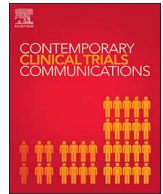




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Home-based aerobic exercise in patients with lacunar stroke: Design of the HITPALS randomized controlled trial

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ABSTRACT

Background: The effects of physical exercise in patients with lacunar stroke, seem promising in secondary prevention and only few studies have investigated the effect of high-intensity interval training in patients with lacunar stroke. This study will be investigating whether high-intensity interval training improves cardiovascular fitness as well as cognitive- and endothelial function and potentially attenuating the risk of recurrent stroke.

Methods: A randomized controlled trial evaluating 12 weeks of home-based, high-intensity interval training compared with usual care. The intervention group will be exercising 15 min a day, 5 days a week, for 12 weeks. Outcomes will be evaluated at baseline, three, six and twelve months post-stroke with 'The Graded Cycling Test with Talk Test' as the primary outcome registered as power output in Watts. Additionally, an annually register-based follow-up will be performed for 5 years from date of inclusion with a composite endpoint of cardiovascular disease or death. Secondary outcomes will be: physical activity, endothelial response, mental well-being, cognition, mood, fatigue, stress, and MRI scan.

Discussion: This study is going to show if early initiated home-based high-intensity interval training is feasible and effective in patients with lacunar stroke. A self-chosen aerobic exercise modality allows a realistic implementation of practice, together with greater chance of long-term adherence. A limitation of the study is that recruitment bias cannot be ruled out, as there may be a preferential enrolment of patients who are self-motivated to engage in exercise.

1. Introduction

Lacunar stroke accounts for one in four of all ischemic strokes [1], and it is associated with a three-fold increase in the risk of a new stroke and a high risk of cognitive decline and dementia [2]. Similar to other stroke subtypes, the risk of a recurrent stroke is increased by co-factors such as diabetes [2], hypertension, smoking [3], and physical inactivity [2]. Recurrent strokes are usually more debilitating, with worse prognosis and outcome, and a higher rate of discharge to long-term care facilities [4]. The current secondary prevention of recurrent stroke is antithrombotic, anticoagulant, antihypertensive and cholesterol reducing treatment in addition to non-pharmacological interventions and lifestyle changes. As the risk of recurrent stroke is between 3.7 and

6.7% within 90 days from stroke [5,6], secondary prevention including lifestyle modifications should be initiated promptly [7]. Physical activity is an important lifestyle modification to many co-morbidities [8]. Physical activity with improved aerobic fitness reduces lipids, blood pressure and weight, thus promoting improved cardiovascular health [9,10] with reduced morbidity and mortality [11]. Regular physical activity also helps minimize the cognitive deficits post stroke [12].

Studies on stroke survivors identifies sedentary behaviour after stroke [13,14], with activity levels below that of people with chronic diseases of musculoskeletal or cardiovascular origin [15]. The cause of the reduced physical activity is not fully understood as many patients with stroke are able to be more physical active but choose not to be [16]. This may represent a knowledge gap on exercise

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recommendations, fear of exercise inducing stroke, or lack of support in daily physical activities [17].

We hypothesize that implementing high-intensity interval training at home (defined as vigorous-intensity physical activity performed at ≥ 6 Metabolic Equivalent of Task (MET) [18]) within the first three weeks of a lacunar stroke will improve cardiovascular fitness, physical activity, cognition, endothelial response, and quality of life. Previous studies have shown that supervised high-intensity interval training in patients with stroke are feasible and effective in the late post-stroke phase [19]. Therefore, the aim of this study will be to compare aerobic change across a 3-month period of home-based high-intensity interval training compared with aerobic change in usual care. Furthermore, we are going to investigate changes in risk profile for a recurrent stroke with long-term follow-up on cardiovascular events.

2. Methods and analysis

The study will be a parallel, two-arm, randomized controlled trial. In addition to usual care (preventive medication and advice on self-managed life-style changes), the intervention group will be doing home-based high-intensity interval training during the first three months post stroke compared with only usual care. Eligible patients with recent (0–21 days) onset of symptoms of a lacunar stroke will be randomized to intervention or control group. Patients will be assessed post-intervention, and at follow-up (6 and 12 months post stroke). (See Fig. 1: work flowchart). Subsequently, the patients will be followed annually for five years after stroke using patient records, national registries and questionnaires evaluating numbers of vascular events or death. Furthermore, baseline data from this RCT will be constituting a cross-sectional study on self-reported pre-stroke physical activity and post-stroke health profile in patients with lacunar stroke.

