High-intensity training in patients with lacunar stroke: A one-year follow-up

Rikke Steen Krawcyk, Ph.D,[a,b] Anders Vinther, Ph.D.,[a,c] Nicolas Caesar Petersen, Ph.D.,[d] Jens Faber, DMSci,[e] Helle K. Iversen, DMSci,[f] Thomas Christensen, DMSci,[g] Tobias Wirenfeldt Klausen, MSc,[h] and Christina Kruuse, Ph.D, DMSci[i]

Objectives: Physical inactivity is a major risk factor for stroke. It is a challenge for patients to initiate and adhere to regular exercise post-stroke. Early initiation of home-based high-intensity interval training (HIIT) may engage patients in physical activity, improve cardiorespiratory fitness, and reduce risk of recurrent stroke. *Materials and Methods:* Post-intervention follow-up of patients with lacunar stroke, randomized to three-months HIIT including weekly motivational calls, or usual care. At follow-up (six- and 12-months post-stroke), we investigated changes in cardiorespiratory fitness, physical activity, fatigue, depression, mental well-being, stress, cognition, cardiovascular function, and recurrent stroke. *Results:* We included 71 patients of whom 59 patients (mean age: 63.9 ± 8.8 years) completed six- and 12-month follow-up. No change was detected in cardiorespiratory fitness between groups from baseline to 12-months follow-up. At six months, vigorous-intensity activity (median hours/week [interquartile range]) was maintained in the intervention group (baseline, 0[0;2]; post-intervention, 2[0;3]; six-month, 2[0;4]) and increased in the usual care group (baseline, 0[0;1]; post-intervention, 1[0;2]; six-month, 1[0;3]), with no difference between groups. Vigorous-intensity activity declined to baseline levels at 12-months in both groups. Secondary outcomes improved from baseline to 12-months with no significant differences between groups. Similar rate of recurrent stroke (n=3) occurred in each group with a three-

From the [a]Department of Physiotherapy and Occupational Therapy, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark; [b]Department of Neurology, Neurovascular Research Unit, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark; [c]Hospital Secretariat and Communications, Research, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark; [d]Center for Translational Neuromedicine, University of Copenhagen, Copenhagen, Denmark; [e]Department of Internal Medicine, Division of Endocrinology, Copenhagen University Hospital - Herlev and Gentofte, and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [f]Department of Neurology, Stroke Center Rigshospitalet, Copenhagen University hospital − Rigshospitalet, Copenhagen, Denmark and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [g]Department of Neurology, Copenhagen University hospital - North Zealand, Copenhagen, Denmark and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [h]Department of Haematology, Copenhagen University Hospital - Herlev and Gentofte, Denmark; and [i]Department of Neurology, Neurovascular Research Unit, Copenhagen University Hospital - Herlev and Gentofte, Copenhagen, Denmark and Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

Received October 14, 2022; revision received December 6, 2022; accepted December 26, 2022.

Department where the work was performed Copenhagen university Hospital - Herlev and GentofteDepartment of Neurology, Neurovascular Research Unit

Grant support The work was funded by The Associations of Danish Physiotherapists; Toyota-Fonden Denmark; The Foundation of Aase & Ejnar Danielsen; The A.P. Møller and Chastine Mc-Kinney Møller Foundation; The Foundation of Axel Muusfeldt, Lions Clubs International Foundation, Denmark, and The Memorial Foundation of C.C Klestrup & Wife Henriette Klestrup. The stationary bicycle used for cardiorespiratory fitness testing was kindly provided by ProTerapi A/S, Denmark. CK was funded by Novo Nordisk Foundation, grant number NNF 18OC0031840. The funding parties did not have any influence on study design, data collection, analyses, or interpretation of the study.

Corresponding authors. E-mails: rikke.steen.krawcyk@regionh.dk, ckruuse@dadlnet.dk.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2022.106973

month delay in the intervention group. *Conclusions:* Early initiated HIIT did not increase long-term cardiorespiratory fitness, but increased time spent doing vigorous-intensity activities post-stroke. Decline to baseline activity level at 12 months warrants identification of motivators to initiate and sustain physical activity post-stroke.

Keywords: Cardiorespiratory fitness—High-intensity-interval-training—Lacunar stroke—Long-term follow-up—Physical activity—Secondary stroke prevention—Stroke recurrence

Introduction

Improving physical activity is a key target in non-pharmacological secondary stroke prevention.[1] Regular physical activity is associated to increased cardiovascular health, improved cardiorespiratory fitness, physical function, blood pressure, lipids, and body weight.[2,3] As much as 90% of all first time strokes are attributed to modifiable risk factors such as hypertension, physical inactivity, diet, body mass index (BMI), current smoking, alcohol consumption, and diabetes.[4,5] Stroke patients show up to 20% risk of recurrent stroke.[6] The recurrence rate after a lacunar stroke is 4-7% within the first 90 days of stroke onset.[7,8] Since patients with lacunar stroke present with minor stroke symptoms and fast remission, they are often left without a structured secondary prevention program at hospital discharge. Instead, patients are given advice regarding self-administered lifestyle changes. Such lifestyle changes may, however, be difficult to implement and control for adherence.[9,10] In a long-term cohort study, healthy unfit men, with a VO_{2max} below 25.2 mL/kg per minute, had a 3.5 times higher risk (95% CI 1,66-7,41) of ischemic stroke compared to healthy men with a VO_{2max} above 35.3mL/kg per minute.[11] Low motivation for physical exercise is a major challenge in stroke prevention.[12,13] Several barriers for engaging in physical activity have been identified. Barriers include environmental factors such as accessibility, costs, transport issues, and personal factors such as fluctuation in symptoms, post-stroke depression, fatigue and lack of motivation and energy.[12-14] Repeated encouragements and verbal instructions alone are not sufficient to increase the level of physical activity after ischemic stroke and to reduce stroke recurrence.[15,16] We hypothesised that, in patients with lacunar stroke an exercise-based intervention initiated early after stroke could lead to a long-term increase in cardiorespiratory fitness and physical activity. We performed the 'High-intensity training in patients with lacunar stroke' (HITPALS) study.[17] Patients did 12-weeks home-based high intensity interval training (HIIT), combined with individual weekly follow-up sessions by telephone, compared to a group assigned to usual care.[18] The initial findings from the intervention period were that early HIIT was feasible and safe, and patients in the intervention group complied to increase their time spent on vigorous-intensity activity compared to usual care.[18] However, the intervention group did not improve their cardiorespiratory fitness significantly compared to the usual care group, which was ascribed to lack of continuous monitoring of physical activity and a high physical activity level at baseline in both groups.[19] As the immediate post-intervention effect has been reported,[18] this paper focus on six- and 12-months follow-up. In this paper we focused on six- and 12-moths follow-up. We aimed to explore if the patients stayed physically active with vigorous-intensity activity after intervention termination, and to identify potential long-term changes in cardiorespiratory fitness, stroke risk profile and recurrent stroke 12-months post-stroke.

