self-initiated responses to cues). Cool-down included walking and breathing exercises. The CON group received government-prescribed standard care, which includes 30 minutes of daily group exercises sitting and 30 minutes of individual physical therapy using walking and balance exercises at local clinics. Exercises in sitting target upper extremity and trunk muscle strength by lifting, lowering, and rotating medicine balls and end-weighted sticks. Exercises standing target lower extremity function, including stepping variations (forward, backward, diagonally while standing on 1 leg), weight shifting, coordinative movements with arms while walking with and without various sensory implements, and squatting movements with arm support on a chairback to strengthen the lower extremity extensor mechanism. After the exercise sessions, every participant in each group received 20 minutes of medical massage of the lower extremities. We asked participants to record their symptoms in a log that was checked by therapists daily and not to change their diet, medication, or physical activity habits for the duration of this study.

Statistical analyses

Data are expressed as mean ±SD. Variables were checked for normal distribution using the Shapiro-Wilk test. We compared the EX2, EX1, and CON groups at baseline using a 1-way parametric or a Kruskal-Wallis analysis of variance. We interpreted the group (EX2, EX1, CON) by sex (men, women) interactions on the post minus pre absolute change scores as a group by sex by time interaction. We used Tukey's post-hoc contrast to identify the means that were different at a P value less than .05. The effect sizes for group, sex, and group by sex effects were characterized by partial eta squared ($p\eta^2$). We used Cohen's within-group effect size, d (small, 0.20; moderate, 0.50; large, 0.80), to determine the size of the effects over time. The Holm method was used to correct for family-wise error.

Results

Participant characteristics

Table 1 shows the frequency, medical, and comorbidity data for the 349 male and 292 female (n=641) PwS enrolled in the study 2.9±0.75 weeks after an ischemic stroke. In both sexes, approximately 50% (n=326) of the strokes occurred in the left hemisphere, followed by stroke in the cerebellum, brainstem, or right hemisphere. None of the participants had more than 2 of the 23 most common comorbidities, of which hypertension (27%), ischemic heart disease (19%), and atherosclerosis (10%) occurred at the highest rates. Fifty-four percent of the participants smoked, approximately 32% consumed 1 to 3 drinks per day, and 93% took medications. A similar proportion of participants in each group took antihypertensive drugs, including thiazide diuretics (38%-45%), calcium channel blockers (15%-20%), angiotensin-converting enzyme inhibitors (10%-15%), and angiotensin receptor blockers (10%-15%), or received polytherapy by taking 3 or more drug classes (18%-22%). The type and frequency of other drugs participants took were not available.

Intervention effects

Groups and sexes were similar at baseline (table 2). The 1.8-point (±0.81; d=4.0) and 1.4-point (±0.95; d=2.6) improvements in mRS in the EX2 and EX1 groups, respectively, did not differ but exceeded the −0.7-point (±0.73; d=0.6) change in the CON group (group main effect: $P<.001$) (table 3, fig 2). Except for body weight, sex did not affect the intervention-induced changes. Men lost more weight (−6.0%±8.69%; d=-1.1) than women (1.3%±9.94%; d=0.20), but both sexes lost more weight in the EX1 (men: −6.5%±8.54% vs women: 2.1%±9.92%) and CON (men: −5.9%±10.53% vs women: 11.5%±14.94%) groups compared with EX2 group (men vs women: not significant). Improvements in the BI differed ($P<.001$) among groups (EX2, d=5.6; EX1, d=2.9; CON, d=1.2). The 100 mm visual analog measure of health-related quality of life (EQ5-VAS) (but not EQ5-Sum) improved in the EX2 group (d=1.6) more ($P<.05$) than in the EX1 group (d=0.8) or CON group (d=0.7). Improvements in BBS differed ($P<.001$) among groups (EX2, d=2.2; EX1, d=1.4; CON, d=1.2). Improvements in the 6MWT differed ($P<.001$) among groups (EX2, d=2.9; EX1, d=2.7; CON, d=1.6). The COP path revealed a uniform group main effect in COP path while standing in a wide stance with eyes open, COP path while standing in a wide stance with eyes closed, COP path while standing in a narrow stance with eyes open, and COP path while standing in a narrow stance with eyes closed (all $P\leq.018$). In these 4 measures combined, the EX2 group shortened the COP path (d range, −1.2 to −2.4) more than the EX1 and CON groups. No changes occurred in the Mini Mental State Examination, DBI, and EuroQol-SUM.