2.1. Recruitment

All patients will be in-patients recruited consecutively from the stroke unit at Herlev Gentofte University Hospital, Copenhagen from January 1st, 2016 with a target of 100 included patients. Recruited patients for inclusion will be first episode lacunar stroke or patients with recurrent lacunar stroke with clinical symptoms and a corresponding ischemic lesion verified on MRI scan.

2.2. Participants

Lacunar stroke is defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST-criteria) [20] where the patients have one of the traditional clinical lacunar syndromes, with relevant brain stem or subcortical hemispheric lesion verified on CT scan or MRI scan. In the acute phase, the lesion has a diameter < 2 cm [21], no cerebral cortical dysfunction, no potential cardiac source for embolism and in case of arterial stenosis, occlusion should be $< 50\%$. During admission patients will be routinely examined with chest x-ray, continuous electrocardiogram (ECG-monitoring) for 48 h (for heart arrhythmias) and carotid artery stenosis screening (ultrasound).

Inclusion criteria will be symptoms of an acute lacunar stroke, either with corresponding acute lesion on MRI scan, or with a previous lacunar stroke on MRI scan (amendment 1, June 2016), age > 18 years, able to speak and read Danish, and be able to give informed consent. Exclusion criteria will be prior large artery stroke, symptoms or co-morbidities in the musculoskeletal system preventing exercise on a stationary bike, uncontrolled hypertension or diabetes, dyspnoea caused by heart or pulmonary disease, atrial fibrillation, carotid artery stenosis (occlusion $> 50\%$), aphasia or cognitive dysfunction interfering with the Talk Test.

2.3. Screening process and enrolment

Eligible patients will be identified by daily screening of medical records and they will be provided with written and oral information about the study. Informed consent will be obtained by the study coordinator and includes consent to collect and store biological specimens. After completion of the baseline assessment, the patients will be assigned to either intervention or control group. Personal information about the patients will be collected, maintained and stored to protect confidentiality before, during and after the trial. Only the study coordinator and physicians involved in the study will have access to the final trial dataset.

2.4. Randomization/blinding

The patients will be randomized consecutively into two groups: exercise intervention and usual care or usual care only, based on equal allocation with randomly varying block size. A computer-generated block-randomization (8 blocks of 10, mixed with 5 blocks of 4) will be administered by a research assistant not involved in the study, and unaware of patient assignment. Outcome assessor, data analysts and, study coordinator will be blinded to the randomization process. Sealed opaque envelopes made by the research assistant will be stored and administered by other personnel not involved in the study.

2.5. Outcome assessments

All outcome measures, except MRI scan, will be obtained at baseline (0–21 days post stroke), post-intervention, 6 and 12 months post stroke and subsequently registry-based outcomes will be obtained yearly (Table 1). The study will be reporting at the prespecified time-points with the same primary outcome (Power output from the Graded Cycling Test with Talk Test (GCT-TT)). The first reported time point (after baseline) is the post-intervention assessment, i.e. after 3 months, where we aim to investigate the acute effect of the intervention (home-based high-intensity interval training).

The subsequent follow-up assessments at 6 months and at 12 months will be reported together after the 12 months assessment to explore whether the intervention group has made sustainable lifestyle changes and kept the achieved exercise level post-intervention assessment. At the 12 months follow-up the explorative analysis on the MRI outcome changes will be done.

The primary outcome, is the change in power output registered in Watts (W) from the GCT-TT. It will be performed by assessors, not involved in the study and not performed in immediate association with the intervention. Prior to the study the assessors will be introduced, trained and calibrated in performing the GCT-TT (3 tests in healthy adults and 3 tests in patients with minor stroke) by the study coordinator.

Data from the secondary outcomes will be collected by the study coordinator with prior training in administering questionnaires and assessment tools. Data containing personal information will be collected, anonymized and stored to protect confidentiality. Data access will be limited to the study coordinator and physician involved in the study.

2.5.1. Primary outcome

The power output registered in Watts (W) from the GCT-TT will be the primary outcome measure.