Materials & methods

The HITPALS-study was a randomised controlled trial with a parallel-group design with three-months of HIIT or usual care.[17] Data on the short-term effect of HIIT was evaluated immediately post-intervention.[18] In this study we analysed data from the six- and 12-months follow-up assessments. All follow-up assessments were carried out at the neurovascular research unit at Copenhagen University Hospital - Herlev and Gentofte between July 2016 and October 2018. The reporting of the study adheres to the CONSORT statement.[20]

The protocol was described in detail previously.[17] In brief, patients were eligible when diagnosed with an acute/subacute small vessel occlusion stroke (lacunar stroke) based on clinical symptoms, and computed tomography (CT) scan or magnetic resonance imaging (MRI) scan (<2 cm in diameter in the acute phase).[21] Patients were also included if they had clinical symptoms of a transient ischemic attack (TIA) with concomitant MRI-verified signs of a previous lacunar stroke. Final diagnostics were done by a stroke neurologist, following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[22] Patients had a mild stroke severity according to the Scandinavian Stroke Scale (SSS: 43-58 points)[23] and were able to speak and read Danish. The following exclusion criteria were applied: previous large-artery stroke, atrial fibrillation, pacemaker, uncontrolled hypertension (patients not responding adequately to their medication) or diabetes, carotid artery stenosis >50% on the relevant side, symptoms or comorbidities not allowing exercise on

a stationary bicycle, dyspnoea caused by heart or pulmonary disease, aphasia, or dementia (≤23 out of 30 points on the Mini-Mental State Examination[24]) interfering with understanding the protocol and physical examinations.

Randomization and blinding

The patients were randomized based on equal allocation (1:1) with a computer-generated block-randomization (8 blocks of 10, mixed with 5 blocks of 4) and carried out by a research assistant not involved in the study. Sealed opaque envelopes were made by the research assistant, stored, and administrated by health personnel not involved in the study. The outcome assessor, data analysts, and study coordinator were all blinded to the randomization process.

Initial intervention

The intervention during the first three-months period was home-based high-intensity interval training (HIIT) 15 minutes a day, 5 days per week for 12 weeks, with weekly telephone calls to ensure compliance. A detailed description of the exercise intervention has previously been published.[17,18] Usual care included self-managed lifestyle changes, and both the intervention and usual care group received secondary preventive medication.

Outcome assessment

The primary outcome, cardiorespiratory fitness was assessed by a physiotherapist not involved in the study and blinded for the randomisation procedure. The secondary outcomes were performed by the study coordinator.

Cardiorespiratory fitness

Cardiorespiratory fitness was evaluated by the Graded Cycling Test with Talk Test (GCT-TT). GCT-TT was a sub-maximal exercise test identifying the intensity at which the patient perceived that it was no longer possible to speak comfortably due to excessive breathing.[25] The cardiorespiratory fitness was monitored as power output in Watts (W) and the test was performed on a stationary bicycle (Monark 928E-G3, Vansbro, Sweden). Clinically relevant improvement over time for an individual (smallest real difference (SRD)) corresponded to 30 W or two steps in the GCT-TT protocol.[26] A detailed test manual has previously been published.[26]

Secondary outcomes were known complications to or risk factors for stroke briefly described below. A detailed description of the secondary outcomes was published previously.[17]

Post-stroke fatigue

Post-stroke fatigue was assessed by the Multidimensional fatigue inventory (MFI-20) including five domains of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[27] Total score ranges from 0-20 with a higher score indicating a higher degree of fatigue.[27]

Depression

Depression was evaluated by major depression inventory (MDI) which included 12 questions on mood-related symptoms within the preceding two weeks. Total score ranged from 0−50 points, and a higher score indicated more severe depression.[28]

Mental well-being

World Health Organisation-Five well-being index (WHO-5) evaluated mental well-being,[29] and included five positive statements to which the patient responded on a 6-point Likert scale, corresponding to the patient's experience for the past two weeks. Total score ranged from 0−100 points, and ≤50 points indicated reduced mental well-being or depression.[30]

Chronic stress

Chronic stress was estimated by a hand-held algometer (Ull-Meter®, Ull Care, Hellerup, Denmark) and recorded pain threshold on the sternum, expressed as pressure pain sensitivity (PPS).[31,32] The algometer automatically transformed the pain threshold into a logarithmic scale of sensitivity ranging from 30−100 PPS units, with a cut-off ≥60 correlating with markers of stress syndrome.[33]

Cognition

Cognitive impairments were detected with the Montreal cognitive assessment (MoCA), based on nine cognitive domains: attention, concentration, executive functions, memory, language, visuospatial ability, conceptual thinking, calculations, and orientation. Total score ranged from 0−30 points, with a score ≥26 points considered as normal cognitive function.[34]

Blood pressure and BMI

Blood pressure was measured after an overnight fast, with the patient in a supine position and after five minutes of rest, using an automatic blood pressure monitor (Microlife® BP A100/ Microlife® BP A3L Comfort, Widnau, Switzerland). BMI was calculated. The weight was assessed by a body composition monitor (OMRON HBF-500-E; Kyoto, Japan) and the height was assessed by measuring tape.