Intervention effects on HR, BP, and RPE

Sex did not affect any of the changes. The results below are presented for data pooled across 25 days. rHR increased ($P<.001$, $p\eta^2=0.11$) in each group (d=1.2 to 2.2) but more in the EX2 and EX1 groups compared with the CON group (table 4). rSBP decreased (d=0.8 to 2.) in all groups ($P=.001$, $p\eta^2=0.41$) but more in the EX2 and EX1 groups than in the CON group. In the EX2 group, the total reduction in rSBP from before session 1 to after session 2 was 4.2 mmHg ($P=.001$; d=2.6; 3.2%±4.08%). Resting diastolic blood pressure decreased (d=1.3 to 3.7) in all 3 groups ($P=.001$, $p\eta^2=0.63$) but more in the EX2 and EX1 groups than in the CON group. In the EX2 group, the total reduction in resting diastolic blood pressure from before session 1 to after session 2 was 5.8 mmHg ($P=.001$; d=3.2; or 5.8%±6.08%). Peak HR during exercise was lower ($P=.001$;

Table 1 Frequency, medical, and comorbidity data for 641 stroke participants

		EX2		EX1		CON		All	
Variable	Sex	Mean, n	±SD, %	Mean, n	±SD, %	Mean, n	±SD, %	Mean, n	±SD, %
Frequency, n	M	154		149		46		349	
	F	132		123		37		292	
	M, F	286		272		83		641	
Time after	M	2.9	0.74	2.9	0.77	2.8	0.72	2.9	0.75
stroke, wk	F	2.8	0.74	2.9	0.76	3.1	0.61	2.9	0.74
	M, F	2.8	0.74	2.9	0.77	2.9	0.70	2.9	0.75
RH stroke, n, %	M	25	16	36	24	12	26	73	21
LH stroke, n, %	M	78	51	74	50	22	48	174	50
Cerebellar, n, %	M	42	27	34	23	9	20	85	24
Brainstem, n, %	M	9	6	5	3	3	7	17	5
	All	154	100	149	100	46	100	349	
RH stroke, n, %	F	21	16	22	18	6	16	49	17
LH stroke, n, %	F	70	53	65	53	17	46	152	52
Cerebellar, n, %	F	36	27	27	22	9	24	72	25
Brainstem, n, %	F	5	4	9	7	5	14	19	7
	All	132	100	123	100	37	100	292	100
RH stroke, n, %	M, F	46	16	58	21	18	22	122	19
LH stroke, n, %	M, F	148	52	139	51	39	47	326	51
Cerebellar, n, %	M, F	78	27	61	22	18	22	157	24
Brainstem, n, %	M, F	14	5	14	5	8	10	36	6
	All	286	100	272	100	83	100	641	100
Hypertension,	M	38	25	47	32	21	46	106	30
n, %	F	35	27	19	15	13	35	67	23
Both	73	26	66	24	34	41	173	27	
Ischemic heart	M	31	20	28	19	11	24	70	20
disease, n, %	F	20	15	21	17	12	32	53	18
Both	51	18	49	18	23	28	123	19	
Atherosclerosis,	M	20	13	11	7	5	11	36	10
n, %	F	9	7	17	14	2	5	28	10
Both	29	10	28	10	7	8	64	10	
mRS	F	3.4	0.65	3.3	0.66	3.6	0.61	3.4	0.65
M	3.4	0.63	3.3	0.67	3.5	0.51	3.4	0.64	
Both	3.4	0.64	3.3	0.67	3.6	0.57	3.4	0.65	
Smoking,	M	88	57	79	33	20	43	187	54
n, %	F	74	56	63	51	20	54	157	54
Both	162	57	142	52	40	48	344	54	
Alcohol (1-3 drinks/d),	M	53	34	48	32	17	37	118	34
n, %	F	40	30	39	32	9	24	88	30
Both	93	33	87	32	26	31	206	32	

NOTE. The mRS ranges from 0 (healthy) to 6 (death).
Abbreviations: LH, left hemisphere; RH, right hemisphere.

$p\eta^2=0.48$) in the CON group than in the EX2 and EX1 groups. RPE during exercise was lower ($P=.001$; $p\eta^2=0.96$) in the CON group than in the EX2 and EX1 groups. Peak HR and RPE did not differ between the EX2 and EX1 groups.

Discussion

We compared the effects of high intensity and frequency agility exergaming and lower intensity standard care programs on clinical symptoms, mobility, BP, and QoL in PwS. Owing to an ischemic stroke approximately 3 weeks earlier, PwS (n=641) had explicit walking limitations but completed all sessions without adverse events. The preponderance of evidence supported the hypothesis. Twice daily compared with once daily high-intensity exergaming or once daily lower intensity standard care produced superior effects on clinical and motor symptoms, BP, and QoL in male and female subacute ischemic stroke participants (see fig 2, tables 3 and 4, and supplemental fig S1 [available online only at https://archives-pmr.org/).