The Talk Test (TT) in itself is a simple and valid estimate to evaluate submaximal exercise intensity [22–29] and it is responsive to measure changes in aerobic capacity following blood donation and aerobic training [25]. The Talk Test has previously been used in combination with various incremental exercise test protocols on treadmill [24,25,27–32] or a stationary bicycle [22,26,32]. We will use TT with the GCT protocol, which is a frequently used protocol in Denmark,

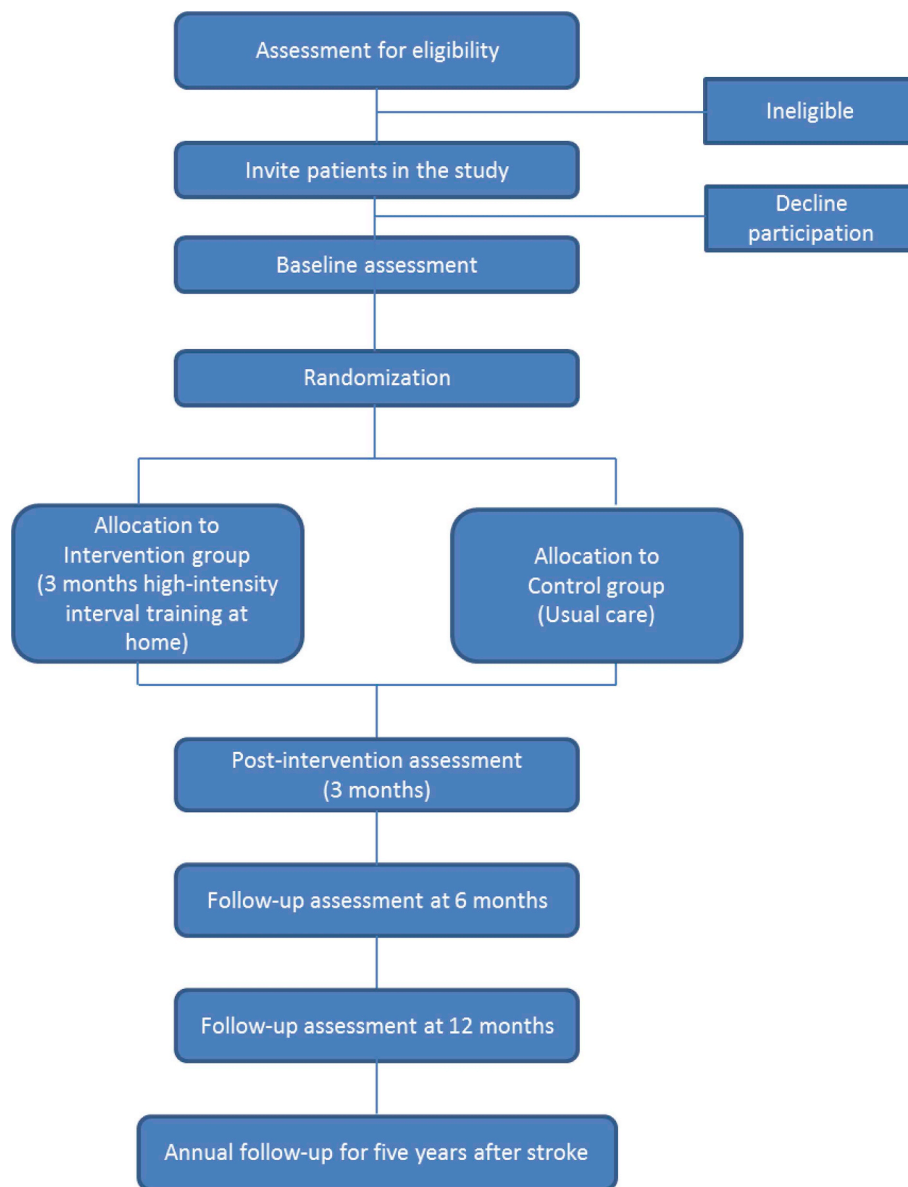


Fig. 1. HITPALS-trial, Work flowchart.

where the general population are accustomed to cycling. The GCT is performed on a stationary bicycle (Monark 928E-G3, Vansbro, Sweden) using a ramp protocol with a 15 Watt increase each minute [33]. During the last 10–15 s of each minute, the patients recite a standardised text passage, followed by the question: “are you able to speak comfortably?”. The patients can answer “yes”, “unsure” or “no”, and the test stops when the patient answers “no” (not able to speak comfortably). This point, identifies the highest possible exercise intensity where the patient can speak comfortably without feeling disturbed by increased breathing. A detailed test-protocol has previously been described [34].