Physical activity

Physical activity was evaluated both objectively by accelerometers (AX3, Axivity, York, UK) and subjectively by the questionnaire; physical activity scale (PAS2).[35]

PAS2 included nine questions regarding daily time spent on sleep, sitting down at work, standing/walking at work, heavy physical work during working hours, active commuting, sedentary behavior, and three questions addressed time spent weekly on: light-intensity-, moderate-intensity-, and vigorous-intensity activity during leisure time.[35] To report mean daily activity, the scores from the three leisure-time activities were divided by seven, and then added to the scores from the daily activities. As recommended by the developers of the PAS2, when total time was reported below or above 24 hours, we added or subtracted time that was not accounted for to the category "light-intensity activity".[35] The wireless three-axis accelerometer (AX3, Axivity, York, UK), was fixed anteriorly on the patient's right medial thigh assessing objective physical activity. It recorded for eight days and seven nights (the first week of each period) with a frequency of 25 Hertz (Hz) to identify everyday physical activity types e.g. walking, standing, sitting down, running, cycling and stair climbing. In calculation of mean daily hours of physical activity, data from less than six days was considered as "days of non-wear" and excluded from the analysis.

Statistics

The initial sample size calculation was based on the GCT-TT power output. Using a two-tailed 5% level of significance and a power of 80%, to detect a minimal clinical important average difference of 23W, a sample size of 84 patients (42 in each group) was needed. To account for a dropout rate of 15%, we aimed to enroll 100 patients in total.

The 12-months follow-up data was analysed by intention-to-treat. All available data for each patient (baseline, post-intervention, 6- and 12-months follow-up) were included in the analysis, and missing data was not imputed. The distribution of investigated variables was explored by Q-Q-plots and histograms. The treatment effect was calculated, both for primary and secondary outcomes, by the constrained longitudinal data analysis (cLDA), which provides unbiased results when missing at random.[36] No other independent variable was included in the analysis. The effect size was calculated as the visit/treatment interaction at the specific visit and given as estimates of mean difference with 95% confidence intervals (CI) for normal distributed data, and as median and interquartile range for non-normal distributed data. All tests were two-sided and p-values <0.05 were considered significant. Data was analysed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

In total, 71 patients were recruited, and 63 were available for initial follow-up. Furthermore, four patients were lost at follow-up, one at six months and three at 12 months. Thus 59 patients, mean age 63.9 $\pm$ 8.8 years (48 men), remained in the study at 12 months follow-up (Fig. 1). The three dropouts at 12-months in the intervention group were due to work obligations (n=2) and a traumatic brain injury (n=1), and the one from the usual care group at six-months was due to reduced mental surplus. The dropouts were considered unrelated to the study intervention. There were no significant differences between groups in demographics or baseline characteristics (Table 1), or in cardiovascular risk factors at baseline (Table 2).

Primary outcome

In total, 57 patients were analysed with GCT-TT at 12-months assessments (Table 3). Drop-out for GCT-TT assessment both at six- months and 12 months were one (male) from the usual care group due to knee pain from osteoarthritis, and two from the intervention group (males) one due to muscle strain in the anterior thigh (at six months) and soreness and fatigue in the affected leg (at 12 months), and one due to acute pain from an inguinal hernia (at 12 months). Furthermore, one patient from the intervention group did not attend the assessment at three-months follow-up due to hospitalization caused by a lumbar discus prolapse but was assessed at the six- and 12-months follow-up assessments.

No significant difference in GCT-TT power output was seen over time from baseline to six- or 12- months follow-up, either within groups or between groups (Fig. 2). The mean score of GCT-TT increased below the clinically relevant improvement in both groups (Table 3). On an individual level, two patients from the usual care group but none from the intervention group obtained an improvement of $\geq$ 30 watts from post-intervention to six-month follow-up. From six to 12-months follow-up three patients from usual care and six from intervention group obtained a GCT-TT improvement of $\geq$ 30 watts.

Secondary outcomes

The intervention group maintained the initial significant increase in vigorous-intensity activity, measured by PAS2, from baseline to six-months follow-up (p=0.03). After the intervention period the usual care group also increased their vigorous-intensity activity significantly from baseline to six-months follow-up (p=0.012) where they matched the level of activity in the intervention group. This significant increase in the usual care group at six-months follow-up was mainly achieved through five male patients with an exceptional increase in vigorous-intensity activity at a mean of 7.4 hours/week.

At 12-months post-stroke vigorous-intensity activity decreased in both groups to a level insignificant from baseline, and with no difference between groups (Fig. 3). There was no significant difference in age of patients engaging in vigorous activity on PAS score at six- and 12