Primary outcome

We included subacute (2-4wk after stroke) instead of chronic PwS, who have greater potential for responsiveness to exercise therapy. The 3.4 mRS and 56.1 BI score at baseline indicated that participants had moderately severe ADL-specific disability (see table 1). However, walking disability was severe because the approximate 182-meter (n=641) distance over 6 minutes is the shortest among

Table 2 Group and sex comparisons at baseline

Variable	Sex	EX2 Mean ± SD	EX1 Mean ± SD	CON Mean ± SD	All Mean ± SD
Age, y	M	67.5±5.44	65.6±6.10	65.2±6.10	66.4±5.89
	F	67.7±5.56	66.2±6.10	64.7±5.49	66.7±5.86
	Both	67.6*±5.49	65.9±6.10	64.9±5.80	66.5±5.87
Height, cm	M	177.3±5.26	178.1±4.48	177.9±4.23	177.7±4.81
	F	169.2±4.10	170.0±4.00	169.8±2.96	169.6†±3.94
	Both	173.6±6.25	174.4±5.87	174.3±5.50	174.0±6.00
Mass, kg	M	76.6±8.17	77.3±7.56	77.3±8.41	77.0±7.93
	F	72.0±6.93	70.4±7.88	64.0±6.68	70.3±7.72
	Both	74.5±7.95	74.2±8.41	71.4±10.15	74.0±8.50
BMI, kg/m^2	M	24.4±2.76	24.4±2.30	24.4±2.41	24.4±2.52
	F	25.2±2.78	24.4±2.88	22.2±2.38	24.5±2.93
	Both	24.8±2.79	24.4±2.57	23.4±2.63	24.4±2.71
MMSE	M	27.2±1.31	26.9±1.45	27.0±1.33	27.0±1.37
	F	26.9±1.53	27.1±1.49	27.1±1.34	27.0±1.49
	Both	27.1±1.41	27.0±1.47	27.0±1.33	27.0±1.43
HR, beats/min	M	89.8±9.86	83.2±5.88	83.6±5.26	86.2±8.46
	F	87.5±8.88	83.6±6.07	83.6±5.07	85.4±7.60
	Both	88.7±9.47	83.4±5.96	83.6±5.15	85.8±8.08
SBP, mmHg	M	131.6±8.86	129.5±8.47	134.1±8.81	131.0±8.80
	F	130.5±9.57	127.8±6.32	131.6±8.97	129.5±8.37
	Both	131.1±9.19	128.7±7.61	133.0±8.91	130.3±8.64
DBP, mmHg	M	87.5±6.84	88.4±7.70	90.5±7.40	88.3±7.33
	F	89.5±7.95	89.0±8.36	94.6±6.08	90.0±8.09
	Both	88.4±7.43	88.7±8.00	92.3±7.10	89.0±7.73
BI	M	56.1±8.01	55.6±8.67	58.3±6.52	56.2±8.14
	F	56.4±8.11	55.0±8.87	57.3±8.05	55.9±8.44
	Both	56.2±8.04	55.4±8.75	57.8±7.21	56.1±8.28
BDI	M	12.2±3.03	12.4±2.80	12.0±3.06	12.2±2.93
	F	12.9±2.93	12.6±2.82	12.7±2.60	12.7±2.84
	Both	12.5±3.00	12.5±2.81	12.3±2.87	12.5±2.90
EQ5-VAS, mm	M	63.6±9.42	65.0±9.51	60.8±9.47	63.8±9.53
	F	63.6±9.43	64.1±9.64	66.0±6.11	64.1±9.17
	Both	63.6±9.41	64.6±9.56	63.1±8.50	63.9±9.37
EQ5-Sum	M	13.1±1.75	13.6±1.69	13.7±1.65	13.4±1.73
	F	13.7±1.65	13.6±1.61	14.0±1.68	13.7±1.64
	Both	13.4±1.74	13.6±1.65	13.8±1.66	13.5±1.70
BBS	M	22.1±4.40	23.2±4.51	22.3±4.68	22.6±4.50
	F	22.2±4.60	22.8±4.91	21.8±4.11	22.4±4.68
	Both	22.2±4.49	23.0±4.69	22.1±4.42	22.5±4.58
6MWT, m	M	179.9±48.50	183.1±48.05	171.2±55.37	180.1±49.26
	F	188.5±43.91	181.2±45.41	185.1±43.60	185.0±44.49
	Both	183.9±46.56	182.2±46.80	177.4±50.65	182.3±47.17
COP path, cm					
WEO	M	8.8±5.95	7.5±4.68	7.8±3.88	8.1±5.22
	F	5.8±3.34	7.9±4.93	7.7±4.31	6.9±4.31
	Both	7.4±5.14	7.7±4.79	7.8±4.05	7.6±4.86
WEC	M	10.4±5.25	8.0±4.19	9.5±6.03	9.2±5.06
	F	6.4±4.14	8.6±4.46	7.9±5.93	7.5±4.64
	Both	8.5±5.16	8.3±4.31	8.8±6.00	8.5±4.94
NEO	M	9.2±5.81	8.4±5.37	8.4±4.72	8.7±5.49
	F	8.3±5.40	8.7±4.51	9.7±6.44	8.6±5.20
	Both	8.8±5.64	8.5±4.99	9.0±5.56	8.7±5.36