The GCT-TT can be performed independently of the ability to assess the maximal heart rate (e.g. in case of atrial fibrillation or beta-blocker). Furthermore, it is easy and time effective to use, and it does not require expensive equipment. Also, the test is assessor-independent, as it is the patient who identifies the intensity level where he/she cannot speak comfortably. These qualities of the GCT-TT make it an attractive outcome measure in various rehabilitation settings. The GCT-TT has shown good reliability and minor measurement error in both patients with ischemic heart disease [35] and in patients with lacunar stroke [34]. The Standard Error of Measurement with 95% certainty

(SEM₉₅) in patients with lacunar stroke is: 12.9 Watt. Thus, a change of ≥ 12.9 W reflects a real change in power output beyond measurement error in a group of patients with lacunar stroke. For an individual patient with lacunar stroke, the Smallest Real Difference (SRD) is 18.3 Watt, indicating that a change of two steps in the incremental test protocol (30 Watt) represents a real clinical change.

2.5.2. Long-term follow-up (5 years)

Patients will be followed 5-years post-stroke using patient journal, registers (The Danish National Patient Registry and The Danish Stroke Registry) and questionnaires to evaluate number of incidence of cerebrovascular events (recurrent stroke) or death.

2.5.2.1. Secondary outcomes. Choices of secondary outcomes are based on an interest to monitor potential improvement in symptoms of stroke and risk factors for recurrent stroke. We also considered whether the questionnaire was validated in a stroke population and was available in Danish, and the total time spend on each outcome.

2.5.2.2. Endothelial function. Endothelial dysfunction is a known risk

Table 1
Outcome assessments.

Outcomes	Abbreviation/device	Function
Primary outcome		
Power output in Watts from the Graded Cycling Test with Talk Test	GCT with TT	Submaximal aerobic exercise test
Secondary outcomes		
Endothelial response	EndoPAT2000	Endothelial function
Physical Activity Scale	PAS2	Self-rated physical activity
Axivity	AX3	Accelerometer monitoring physical activity
Mental well-being	WHO-5 Well-Being Index	Self-reported mental well-being
Montreal Cognitive Assessment	MoCA	Assessment of cognitive function
Major Depression Inventory	MDI	Self-reported depression symptoms
Multidimensional Fatigue Inventory	MFI-20	Self-reported fatigue symptoms
Chronic stress	Ull-Meter	Objective measurement of the body and mind's state of stress
Vascular risk factors:		
Blood pressure (resting)	BP	Systolic and diastolic blood pressure
Blood samples	BS	Measure of total cholesterol/ high-density lipoprotein ratio, cardiovascular biomarkers, inflammatory biomarkers and endothelial biomarkers
Body Mass Index	BMI	Quantify the amount of tissue mass (muscle and fat)
MRI scan	MRI	Changes in brain structure after 12 months (regarding infarcts, white matter lesions, micro bleeds)

factor for cardiovascular diseases [36], hypertension [37], hypercholesterolemia [37], and stroke [38].

Endothelial function is measured by a non-invasive method determining the Peripheral Arterial Tonometry (PAT) by EndoPAT2000 (Itamar Medical Ltd, Caesarea, Israel). The PAT is measured by plastic probes that impart a uniform pressure to the distal two third of the index finger. The endothelial function estimates the changes in Pulse Wave Amplitude (PWA) and is registered as the Reactive Hyperemia Index (RHI). RHI is the post-to pre-occlusion signal ratio in the occluded arm compared to the same ratio in the control arm and corrected for baseline vascular tone of the occluded arm. A detailed test procedure is previously described [39]. A lower RHI-value is associated with impaired endothelial function [40]. A RHI-value > 1.67 is recommended as cut-off for normal endothelial function (abnormal function is ≤ 1.67), recommended by the EndoPAT2000-user manual. Furthermore, arterial stiffness is estimated using the Augmentation Index (AI) and based on computerized averaging and analysis of multiple pulse waveforms registered during baseline measurement on the occluded arm. AI register change in peak systolic pulse wave after baseline occlusion (%). Also, the heart rate-corrected Augmentation Index (AI@75) is measured at the heart rate of 75 beats per minute. A previous study investigating validation of repeated measurement of endothelial function in patients with acute stroke found good day-to-day reliability [39].

To reduce potential day-to-day variability, the assessment will be carried out in the morning and the patients will be asked to refrain from consuming any food or beverages after midnight. Assessment will be performed in an undisturbed, dark room with a room temperature of 21–24 °C. Before assessment the patient will relax in supine position for 25 min to reach cardiovascular steady state.

2.5.2.3. Physical activity. Physical inactivity is one of the major risk factors for stroke why it is relevant to explore [41]. Physical activity will be measured using a self-reported questionnaire; Physical Activity Scale version 2.1 (PAS2) [42] and objectively with accelerometers worn by the patient for a week at baseline, post-intervention and at 6 and 12 months, respectively.