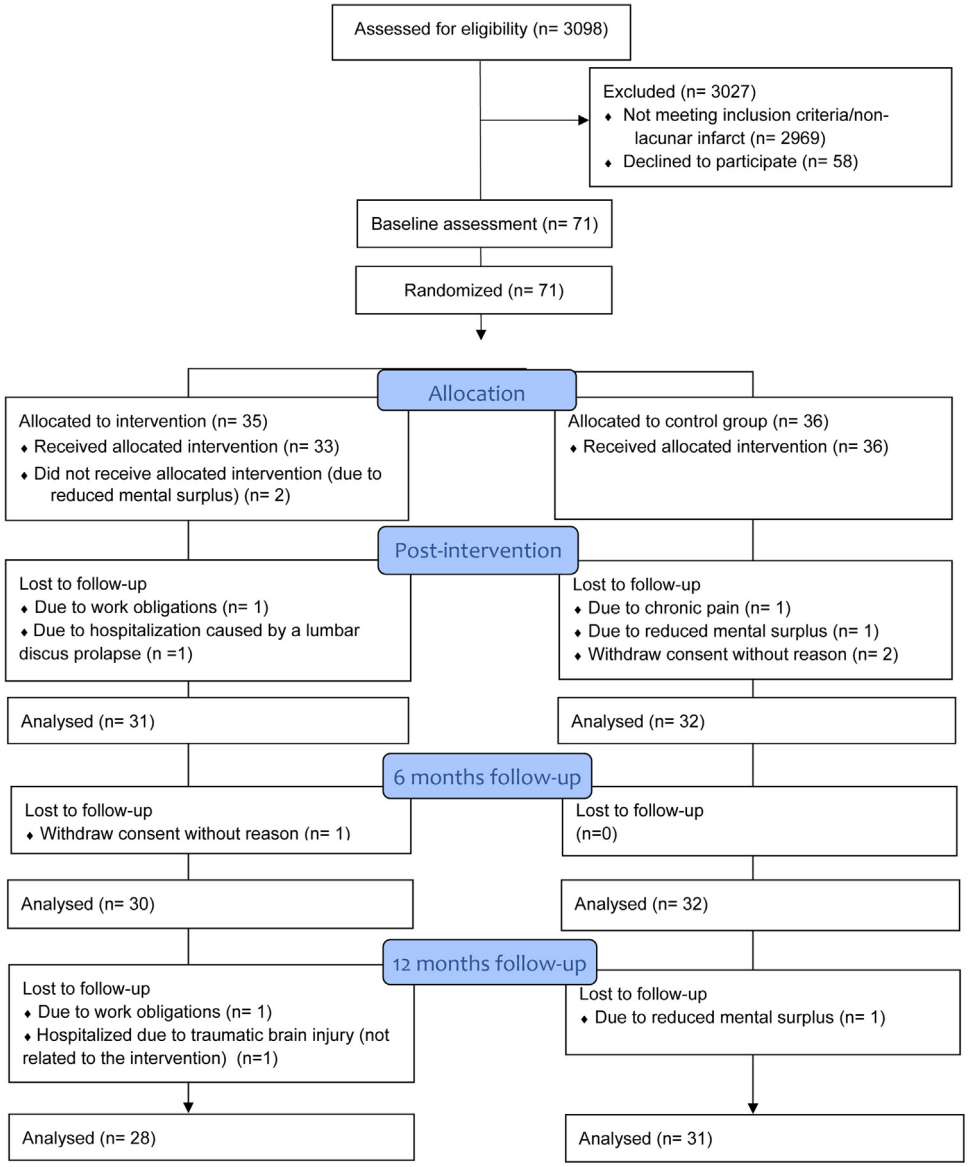

Fig. 1. *Flow diagram.*

Flow diagram of recruitment, allocation, and dropouts during the study.

The screened patients included all patients admitted to our non-comprehensive stroke unit with possible symptoms of stroke or TIA. After a full work-up by neuroimaging and clinical assessment, some patients were found not to have had a stroke or to have a TIA with no signs of small vessel disease. Based on the Danish Stroke Register we have approximately 900 stroke patients and 300 TIA patients admitted yearly of these approximately 25% have cerebral small vessel disease.

months, when testing for mean age above and below the median activity score ($p>0.2$).

The systolic and diastolic blood pressures decreased from baseline to six-months follow-up in both groups (intervention, $p=0.03$ and $p=0.00$; usual care, $p=0.01$ and $p=0.01$, systolic and diastolic, respectively) with no difference between groups (Table 3).

None of the secondary outcome measures were significantly different between groups from baseline to six- and 12 months follow-up. Within groups significant changes were seen in mental well-being, chronic stress, and cognition from baseline to six- and 12-months follow-up (Table 3). In the intervention group, mental well-being improved from baseline to six-months follow-up ($p=0.02$) and in the usual care group from baseline to 12-months follow up ($p=0.04$). Chronic stress was reduced in the intervention group from baseline to 6-months follow-up ($p=0.02$) and for the usual care group from baseline to 12-months follow up ($p=0.00$). Cognition was improved in both groups from baseline to all time points ($p<0.01$ in both groups).

In total, seven patients (10%) were readmitted to the hospital for a stroke or TIA during the study. Five patients were readmitted for observation of TIA within

Table 1. *Baseline characteristics on patients who have completed the primary outcome at 12-months follow-up.*

Variable	Intervention (n=28)	Usual care (n=31)
Men, n (%)	22 (79)	26 (84)
Age, years (mean ± SD)	64.4±8.5	63.4±9.2
Mobility		
Without walking aids at baseline, n (%)	24 (86)	29 (94)
Scandinavian stroke scale, points (mean ± SD)	54.4±6.0	55.2±4.5
Marital status		
Cohabitants, n (%)	20 (71)	23 (74)
Living alone, n (%)	8 (29)	8 (26)
Education		
Primary education, n (%)	0 (0)	3 (10)
Apprenticeship, n (%)	9 (32)	9 (29)
Upper secondary education/high school, n (%)	0 (0)	1 (3)
Short-cycle tertiary education, n (%)	6 (21)	2 (6)
Bachelor or equivalent, n (%)	8 (29)	4 (13)
Masters, equivalent or higher, n (%)	5 (18)	12 (39)
Lesion type		
First-time stroke, n (%)	17 (61)	17 (55)
Recurrent stroke, n (%)	2 (7)	2 (6)
Only older infarct verified on MRI, with clinical symptoms, n (%)	1 (3)	3 (10)
First-time stroke plus sequela stroke verified on MRI, n (%)	8 (29)	9 (29)
Hemispheric localisation of lesion		
Right hemisphere, n (%)	17 (61)	18 (58)
Left hemisphere, n (%)	11 (39)	12 (39)
Bilateral, n (%)	0 (0)	1 (3)

Table 2. *Cardiovascular risk factors at baseline, on patients who have completed the primary outcome at 12-months follow-up.*

Variable	Intervention (n=28)	Usual care (n=31)
Hypertension at hospital admission, n (%)	24 (86)	24 (77)
Hypertension previously known, n (%)	16 (57)	13 (42)
Blood pressure		
Systolic pressure, mmHg (mean ± SD)	152±21	147±21
Diastolic pressure, mmHg (mean ± SD)	87±9	89±11
Pre-existing diabetes, n (%)	3 (11)	2 (6)
BMI, kg/m^2 (mean ± SD)	28±5	25±4
Smoking		
Current smokers, n (%)	5 (18)	6 (19)
Previous smokers, n (%)	12 (43)	15 (49)
Non-smokers, n (%)	11 (39)	10 (32)
Alcohol consumption[†]		
> health authorities' recommendations, n (%)	13 (46)	10 (32)
Lipids		
Total cholesterol, mmol/L (mean ± SD)	5.5±1.3	5.5±1.4
LDL, mmol/L (mean ± SD)	3.2±1.3	3.1±1.0
HDL, mmol/L (mean ± SD)	1.5±0.5	1.4±0.4

[†]The Danish Health authority recommends <7 units per week for women (1 unit equals 1 glass of wine) and <14 units per week for men.[45]

the first three months after stroke (one from the intervention group and four from usual care group). Two patients from the intervention group were readmitted, one due to a TIA within six months and one due to a recurrent stroke within twelve months from the first stroke.