(*continued on next page*)

Table 2 (*continued*)

Variable	Sex	EX2	EX1	CON	All
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
NEC	M	11.0±6.01	9.6±5.36	10.2±6.29	10.3±5.80
	F	10.0±6.15	10.6±5.99	10.0±4.26	10.3±5.86
	Both	10.6±6.08	10.1±5.66	10.1±5.45	10.3±5.82

NOTE. The MMSE ranges from 0 to 30 (higher is better). The BI ranges from 0 to 100, with 0 to 20 indicating total dependency, 21 to 60 indicating severe dependency, 61 to 90 indicating moderate dependency, and 91 to 99 indicating slight dependency. The BDI ranges from 0 to 63, with 0 to 7 indicating normal, 8 to 12 indicating mild depression, 13 to 17 indicating moderate depression, and greater than 18 indicating severe depression. Higher scores on the EQ5-VAS indicate a better perceived quality of life. The EQ5-Sum is the sum of the EuroQol questionnaire mobility, self-care, usual activities, pain/discomfort, and anxiety/depression sub-scales, each scored from 1 to 5 (worst to best), with 5 being the best and 25 the worst score. The BBS is scored on a scale with 0 to 20 indicating a high fall risk, 21 to 40 indicating a medium fall risk, and 41 to 56 indicating a low fall risk.
Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; MMSE, Mini-Mental State Examination; NEC, COP path while standing in a narrow stance with eyes closed; NEO, COP path while standing in a narrow stance with eyes open; WEC, COP path while standing in a wide stance with eyes closed; WEO, COP path while standing in a wide stance with eyes open.
* EX2 different from EX1 and CON.
† Men different from women.

age- and sex-similar PD (232 m) and multiple sclerosis patients (240 m), older adults with mobility disability (334 m), and healthy older adults (529 m).[13,14,26] Despite subacute status, severity of disability, and moderate hypertension (see table 2), intensive and frequent exercise proved to be an effective therapy option for these subacute PwS.[32]