PAS2 measures physical activity as daily hours and minutes of sleep, sitting, standing or walking, and heavy physical work, transportation to and from work, as well as TV-watching or reading. In addition, PAS2 measures weekly hours and minutes of light-intensity physical activity, moderate intensity activity, and vigorous-intensity activity [42]. Each of these domains correspond to a specific level of MET-intensity (The

Metabolic Equivalent of Task) [43], where 1 MET is the rate of energy expenditure while sitting at rest and corresponds to an oxygen uptake of 3.5 ml/kg of body weight per minute. Moderate-intensity activity refers to the physical activity performed at 3.0–5.9 METs and vigorous-intensity activity correspond to > 6 METs [18]. The total measurement of METs allows for indirect estimation of total physical activity during 24-h. The construct validity of the Physical Activity Scale has been validated in 342 Danish men and women aged 35–66 years [42].

2.5.2.4. Objective assessment of activity by accelerometer. Objective assessment of physical activity will be measured with a water resistant and wireless three-axis accelerometer, AX3 (Axivity, York, UK), recording with a frequency of 25 Hz. It will be fixed with double sided adhesive tape (VIP Tape, Skinlock International, Charleroi, Belgium), and sealed with a water-resistant patch (Fixomull[®] transparent, BSN medical Inc, Hamburg, Germany) anteriorly on the thigh. The position of the AX3 will be right medial thigh; midway between the hip and knee joint, orientated with the x-axis pointing downward, y-axis horizontally to the left, and z-axis horizontally forward. The accelerometer will be initialized for recording and data downloaded using manufacturer's software (Open Movement v.1.0.0.28). Data from the accelerometer will be analysed using Acti4, a custom made script in MATLAB (version R2013a) including a previously described algorithm to identify everyday physical activity types such as walking, running, cycling, climbing stairs, standing and sitting [44]. Activity patterns will be recorded for 8 days and 7 nights, including data from both weekdays and weekends. The AX3 is validated in healthy subjects with a high specificity and sensitivity to differentiate between the above-mentioned activities [44,45]. The monitor device will be set during patient assessments at the hospital and returned by mail using pre-paid envelopes. Furthermore, all patients will keep an exercise diary reporting type, amount (in minutes) and intensity of activity daily for 12 weeks.

2.5.2.5. Well-being. To evaluate well-being, we will be using the WHO-5 Well-Being Index. It is a short, self-rated questionnaire evaluating mental well-being [46]. It has adequate validity both as a screening tool for depression and as an outcome measure in clinical studies [46]. The WHO-5 Well-Being Index includes five positive statements on mental well-being over the last two weeks, with respondent answers distributed on a 6-point Likert-scale. The raw-score is calculated by summation and ranges from 0 to 25 (the higher the score the better mental well-being) and is often expressed as percentage of the maximal

Table 2
List of routine blood samples.

Category	Name of blood sample	Units
Hematology	Hemoglobin	mmol/L
	Leucocytes	$\times 10^9/L$
	Thrombocytes	$\times 10^9/L$
Electrolytes	P-Glucose	mmol/L
	P-Creatinine	$\mu\text{mol/L}$ mmol/L
	P-Potassium	mmol/L
	P-Sodium	mmol/L
Proteins	P-Albumin	g/L
	P-Reactive Protein (CRP)	mg/L
	P-Reactive Protein (HSCRP)	mg/L
Enzymes	P-Creatine	U/L
	P-Alanintransaminase (ALAT)	U/L
	P-Aspartatransaminase (ASAT)	U/L
Hemostasis	P-Coagulation factors (APTT)	S
	P-Coagulation factors (INR)	S
	Endocrinology	Glucose (HbA1c)
P-Thyrotropin (TSH)		$\times 10^{-3}\text{IU/L}$
Lipids		P-Cholesterol
	P-cholesterol (LDL)	mmol/L
	P-cholesterol (HDL)	mmol/L
	P-Triglyceride	mmol/L

P: plasma, U/L: units/litre, S: Seconds.

score [47]. To monitor changes in mental well-being, a relative (percentage) score change of 10% is used to indicate significant change [48]. The cut-off score indicating risk of depression or long-term stress is set to 50 points [49] while the average score for the Danish population is 69 points [47].

2.5.2.6. Cognition. The Montreal Cognitive Assessment (MoCA) is a brief screening tool designed to identify mild cognitive impairments. It assesses different cognitive domains: attention, concentration, executive functions, memory, language, visuospatial ability, conceptual thinking, calculations and orientation. The total score is 30 points and a score ≥ 26 is considered as normal [50]. The MoCA is valid and reliable in patients with lacunar stroke and white matter lesions [51].