Discussion

The present study was a follow-up to a three-months home-based HIIT training RCT after lacunar stroke. No improvement was seen in long-term cardiorespiratory fitness estimated by GCT-TT power output. The most

Table 3. *Results from baseline to 12-months follow-up for intervention, and the usual care group, on the primary- and secondary outcomes.*

Variables	Intervention				Usual care			
	Baseline	Post-intervention assessment	6-months follow-up post-stroke	12-months follow-up post-stroke	Baseline	Post-intervention assessment	6-months follow-up post-stroke	12-months follow-up post-stroke
Primary outcome	**(n=35)**	**(n=30)**	**(n=30)**	**(n=27)**	**(n=34)**	**(n=30)**	**(n=31)**	**(n=30)**
GCT-TT, W, (mean ± SD)	115.3±48.8	123.5±47.9	123.5±47.9	135±53.8	113.8±46	124±48.6	121.5±42.5	123±45.8
Secondary outcome	**(n=35)**	**(n=31)**	**(n=31)**	**(n=29)**	**(n=36)**	**(n=32)**	**(n=32)**	**(n=31)**
Post-stroke fatigue, points (mean ± SD)	9.9±4.7	11.3±4.7	10.3±4.0	10±4.2	11.0±3.4	10.3±3.9	10.2±4.3	9.8±4.2
Chronic stress, points (mean ± SD)	61.7±15.5	58.6±14.5	54.4±14.2*	53.9±18.0	57.1±16.0	54.7±17.0†	56.9±16.6†	49.9±14.4†,*
Depression, points (median [IQR])	5[1;11]	6[4;13]	7[3;11]	6[4;9]	10[4;13]	7[4;14]	7[4;12]	7[2;12]
Mental well-being, points (mean ± SD)	66.6±23.1	69.3±15.5	72.3±14.5*	69.7±17.9	63.6±17.7	69.3±17.5	67.8±17.5	70.6±20.5*
Cognition, points (median, [IQR])	27[27;29]	29[28;30]*	29[28;30]*	29[28;30]*	28[27;29]	29[28;30]*	29[28;30]*	29[29;30]*
Physical activity (PAS2)	**(n=35)**	**(n=31)**	**(n=31)**	**(n=29)**	**(n=36)**	**(n=32)**	**(n=32)**	**(n=31)**
-Total physical activity, MET-hours/day, (mean ± SD)	39.9±5.1	39.1±4.8	39.7±6.1	38.7±4.4	38.8±4.9	40.5±4.2	40.4±4.6	39.3±5.3
-Sleep, hours/week, (mean ± SD)	52.2±6.7	55.1±8.3*	55.3±10.8*	53.8±7.8	50.8±9.3	52.1±8.6	52.7±9.4	51.8±7.8
-Sedentary behaviour, hours/week (mean ± SD)	39.9±15.3	42.1±17.9	42.2±20.4	42.6±14.8	46.6±19.8	39.6±17.3	38.3±17.0	43.7±20.0
-Light activity, hours/week (mean ± SD)	67.2±16.5	62.3±19.1	68.1±25.4	63.8±15.9	63.1±18.9	66.8±19.5	67.9±21.0	63.9±17.4
-Moderate activity, hours/week (median [IQR])	6[3;10]	6[2;9]	5[2;7]	4[2;10]	5[2;9]	7[4;10]	6[3;8]	5[2;10]
-Vigorous activity, hours/week (median [IQR])	0[0;2]	2[0;3]*,‡	2[0;4]*	1[0;3]	0[0;1]	1[0;2]	1[0;3]*	1[0;3]
Systolic, mmHg (mean ± SD)	149±21	144±18	142±17*	143±16	148±21	141±16*	139±14*	139±19*
Diastolic, mmHg (mean ± SD)	86±9	83±9*	82±9*	86±7	90±13	84±7*	84±9*	84±9*
BMI, kg/m^2 (mean ± SD)	27.4±4.4	27.4±4.3	27.6±4.6	27.8±5.0	25.9±3.7	25.3±3.6	25.5±3.6	25.2±3.5
Objective physical activity	**(n=30)**	**(n=29)**	**(n=30)**	**(n=28)**	**(n=31)**	**(n=30)**	**(n=31)**	**(n=29)**
Activity (including cycling, climbing stairs, running, and walking), hours/day (median [IQR])	1.26 [0.96;1.70]	1.07 [0.74;1.57]	1.10 [0.73;1.83]	1.28 [0.74;1.62]	1.43 [0.97;1.70]	1.32 [0.97;1.63]	1.36 [1.16;1.70]	1.47 [1.07;1.69]

(*Continued*)

Table 3 (*Continued*)

Variables	Intervention				Usual care			
	Baseline	Post-intervention assessment	6-months follow-up post-stroke	12-months follow-up post-stroke	Baseline	Post-intervention assessment	6-months follow-up post-stroke	12-months follow-up post-stroke
Stand/move around, hours/day (median [IQR])	3.41 [2.72;3.90]	3.69 [2.64;4.59]	3.45 [2.91;4.94]	3.92 [3.34;4.78]	3.37 [2.61;4.48]	3.55 [2.86;4.73]	3.60 [2.64;4.62]	3.75 [2.76;4.61]
Sedentary behaviour (including sitting/lying), hours/day (median [IQR])	19.1 [17.9;20.2]	18.4 [17.2;20.2]	19.2 [17.3;20.2]	18.4 [17.2;20.1]	19 [17.6;20.1]	18.7 [17.4;19.8]	18.5 [17.1;19.8]	18.6 [17.6;19.8]
Total steps/day (mean ± SD)	7270±3994	7506±3860	7372±4280	7731±3908	7989±2820	7863±2830	8221±2642	7736±2732

†Missing data on one patient due to surgical resection of cardiac myxoma.
*Statistically significant change within group from baseline.
‡Statistically significant change between groups.

interesting finding was that the significant increase in vigorous-intensity activity obtained during the intervention, was maintained at six months in the intervention group. Also, the usual care group reported a significant increase after the intervention period, which matched the level of vigorous-intensity activity on the intervention group at six months. This significant increase in vigorous-intensity activity seen in both groups was not maintained at the 12-months assessment, where both groups returned to baseline levels.

Other secondary outcomes as blood pressure, chronic stress, mental well-being, and cognition improved over time, with no difference between groups. These significant improvements within groups were seen at six months in the intervention group, and at 12-months in the usual care group, indicating that HIIT may speed recovery post stroke. The improvement in mental well-being was interesting and it may reflect a habituation to the life after stroke.