Table 3 Effects of interventions on outcomes

Variable		EX2	EX1	CON	All	Group	Sex
		Mean± SD	Mean± SD	Mean± SD	Mean± SD		
mRS	M	-1.8±0.79	-1.4±0.94	-0.8±0.74	-1.5±0.92	F=55.3	NS
	F	-1.8±0.84	-1.4±0.96	-0.6±0.73	-1.5±0.95	*P*=.001	
	Both	-1.8±0.81a	-1.4±0.95	-0.7±0.73	-1.5±0.93	$p\eta^2$=0.15	
Mass,	M	-4.8±7.26	-5.5±7.40	-5.2±9.32	-5.2±7.60	F=12.1	127.8
kg	F	-2.0±3.70	1.0±6.08	6.7±8.41	0.4±6.17	*P*=.001	0.001
	Both	-3.5±6.05	-2.6±7.56	0.1±10.68	-2.6±7.51	$p\eta^2$=0.04	0.17
BI	M	27.0±8.85	19.3±12.22	10.9±7.02	21.6±11.61	F=97.8	NS
	F	27.5±9.03	19.0±12.59	9.6±9.01	21.7±12.25	*P*=.001	
	Both	27.2±8.92	19.2±12.37	10.3±7.94	21.6±11.9	$p\eta^2$=0.24	
EQ5,	M	9.9±8.47	5.3±8.09	5.4±9.42	7.3±8.72	F=25.6	4.8
mm	F	9.0±9.05	5.0±8.40	1.5±5.88	6.4±8.81	*P*=.001	0.028*
	Both	9.5±8.74	5.2±8.22	3.7±8.23	6.9±8.77	$p\eta^2$=0.08	0.00
BBS	M	7.3±6.28	4.7±5.93	2.1±3.53	5.5±6.10	F=32.4	NS
	F	6.3±6.25	4.4±6.71	3.7±5.41	5.2±6.42	*P*=.001	
	Both	6.8±6.28	4.6±6.29	2.8±4.51	5.3±6.24	$p\eta^2$=0.10	
6MWT,	M	117.3±77.71	108.9±78.74	61.8±60.93	106.4±78.04	F=21.8	NS
m	F	132.5±78.10	108.4±68.91	64.0±73.18	113.7±76.72	*P*=.001	
	Both	124.3±78.13	108.6±74.32	62.8±66.25	109.7±77.47	$p\eta^2$=0.14	
WEO,	M	-2.4±6.07	-1.2±5.44	-0.1±6.58	-2.5±6.13	F=11.8	NS
cm	F	0.4±4.00	-1.4±5.81	-0.4±5.72	-0.5±5.11	*P*=.001	
	Both	-1.4±5.75	-1.3±5.60	-0.2±6.17	-1.6±5.77	$p\eta^2$=0.20	
WEC,	M	-4.8±6.84	-1.0±5.70	-1.3±6.06	-2.7±6.53	F=4.1	NS
cm	F	-0.4±4.40	-2.4±5.44	-0.2±5.74	-1.2±5.12	*P*=.018	
	Both	-2.8±6.23	-1.6±5.62	-0.8±5.91	-2.0±5.97	$p\eta^2$=0.12	
NEO,	M	-3.2±6.33	-1.4±7.45	-0.4±5.88	-2.1±6.84	F=4.4	NS
cm	F	-2.5±5.44	-1.4±6.42	-1.5±7.52	-1.9±6.16	*P*=.010	
	Both	-2.9±5.93	-1.4±6.99	-0.9±6.64	-2.0±6.53	$p\eta^2$=0.11	
NEC,	M	-3.9±6.84	-1.8±6.64	-1.9±6.67	-2.8±6.79	F=7.2	NS
cm	F	-4.5±6.21	-3.0±6.31	-1.6±5.66	-3.5±6.24	*P*=.001	
	Both	-4.2±6.55	-2.4±6.51	-1.8±6.21	-3.1±6.55	$p\eta^2$=0.22	

NOTE. Values are post minus pre mean ± SD change scores in absolute units computed from individual change scores.
Abbreviation: NS, not significant.
* Did not survive Holm correction for family wise error (*P*=.02, cutoff).

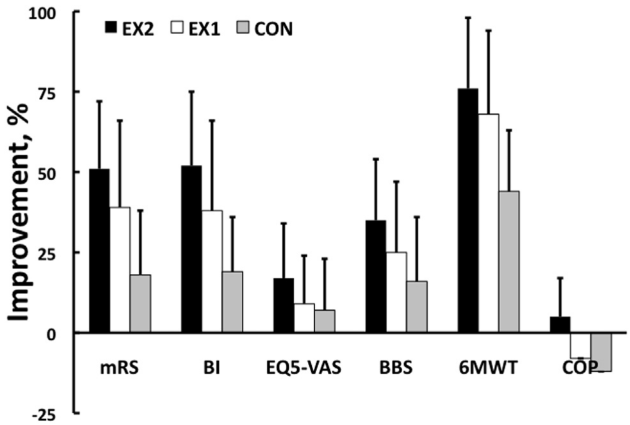

Fig 2 Improvements in primary (mRS, shaded gray) and secondary outcomes after twice daily exergaming (50 sessions, EX2), once daily exergaming (25 sessions, EX1), and once daily standard care physical therapy (25 sessions, CON) on 5 consecutive days for 5 consecutive weeks. In each outcome the changes in the 3 groups were significantly different from each another (*P*<.05).

Improvements of 1.8 (EX2) and 1.4 (EX1) (see table 3) in mRS, the primary outcome, exceeded the clinically meaningful change of 1 unit irrespective of sex.[29-31] Against expectations, these changes in mRS were the only improvements that did not differ between the twice versus once daily interventions. Perhaps the sensitivity of mRS has a ceiling at once weekly training or a total of 25 sessions.[29-31] Only a handful of studies have examined the effects of high intensity exercise on mRS in subacute PwS, but the gains we observed were much greater. For example, exergaming plus standard therapy (n=100) compared with standard therapy (n=100) for 7 consecutive days for 1 hour per day improved mRS by 0.58 versus 0.23, respectively in subacute PwS who experienced a stroke 7 days earlier.[33] Likewise, high intensity physical exercise 48 hours after a stroke (n=86) improved mRS at a follow-up of 3 months more than standard (n=80) or very early mobilization 24 hours after a stroke (n=82).[34] The data suggest that high intensity exercise therapy, especially with an exergaming element, is effective for improving ADL independence in subacute PwS, but such improvements can be especially sizeable if therapy is administered twice daily (see table 3). The intervention effects in the present study could be also greater than in previous studies because the time after stroke was 1 to 7 days in the previous studies, whereas we started the intervention 3 weeks after stroke on average. We found no evidence for the responsiveness to exercise in terms of rMS being higher in men than women.[24,25]