2.5.2.7. Depression. The Major Depression Inventory (MDI) is a self-reported questionnaire for diagnosing and assessing depression [52]. The questionnaire includes twelve questions on how the patient has been feeling over the past two weeks. The response is given on a 6-point Likert-scale, where 0 corresponds to: "At no time" and 5 corresponds to "All the time". The maximum score is 50 points and the higher score the more severe the depression [52]. A score > 20 points indicates mild depression, while a score > 15 points indicates incipient depression [53].

2.5.2.8. Fatigue. Multidimensional Fatigue Inventory (MFI-20) is a 20-item self-report instrument evaluating five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [54]. Each dimension is covered by four questions and the responder indicates on a 5-point Likert-scale, to what extent the statement applies to him/her. Each dimension of fatigue is calculated on a score from 4 to 20, with higher scores representing increased fatigue [54,55]. We use the domain of general fatigue as a measure of overall fatigue as proposed in the original development of the scale [54].

2.5.2.9. Chronic stress. Chronic stress will be measured using an algometer (Ull-Meter[®]), an objective instrument measuring the pain threshold on the sternum, called pressure pain sensitivity (PPS) [56,57]. The algometer is the size of a whiteboard marker and is easy to use. The patient will be in a supine position, and for 5 s the Ull-Meter will be gradually pushed against the area identified as the most

sensitive point of the sternum. When the patient experiences discomfort, the pressure is stopped and the PPS is read on a scale from 30 to 100, with a cut-off point ≥ 60 , correlating with markers of a stress syndrome [58]. The result is blinded from the observer until the measurement has finished [56,57]. In both healthy people and patients with chronic disease such as ischemic heart disease, PPS is associated with several elements of the chronic stress syndrome: depression score, quality of life scores, and numbers of stress reactions [56–58]. Stress intervention studies aiming at reducing PPS have demonstrated clinically relevant reduction in several risk factors for ischemic heart disease and in healthy control subjects [59]. Furthermore, in a previous study on patients with ischemic heart disease, stress-reducing treatment aiming at reducing PPS demonstrated a concomitant decline in Major Depression Inventory (MDI) and an increase in mental well-being (WHO-5 Well-Being Index) [60].

2.6. Blood pressure

The blood pressure (systolic and diastolic pressure) will be measured following an overnight fast. With the patient in a supine position and after 5 min of rest, blood pressure will be measured with an automatic blood pressure monitor (Microlife[®] BP A100/Microlife[®] BP A3L Comfort, Widnau, Switzerland).

2.6.1. Blood samples

To evaluate possible endothelial dysfunction, inflammation and risk of cardiovascular event we hypothesize changes in endothelial biomarkers (Vascular endothelial growth factor (VEGF), vascular cell adhesion molecule 1 (VCAM-1), intercellular Adhesion Molecule 1 (ICAM-1), E-selectin), inflammatory biomarkers (Interleukin-6 (IL-6), tumour necrosis factor (TNF), high sensitivity C-reactive protein (hsCRP); lipoprotein(a) (LIPA)) and in cardiovascular biomarkers (pro-Adrenomedullin, pro-atrial natriuretic peptide and Copeptin); glucose metabolism. Furthermore, a battery of routine analyses will be performed on the day of examination (See Table 2: list of routine blood samples). The inflammatory biomarkers and endothelial biomarkers will be analysed according to the manufacturer's instructions, using commercially available kits from Mesoscale, Rockville, USA. (V-PLEX Plus human: IL-6 kit, TNF kit, ICAM-1 kit, VCAM-1 kit, VEGF kit, and E-selectin kit). The cardiovascular biomarkers will be analysed according to the manufacturer's instructions using commercially available kits and software from BRAHMS GmbH, Hennigsdorf, Germany. (KRYPTOR compact PLUS human: Pro-ADM kit, Pro-ANP kit, and copeptin kit). All blood samples will be collected during fasting state and stored at -80°C until analysis.

2.6.2. Body Mass Index

Information on body weight and Body Mass Index (BMI) will be acquired with a body composition monitor (OMRON HBF-500-E; Kyoto, Japan). The height will be measured in centimetres and entered in the body composition monitor together with sex and age.