A limitation in our study was the relatively small sample size of 71 patients in the original study, and with only 59 patients available for follow-up after intervention. An inclusion of 100 patients was planned, but we experienced a low recruitment rate and had to stop due to time and finance. However, given the current data a further inclusion of 15 subjects would be unlikely to change outcomes. A low sample size could infer bias by indications, so only those interested in physical activity accepted inclusion and continued engagement in physical activity. An indication that this bias may be relevant to our study was that the included patients in general met the WHO recommended level of physical activity at baseline,[19] and thus were already more physically active than the general population. Not fulfilling the planned inclusion of 100 patients may have reduced chances to detect minor changes, and thus reduce generalizability. However, a trend in effect would have been expected and we had a low dropout-rate from three- to 12 months. For the reason of feasibility and safety when engaging in HIIT, we only included patients with lacunar stroke and minor stroke, hence the results may not apply to other stroke subtypes or severe stroke. Also, more men than women participated in the study which may raise concerns for generalizability. However, our study population reflects the general population of patients with stroke quite well i.e., higher incidence of stroke in younger men compared to aged-matched women.[37] Due to the early initiation of HIIT within three weeks of stroke, we considered the physical strain of testing VO_{2max} to be of too high risk of cardiovascular or physical complications. Instead, we used the submaximal GCT-TT, proven feasible in a similar group of patients, tested within a few weeks from a stroke.[26] For technical reasons we were unable to provide continuous heart rate monitoring during home-based exercise. Instead, we applied accelerometers recording physical activity for eight days at each assessment point

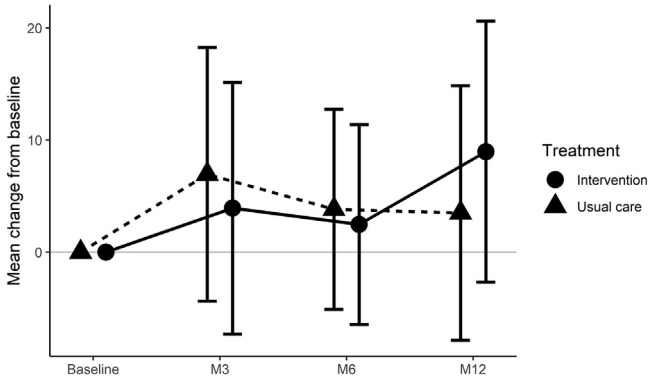

Fig. 2. *Change over time in cardiorespiratory fitness (measured by GCT-TT) for both groups*

No statistically significant differences were seen either between groups nor within groups, from baseline to any of the time points (post-intervention, 6- and 12-months follow-up).

GCT-TT: Graded cycling test with talk test. The x-axis shows the four assessment points: at baseline, post-intervention (M3), six-months follow-up (M6), and 12-months follow up (M12). The y-axis shows mean change in cardiorespiratory fitness given in Watts. Both groups were assessed at the same time points, but the estimates are jittered, to improve the illustration of the 95% confidence intervals.

together with self-reported diaries on physical activity. Though self-reporting questionnaires may introduce recall bias, or reflect a subconscious wish to meet external expectations, they reflected the practice of the patients and their mindset towards physical activity.

A major strength of this study was the randomized controlled design with blinded primary outcome assessments, and follow-up for one year. Furthermore, the choice of a home-based training scenario made training feasible for all patients.

Few studies have investigated the effect of early initiated HIIT on cardiovascular fitness and continued physical activity after stroke.[38] Of these, only three applied a randomized controlled study design.[39-41] In these randomized studies, the HIIT-intervention was initiated during a chronic stage (> six months) post-stroke and supervised individually using either a treadmill or a stationary bicycle. In our study the HIIT-intervention was performed at home in the sub-acute phase (< one-month post-stroke) on a stationary bicycle with additional motivational telephone calls, to make it less costly and to improve feasibility in clinical practice. A further strength of our study was our reporting of the one-year follow-up on cardiorespiratory fitness and stroke risk factors which is only done in few post-stroke exercise studies. A recent multicentre randomized controlled trial with one-year follow-up did not find improved VO_{2peak} 12 months after a HIIT-intervention compared to usual care in patients with chronic stroke.[42]

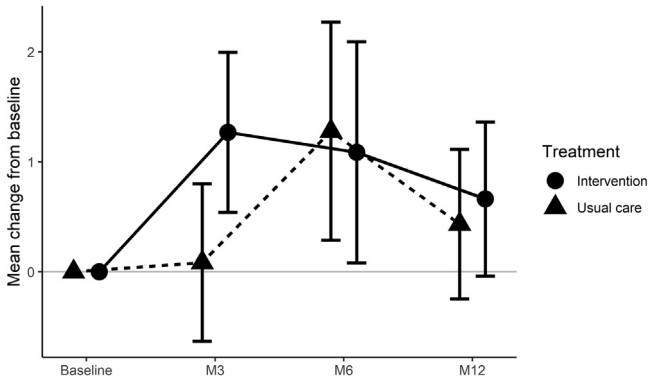

Fig. 3. *Change over time in vigorous-intensity activity (measured by PAS2) for both groups.*

Statistically significant increase between groups were seen from baseline to post-intervention in vigorous-intensity activity (p=0.02). Only a significant within group increase was seen in the intervention group from baseline to post-intervention (p=0.001). However, both groups increased significantly within groups from baseline to six months follow-up, (p=0.03 and p=0.012) intervention and usual care group, respectively, but no statistically significant difference between groups at six months follow-up (p=0.78). From baseline to 12-months follow-up, no statistically significant differences were seen either between groups (p=0.63) nor within groups p=0.06 and p=0.21 for intervention and the usual care group, respectively.

The x-axis shows the four assessment points: at baseline, post-intervention (M3), six-months follow-up (M6), and 12-months follow up (M12), and the y-axis shows mean change in time (hours/week). Both groups were assessed at the same time points, but the estimates are jittered, to improve the illustration of the 95% confidence intervals.

The fact that the usual care group did not increase their vigorous-intensity activity until after the intervention period could perhaps be explained by a wish to be loyal to the study design. Also, the engagement in physical activity post intervention may reflect that the patients acknowledge that exercise is important post stroke, or that the usual care group experienced a reduction of fatigue after the three-months follow-up. However, contamination induced by interaction between patients from the intervention and control group was unlikely due to the large catchment area of the hospital (400.000 inhabitants). The supervised tests of cardiorespiratory fitness may have reassured the usual care group that physical activity was safe to perform and thus increased their inclination towards engagement in vigorous-intensity activity. In support of the latter, the significant increase in the usual care group at six-months follow-up was partly achieved by five male patients with an exceptional increase in vigorous-intensity activity.