Secondary outcomes

Secondary outcomes addressed life domains, which all improved by a clinically meaningful margin in the expected hierarchical response pattern according to exercise intensity and frequency (see fig 2, table 3). The BI measures the perceived ability to perform ADLs, which improved by 8 to 9 points, strongly favoring exercise intensity and frequency versus standard care. The improvements in 6MWT were particularly impressive because PwS in the EX2 groups walked approximately 125 meters further than at baseline. This gain was nearly twice the gain in the lower frequency (EX1) and intensity (CON) groups (see table 3). These changes are substantially greater than the highest change of 37 meters reported in a meta-analytical review of 4 studies also using high-intensity but not twice daily training.[32] The improvements in the BI, BBS, 6MWT, and standing balance were paralleled by changes in EQ5-VAS, implying that participants perceived an increase in their QoL owing to being more effective in executing ADLs, lower likelihood of a fall, greater walking ability and fitness, and higher standing stability. The changes contrast with a lack of reduction in depression, which might have been too low at baseline to reflect improvements from exercise.

Participants had stage 1 hypertension (130/89 mmHg) with a somewhat elevated rHR (86 beats/min; see table 2). As expected, the rHR was elevated approximately 10 beats per minute 10 minutes after exercise, but systolic BP and especially diastolic BP decreased 10 minutes after exercise. More importantly, resting BP (rBP) chronically decreased by up to 4 to 6 mmHg in the EX2 group. The acute reductions in rBP are related to the postexercise hypotension, which can last up to 24 hours after an exercise bout

Table 4 Changes in rHR, BP, peak HR, and RPE during exercise

		EX2	EX1	CON
Variable	Session	Mean ± SD	Mean± SD	Mean ± SD
Rest				
HR	1	10.5±8.58	10.7±8.37	3.5±7.79
	2	9.4±8.89	NA±NA	NA±NA
SBP	1	-3.6±10.54	-1.9±10.86	-2.5±12.53
	2	-2.6±9.40	NA±NA	NA±NA
DBP	1	-6.0±10.84	-6.1±11.29	-4.5±12.1
	2	-2.9±10.09	NA±NA	NA±NA
Exercise				
HR	1	133.9±7.58	133.6±8.35	126.2±7.53
	2	133.6±7.64	NA±NA	NA±NA
RPE	1	15.3±1.56	15.2±1.53	9.5±1.58
	2	15.0±1.55	NA±NA	NA±NA

NOTE. Session refers to an intervention session in each group with a morning and an afternoon (ie, 2 sessions per day in EX2 and 1 session per day in EX1 and CON). Values for the top, Rest panel, are postintervention minus the preintervention values averaged across the 25 days. Values for the bottom Exercise panel are the average during 25 days of exercise.
Abbreviation: NA, not applicable.

in PwS.[35] Because systolic BP at the start of the 25th session was approximately 5 mmHg lower than at the start of the EX2 program (131 mmHg; see supplemental fig S1), the exercise program afforded an antihypertension benefit, which is most likely owing to a reduction in peripheral resistance.[35] Such reductions in rBP are known to reduce risks for a recurrent ischemic event. Our data are in clear support of recent recommendations for prescribing vigorous-intensity exercise for hypertensive adults.[35]

Exercise intensity

A novel element of the present study was the use of twice daily exercise sessions. Our rationale was that most PwS in the early, subacute phase of recovery respond well to exercise stimuli. The ensuing adaptations induce brain plasticity in a dose-dependent manner that lasts beyond the immediate training period and underlie motor recovery.[36] The unusual twice daily paradigm does indeed go against recent recommendations. For example, a meta-regression of exercise frequency revealed that high frequency was actually associated with a reduced effect on a number of outcomes in PwS.[37] The conceptual basis for using low versus high exercise frequency for subacute PwS mobility treatment is that patients need to rest for neuroplasticity to emerge, allowing them to learn new and relearn impaired movements.[37] However, we did not observe any signs that the high exercise frequency and intensity (see table 4) would have interfered with clinical or motor adaptations. In fact, we observed just the opposite. In 5 of 6 outcomes, the EX2 group improved the most compared with the EX1 and CON groups. In addition, neurologic patients are physically so deconditioned that PwS adapt rapidly to the high-intensity stimulus, which in fact facilitates motor learning, even if the conditioning stimulus is not specific to a given motor deficit.[3,13-17] This could be the reason for uniform increases across the outcomes (see table 3). However, we point out that there is also evidence in support of low intensity exercise being effective to improve gait and balance in PwS, increasing participants' treatment options.[38]