2.6.3. Magnetic resonance imaging

Magnetic resonance Imaging (MRI) will be obtained at baseline and at 12 months post stroke at Herlev Gentofte University Hospital, Department of Radiology. Data is blinded for patient participation and stored in a secure departmental network system. The scanning protocol will consist of an initial set of anatomical scans (T1W, T2W, inversion recovery and FLAIR), that serve as basis for radiological assessment. Furthermore, a diffusion tensor imaging (DTI) sequence is acquired followed by an Arterial Spin Labelling sequence (ASL) to quantify tissue perfusion, two 3D T1W sequences at different flip angles (FA 7 and FA 20) to estimate the T1 time of the tissue and finally, a high spatial resolution dynamic contrast-enhanced sequence (DCE) will be used to gauge blood-brain barrier permeability. For the DCE sequence a single dose (0.2 ml/kg) of gadolinium (DOTAREM, Guerbet, France) will be

Table 3
Order and type of MRI-sequences.

Sequence order	MRI-sequence	Purpose	MRI parameters
1	T1W 3D gradient seq. (GRE).	First seq. merely for planning purposes	TR/TE (ms) 25/1.68
2	(sagittal – S)		Voxel (mm) 1 × 1 × 6
3	Inversion recovery with 3D GRE		TR/TE 6.9/1.68
4	acquisition (S)		Voxel 1.1 × 1.1 × 1.1
	T2W spin echo (SE) seq. (axial – Ax)		TR/TE 3000/80
	T1W GRE (Ax)		Voxel 0.5 × 0.5 × 4
			TR/TE 288/4.6
			Voxel 0.5 × 0.5 × 4
5	Fluid Attenuated Inversion Recovery (FLAIR)	For delineation of white matter lesions, hyperintensities corresponding to leukoaraiosis (Ax)	TR/TE 11000/2800
6	Diffusion Tensor Imaging seq. (Ax)	For 3D indication of neural bundles and DWI assistance in the radiological assessment	Voxel 0.5 × 0.5 × 4
7	Pseudo-continuous Arterial Spin Labelling (PCASL) (Ax)	For the assessment of tissue perfusion (resting-state CBF)	TR/TE 11000/2800
			Voxel 0.5 × 0.5 × 4 b = 0,1000, 32 directs
			TR/TE 4040/17
			Voxel 2.75 × 2.75 × 5
			Label distance 90 mm, post delay 1600 ms
8	T1W 3D GRE with flip angle (FA) 7	Used to give a rough estimate of the tissue T1 time, which is a parameter in the perfusion model (Patlak) applied to the DCE data	TR/TE 25/1.88
9	(Ax)		Voxel 0.75 × 0.75 × 4
	T1W 3D GRE with FA 20 (Ax)		TR/TE 25/1.92
			Voxel 0.75 × 0.75 × 4
10	DCE	To gauge blood-brain barrier permeability.	TR/TE 25/2.2
		A single dose (0.2 ml/kg) of gadoterate meglumine is injected at the rate of 3 ml/s	Voxel 0.75 × 0.75 × 4
			Dyn. scan time 55.7 s
			No. of dyn. 24

injected at the rate of 3 ml/s. All scans will be performed on a 3T clinical system (Ingenia, Philips Healthcare, Best, The Netherlands) using a 32 element headcoil. The total scanning time per patient is 50 min at each time-point (See Table 3 for the order and type of MRI-sequences).

2.6.4. Other data collection

The following data will be retrieved from the patient record or the patient: co-morbidity, symptoms, medication, smoking- and drinking habits, educational level and occupation.

3. Intervention

Physical activity is one of the modifiable risk factors for stroke [41] and should be initiated early after stroke. Many patients with stroke are not familiar with regular physical exercise hence the intervention must be simple, motivating, not time-consuming, realistic and easy to perform during daily living routines. To describe the intervention, Consensus on Exercise Reporting Template (CERT) has been used [61].

In addition to usual care, the intervention group will perform unsupervised high-intensity interval training at home, 15 min a day, five days a week for twelve weeks. High-intensity interval training is performed in short bouts of rather high, but not maximal-intensity cardiovascular exercise alternating with short periods of low intensity exercise [62]. The 15 min of high-intensity interval training corresponds to the WHO global recommendations on physical activity for health. WHO recommend at least 75 min of aerobic physical activity at vigorous-intensity throughout a five-day week. The exercise modality will be tailored under the condition that it is aerobic, and the intensity will reach the level where the patient is not able to speak comfortably.

All patients will attend a motivational talk with the study coordinator at baseline with the purpose to encourage lifestyle behavioural changes. The patients will also be introduced to an exercise catalogue, presenting various modes of aerobic exercise. The catalogue will consist of: brisk walking/Nordic walking, stair stepping, knee lifting, outdoor cycling/cycling on a stationary bike, and running – all exercise modalities aim to elicit an increase in heart rate.