Though our intervention succeeded in engaging patients early in vigorous-intensity activity, it was not maintained 12-months post-intervention. This suggests that other approaches might be needed to keep the patients engaged in vigorous-intensity activity. These findings correspond to those previously reported in the ExStroke trial[15] and the recent INSPiRE-TMS trial[16] where repeated encouragements and verbal instructions in being physically active did not motivate patients to increase long-term physical activity after ischemic stroke.[15] Our results suggest that this patient group may need further prolonged physical guidance to continue training or different supportive actions. One such supportive action might be to involve a partner or a relative in the physical activity. A recent study reported on motivators for being physically active after hospital discharge for a minor stroke. The study found that patients were positive towards physical activity after hospital discharge, and they were motivated for local group exercise opportunities supervised by health professionals with knowledge of stroke. The most frequent barriers for patients to engage in physical activity were post-stroke fatigue, lack of energy and initiative, which should be considered when designing secondary prevention programs.[14] This high prevalence of post-stroke fatigue (30%) was previously confirmed in patients with minor stroke, both in early phase (three-months post-stroke) and in late phase (one-year post-stroke).[43] Another challenge which needs attention in secondary prevention programs for patients with minor stroke is the prevalence of post-stroke depression (31%).[44] However, we did not experience significant post-stroke depression symptoms in our study sample.

The observed reduction over time of pharmacologically modifiable risk factors such as blood pressure and lipids are likely to reflect the medical practice and patient compliance to medication post-stroke. The result cannot be concluded to reflect potential effects of the increased physical activity.

Several issues in non-pharmacological secondary stroke prevention need to be addressed. Firstly, how do we encourage patients with stroke to become and/or continue to be long-term physically active? Secondly, which intensity of activity is required to reduce subsequent cardiovascular disease, including stroke? Thirdly, there are still ongoing discussions on which exercise intervention is most efficient for secondary prevention of vascular disease in terms of recommended type of exercise, length of program, frequency, duration, and intensity of sessions.[45]

Cardiorespiratory training alone, and mixed cardiorespiratory- and resistance training, improve mobility and balance after stroke, allowing patients to perform activities of daily living such as walking and climbing stairs.[2] Studies investigating long-term benefits of physical activity with an intention to prevent stroke are warranted.

It is essential that future studies investigate strategies aiming at promoting physical activity. Identification of motivators and barriers for daily physical activity including ways to reduce sedentary behaviour seems highly relevant.

Conclusion

Early home-based high-intensity interval training in patients with lacunar stroke led to an immediate increase in self-reported vigorous-intensity activity that was maintained in the period after the intervention but returned to the baseline levels after 12 months. The usual care group experienced a similar, but delayed, increase in vigorous-intensity activity also followed by a return to baseline level after 12 months. Despite the observed periods of increased physical activity, no significant effects were seen for cardiorespiratory fitness at any time point in the intervention or usual care group. Future studies are required to investigate how to engage patients with stroke in long-term physical activity of vigorous intensity to increase cardiovascular health and potentially prevent deterioration of cardiovascular disease and recurrent cardiovascular events.

Ethical approval

The trial was approved by the Research Ethics Committee in the Capital Region of Denmark (Trial Registration number: H-15012371) and by the Danish Data Protection Agency (ID: HGH-2015-021). Furthermore, the study was registered at ClinicalTrials.gov in January 2016 (ID: NCT02731235), and all patients gave written informed consent prior to study enrolment.

Author Contributions

All the authors contributed to study conception and design whereas RSK and CK obtained the funding. RSK,

AV and CK drafted the manuscript, while all other authors reviewed the manuscript, provided comments and revisions, as well as read and approved the final manuscript.

Data availability

Data supporting the findings of this study are not publicly available because: according to The Danish Data Protection Agency, a general sharing of patient data is not allowed. Requests to access the datasets should be directed to Christina Kruuse, ckruuse@dadlnet.dk.

Declaration of Competing Interests

There are no conflicts of interest.

Acknowledgments: The authors thank the physiotherapists Signe Wildenskov, Tommy Olsen, Sus Ven, Mette Mou Garborg, and Gitte Sone Larsen for assisting with the cardiorespiratory fitness tests.