Study limitations

Although stroke prevalence is highest among older women who are underrepresented in exercise trials, we also were unable to include such PwS. A lack of difference between groups in the outcomes at baseline dampens the severity of the limitation that the study was a pseudorandomized and not a fully randomized trial, which could bias the results for the CON group. We did not control physical activity and diet. Men were 7 kg heavier than women at baseline (see table 1). Although men lost approximately 5 kg, women were weight-stable or gained weight up to approximately 7 kg (see table 3), implying an interaction between diet or physical activity (or both) and sex. PwS often present with fatigue, but we did not measure this.[3] Although the 95% adherence and 5% dropout make high exercise intensity feasible, therapists delivered exercise sessions in a hospital facility. Many PwS have no access to such facilities, a setting that counters trends to reduce care costs by having PwS exercise at home. However, the efficacy of high intensity rehabilitation of subacute PwS at home is uncertain.[10] Assessors were blinded to the participants' group assignment, but we did not assess whether the blinding was maintained and assessments remained unbiased. It is unclear whether the current paradigm is feasible in a home setting using remote monitoring and off-the-shelf technology. Without neural, biomechanical, or behavioral markers, we were unable to determine the mechanisms of improvements in clinical and motor symptoms.

Conclusions

Twice daily compared with once daily high-intensity exergaming or once daily lower intensity standard care produced superior effects on clinical and motor symptoms, BP, and QoL in male and female subacute stroke participants.

Suppliers

a. Posture Evaluation Platform; MED-EVAL Ltd.
b. Polar RS800CX HR watch; Polar Electro Co Ltd.
c. Omron M7 Intelli IT; OMRON Healthcare UK Ltd.
d. Microsoft Corp.
e. Just Dance; Ubisoft.

Keywords

Activities of daily living; Exercise; Quality of life; Rehabilitation; Virtual reality

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References

1. Bejot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. Presse Med 2016;45:e391-8.
2. Collaborators GS. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 2019;18:439-58.
3. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2532-53.
4. Kim Y, Lai B, Mehta T, et al. Exercise training guidelines for multiple sclerosis, stroke, and parkinson disease: rapid review and synthesis. Am J Phys Med Rehabil 2019;98:613-21.
5. Tollar J, Nagy F, Kovacs N, Hortobagyi T. A high-intensity multicomponent agility intervention improves parkinson patients' clinical and motor symptoms. Arch Phys Med Rehabil 2018;99:2478-84.
6. Frazzitta G, Maestri R, Bertotti G, et al. Intensive rehabilitation treatment in early Parkinson's disease: a randomized pilot study with a 2-year follow-up. Neurorehabil Neural Repair 2015;29:123-31.
7. Keytsman C, Hansen D, Wens I, Eijnde BO. Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. Disabil Rehabil 2019;41:430-5.
8. Graham K, Yarar-Fisher C, Li J, et al. Effects of high-intensity interval training versus moderate-intensity training on cardiometabolic health markers in individuals with spinal cord injury: a pilot study. Top Spinal Cord Inj Rehabil 2019;25:248-59.
9. Tally Z, Boetefuer L, Kauk C, Perez G, Schrand L, Hoder J. The efficacy of treadmill training on balance dysfunction in individuals with chronic stroke: a systematic review. Top Stroke Rehabil 2017;24:539-46.