References

1. D'Isabella NT, Shkredova DA, Richardson JA, Tang A. Effects of exercise on cardiovascular risk factors following stroke or transient ischemic attack: a systematic review and meta-analysis. Clin Rehabil 2017;31(12):1561-1572.
2. Saunders DH, Sanderson M, Hayes S, Johnson L, Kramer S, Carter DD, et al. Physical fitness training for stroke patients. Cochrane Database Syst Rev 2020;3(3): Cd003316.
3. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45(12):3754-3832.
4. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet 2016;388(10046):761-775.
5. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol 2016;15(9):913-924.
6. Kolmos M, Christoffersen L, Kruuse C. Recurrent ischemic stroke—a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2021;30(8):105935.
7. Amarenco P, Lavallee PC, Labreuche J, Albers GW, Bornstein NM, Canhao P, et al. One-year risk of stroke after transient ischemic attack or minor stroke. N Engl J Med 2016;374(16):1533-1542.
8. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med 2016;375(1):35-43.
9. Crump C, Sundquist J, Winkleby MA, Sundquist K. Interactive effects of physical fitness and body mass index on risk of stroke: a national cohort study. Int J Stroke 2016;11(6):683-694.
10. Högström G, Nordström A, Eriksson M, Nordström P. Risk factors assessed in adolescence and the later risk of stroke in men: a 33-year follow-up study. Cerebrovasc Dis 2015;39(1):63-71.
11. Kurl S, Laukkanen JA, Rauramaa R, Lakka TA, Sivenius J, Salonen JT. Cardiorespiratory fitness and the risk for stroke in men. Arch Intern Med 2003;163(14):1682-1688.
12. Newitt R, Barnett F, Crowe M. Understanding factors that influence participation in physical activity among people with a neuromusculoskeletal condition: a review of qualitative studies. Disabil Rehabil 2016;38(1):1-10.
13. Nicholson S, Sniehotta FF, van Wijck F, Greig CA, Johnston M, McMurdo ME, et al. A systematic review of perceived barriers and motivators to physical activity after stroke. Int J Stroke 2013;8(5):357-364.
14. Krawcyk RS, Christoffersen LC, Danielsen AK, Kruuse C. Motivators for physical activity in patients with minor stroke: a qualitative study. Disabil Rehabil 2022 Feb 4:1-9. ahead of print (PMID 35119324).
15. Boysen G, Krarup LH, Zeng X, Oskedra A, Kõrv J, Andersen G, et al. ExStroke Pilot Trial of the effect of repeated instructions to improve physical activity after ischaemic stroke: a multinational randomised controlled clinical trial. BMJ 2009;339:b2810.
16. Ahmadi M, Laumeier I, Ihl T, Steinicke M, Ferse C, Endres M, et al. A support programme for secondary prevention in patients with transient ischaemic attack and minor stroke (INSPiRE-TMS): an open-label, randomised controlled trial. Lancet Neurol 2020;19(1):49-60.
17. Steen Krawcyk R, Vinther A, Petersen NC, Faber J, Hansen RH, Rostrup E, et al. Home-based aerobic exercise in patients with lacunar stroke: design of the HITPALS randomized controlled trial. Contemp Clin Trials Commun 2019;14:100332.
18. Steen Krawcyk R, Vinther A, Petersen NC, Faber J, Iversen HK, Christensen T, et al. Effect of home-based high-intensity interval training in patients with lacunar stroke: a randomized controlled trial. Front Neurol 2019;10:664.
19. Steen Krawcyk R, Vinther A, Petersen NC, Faber J, Rehman S, Iversen HK, et al. Self-reported physical activity and cardiovascular disease risk factors in patients with lacunar stroke. J Stroke Cerebrovasc Dis 2019;28(8):2168-2176.
20. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Int J Surg 2011;9(8):672-677.
21. Rosenberg GA, Wallin A, Wardlaw JM, Markus HS, Montaner J, Wolfson L, et al. Consensus statement for diagnosis of subcortical small vessel disease. J Cereb Blood Flow Metab 2016;36(1):6-25.
22. Adams Jr. HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24(1):35-41.
23. Govan L, Langhorne P, Weir CJ. Categorizing stroke prognosis using different stroke scales. Stroke 2009;40(10):3396-3399.
24. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40(9):922-935.
25. Foster C, Porcari JP, Ault S, Doro K, Dubiel J, Engen M, et al. Exercise prescription when there is no exercise test: the Talk Test. Kinesiology 2018;50(1):33-48.

26. Steen Krawcyk R, Vinther A, Caesar Petersen N, Kruuse C. Graded cycling test with Talk Test" is a reliable test to monitor cardiovascular fitness in patients with minor stroke. J Stroke Cerebrovasc Dis 2017;26(3):494-499.
27. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39(3):315-325.
28. Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the major depression inventory, using the present state examination as the index of diagnostic validity. J Affect Disord 2001;66(2-3):159-164.
29. Bech P, Olsen LR, Kjoller M, Rasmussen NK. Measuring well-being rather than the absence of distress symptoms: a comparison of the SF-36 mental health subscale and the WHO-Five Well-Being Scale. Int J Methods Psychiatr Res 2003;12(2):85-91.
30. Awata S, Bech P, Yoshida S, Hirai M, Suzuki S, Yamashita M, et al. Reliability and validity of the Japanese version of the World Health Organization-Five Well-Being Index in the context of detecting depression in diabetic patients. Psychiatry Clin Neurosci 2007;61(1):112-119.
31. Bergmann N, Ballegaard S, Holmager P, Kristiansen J, Gyntelberg F, Andersen LJ, et al. Pressure pain sensitivity: a new method of stress measurement in patients with ischemic heart disease. Scand J Clin Lab Investig 2013;73(5):373-379.
32. Ballegaard S, Petersen PB, Gyntelberg F, Faber J. The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study. Scand J Clin Lab Investig 2012;72(6):459-466.
33. Ballegaard S, Karpatschof B, Trojaborg W, Hansen AM, Magnusson G, Petersen PB. A simple and objective marker for stress. Scand J Clin Lab Investig 2009;69(6):713-721.
34. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-699.
35. Andersen LG, Groenvold M, Jorgensen T, Aadahl M. Construct validity of a revised physical activity scale and testing by cognitive interviewing. Scand J Public Health 2010;38(7):707-714.
36. Coffman CJ, Edelman D, Woolson RF. To condition or not condition? Analysing 'change' in longitudinal randomised controlled trials. BMJ Open 2016;6(12):e013096.
37. Giroud M, Delpont B, Daubail B, Blanc C, Durier J, Giroud M, et al. Temporal trends in sex differences with regard to stroke incidence: the Dijon Stroke Registry (1987-2012). Stroke 2017;48(4):846-849.
38. 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(8):868-878.
39. Boyne P, Dunning K, Carl D, Gerson M, Khoury J, Rockwell B, et al. High-intensity interval training and moderate-intensity continuous training in ambulatory chronic stroke: feasibility study. Phys Ther 2016;96(10):1533-1544.
40. Lau KW, Mak MK. Speed-dependent treadmill training is effective to improve gait and balance performance in patients with sub-acute stroke. J Rehabil Med 2011;43(8):709-713.
41. Pohl M, Mehrholz J, Ritschel C, Ruckriem S. Speed-dependent treadmill training in ambulatory hemiparetic stroke patients: a randomized controlled trial. Stroke 2002;33(2):553-558.
42. Gjellesvik TI, Becker F, Tjønna AE, Indredavik B, Nilsen H, Brurok B, et al. Effects of high-intensity interval training after stroke (the HIIT-Stroke Study): a multicenter randomized controlled trial. Arch Phys Med Rehabil 2020;101(6):939-947.
43. Kirchberger I, Wallner F, Linseisen J, Zickler P, Ertl M, Naumann M, et al. Factors associated with early and late post-stroke fatigue in patients with mild impairment. Results from the stroke cohort study Augsburg. Front Neurol 2022;13:852486.
44. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. Int J Stroke 2014;9(8):1017-1025.
45. Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, et al. Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database Syst Rev 2014;2014(4):CD001920.