10. Steen Krawcyk R, Vinther A, Petersen NC, et al. Effect of home-based high-intensity interval training in patients with lacunar stroke: a randomized controlled trial. Front Neurol 2019;10:664.
11. Dun Y, Smith JR, Liu S, Olson TP. High-intensity interval training in cardiac rehabilitation. Clin Geriatr Med 2019;35:469-87.
12. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334-59.
13. Tollar J, Nagy F, Hortobagyi T. Vastly different exercise programs similarly improve parkinsonian symptoms: a randomized clinical trial. Gerontology 2019;65:120-7.
14. Tollar J, Nagy F, Moizs M, Toth BE, Sanders LMJ, Hortobagyi T. Diverse exercises similarly reduce older adults' mobility limitations. Med Sci Sports Exerc 2019;51:1809-16.
15. Sullivan KJ, Brown DA, Klassen T, et al. Effects of task-specific locomotor and strength training in adults who were ambulatory after stroke: results of the steps randomized clinical trial. Phys Ther 2007; 87:1580-602.
16. Lloyd M, Skelton DA, Mead GE, Williams B, van Wijck F. Physical fitness interventions for nonambulatory stroke survivors: a mixed-methods systematic review and meta-analysis. Brain Behav 2018;8: e01000.
17. Rintala A, Paivarinne V, Hakala S, et al. Effectiveness of technology-based distance physical rehabilitation interventions for improving physical functioning in stroke: a systematic review and meta-analysis of randomized controlled trials. Arch Phys Med Rehabil 2019;100: 1339-58.
18. Askin A, Atar E, Kocyigit H, Tosun A. Effects of kinect-based virtual reality game training on upper extremity motor recovery in chronic stroke. Somatosens Mot Res 2018;35:25-32.
19. Jie LJ, Kleynen M, Meijer K, Beurskens A, Braun S. The effects of implicit and explicit motor learning in gait rehabilitation of people after stroke: protocol for a randomized controlled trial. JMIR Res Protoc 2018;7:e142.
20. Karasu AU, Batur EB, Karatas GK. Effectiveness of Wii-based rehabilitation in stroke: a randomized controlled study. J Rehabil Med 2018;50:406-12.
21. Tollar J, Nagy F, Kovacs N, Hortobagyi T. Two-year agility maintenance training slows the progression of Parkinsonian symptoms. Med Sci Sports Exerc 2019;51:237-45.
22. Christensen H, Bentsen L, Christensen L. Update on specificities of stroke in women. Presse Med 2016;45:e409-18.
23. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017;135:e146-603.
24. Hooker SP, McDonnell MN. Cardiorespiratory fitness, physical activity, and stroke. In: Kokkinos K, Narayan P, editors. Cardiorespiratory fitness in cardiometabolic diseases. Cham, Switzerland: Springer; 2019. p 335-48.
25. Draca S. Gender and stroke lateralization: factors of functional recovery after the first-ever unilateral stroke? NeuroRehabilitation 2012;30:247-54.
26. Tollár J, Nagy F, Tóth BE, et al. Exercise effects on multiple sclerosis quality of life and clinical-motor symptoms. Med Sci Sports Exerc 2020;52:1007-14.
27. Choi SD, Guo L, Kang D, Xiong S. Exergame technology and interactive interventions for elderly fall prevention: a systematic literature review. Appl Ergon 2017;65:570-81.
28. Parra-Moreno M, Rodriguez-Juan JJ, Ruiz-Cardenas JD. Use of commercial video games to improve postural balance in patients with multiple sclerosis: a systematic review and meta-analysis of randomised controlled clinical trials. Neurologia 2018 Mar 7 [Epub ahead of print].
29. Balu S. Differences in psychometric properties, cut-off scores, and outcomes between the barthel index and modified rankin scale in pharmacotherapy-based stroke trials: Systematic literature review. Curr Med Res Opin 2009;25:1329-41.
30. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin Scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 2007;38:1091-6.
31. Tilson JK, Sullivan KJ, Cen SY, et al. Meaningful gait speed improvement during the first 60 days poststroke: minimal clinically important difference. Phys Ther 2010;90:196-208.
32. Wiener J, McIntyre A, Janssen S, Chow JT, Batey C, Teasell R. Effectiveness of high-intensity interval training for fitness and mobility post stroke: a systematic review. PM R 2019;11:868-78.
33. Ho TH, Yang FC, Lin RC, et al. Impact of virtual reality-based rehabilitation on functional outcomes in patients with acute stroke: a retrospective case-matched study. J Neurol 2019;266:589-97.
34. Tong Y, Cheng Z, Rajah GB, et al. High intensity physical rehabilitation later than 24 h post stroke is beneficial in patients: a pilot randomized controlled trial (RCT) study in mild to moderate ischemic stroke. Front Neurol 2019;10:113.
35. MacDonald HV, Pescatello LS. Exercise and blood pressure control in hypertension. In: Kokkinos K, Narayan P, editors. Cardiorespiratory fitness in cardiometabolic diseases. Cham, Switzerland: Springer; 2019. p 137-68.
36. Sampaio-Baptista C, Sanders ZB, Johansen-Berg H. Structural plasticity in adulthood with motor learning and stroke rehabilitation. Ann Rev Neurosci 2018;41:25-40.
37. Lee HS, Park YJ, Park SW. The effects of virtual reality training on function in chronic stroke patients: a systematic review and meta-analysis. Biomed Res Int 2019;2019:7595639.
38. Zou L, Yeung A, Zeng N, et al. Effects of mind-body exercises for mood and functional capabilities in patients with stroke: an analytical review of randomized controlled trials. Int J Environ Res Public Health 2018;15:721.