To ensure an easy accessible exercise modality, all patients will be offered to borrow a stationary bicycle (Kilberry® Magnetic Bike JC-950, Proteus Sports Inc, Linkou Township, Taiwan) to use at home. The bike monitors: time (minutes), distance (kilometre), energy expenditure

(calories), Speed (kilometres per hour), resistance (level 1–9), heart rate (pulse) and cadence (rounds per minute), all of which are used for motivation purpose. Furthermore, all patients will be provided with a pocket sized, laminated standardised text passage (cue card), which they will use to find the exercise intensity.

Duration of intervals and mode of recovery vary between different study-protocols [63] thus, we have chosen an easy, realistic and clinical implementable exercise program. The aerobic exercise will be performed in intervals. Two minutes of warm-up (at self-chosen level) followed by 3 min of high-intensity interval training at the intensity where the patient cannot speak comfortably any longer (corresponding to the answer “No” in the Talk Test). This will be followed by 2 min of moderate intensity, followed by 3 min of high intensity and so forth for 15 min, each session. The feasibility of each exercise modality on how to achieve out-of-breath level (e.g. TT) was tested in four healthy individuals prior to study planning. Before patients start exercising the study coordinator will visit the patients at home to introduce the exercise program, including an introduction to the Talk Test (how to reach the right exercise intensity and how to progress the exercise program). The Talk Test will determinate the starting level of the intervention and the patients will progress the intensity of the exercise modality (e.g. when using the bicycle by increasing the work load or the cadence) as they improve throughout the exercise program. At every session patients will be encouraged to reach an exercise-intensity level where they can no longer speak comfortably. For further motivation and control of completion of work-out, the patients will be contacted by phone, text message or e-mail on a weekly basis to ensure compliance. The weekly call(s) will also be an opportunity to identify equipment malfunction or adverse events. Adverse events will be documented in the case report form (CRF). All exercise sessions will be tracked by an individual exercise diary to ensure adherence. Adherence to the study in general is encouraged by highlighting the importance of both groups in producing valid study results.

3.1. Control group

The control group will receive usual care, consisting of individually adapted preventive medication and advice on lifestyle changes. Furthermore, they will be asked to resume their usual level of physical activity and to track their activity in an individual exercise diary, documenting type-, time and intensity of exercise.

Both control- and intervention group will be offered a control visit with a nurse at the preventive outpatient clinic (Herlev Gentofte University Hospital) within 2 months from stroke onset. The purpose of the visit is to evaluate blood pressure and cholesterol level and to ensure appropriate medication. Furthermore, the purpose is to provide advice on lifestyle changes regarding; food, smoking and alcohol intake.

3.1.1. Adverse events/Discontinuing

Adverse events will be monitored and registered during the study. Discontinuation will be considered if a patient is either unexpectedly readmitted to the hospital or emergency department for a disease other than stroke, or if they experience severe symptoms such as musculoskeletal pain, fracture or cardiac symptoms of any kind.

4. Statistical analyses

4.1. Sample size and statistical analyses

A sample size calculation based on the primary outcome (Graded Cycling Test with Talk Test) was conducted with a standard deviation (SD) of 37 Watt and a meaningful difference of 23 Watt. 84 patients (42 in each group) are needed with a power of 80% and a two-tailed α of 0.05. With dropouts taken into account (15%), we will aim to include 100 patients in total.

Data, from patients with complete outcome data, will be analysed according to the group to which they were randomized, independent of patient compliance. All available data for each patient will be included in the analysis, also if the patient does not have all observations. Missing data will not be imputed. The estimated treatment effects will be calculated by the constrained longitudinal data analysis (cLDA) which will give unbiased result under missing at random. In case of one patient is missing all observations post baseline, the patient will be excluded in the analysis. An explorative analysis will be conducted to test for interaction effects on the following parameters; sex, age, family status, and education. The rationale for performing this analysis is that no prior studies have explored the effect of these parameters on exercise efficacy in lacunar stroke. A general linear mixed effect model with baseline constrains will be used for both primary and secondary outcomes using constrained longitudinal data analysis (cLDA) [64]. No other independent variables will be included in the analysis. The effect-size will be calculated as the visit/treatment interaction at the specified visit and given as model estimates of mean difference with 95% Confidence Interval (CI). Changes over time within each assessment day on all relevant outcomes will be performed with linear mixed effect model and patients who do not show up at the assessment visits will be counted as missing at that specific assessment point.

The 5-year outcomes, survival and cerebrovascular events, will be analysed using time-to-events method. The Kaplan-Meier method will be used for descriptive survival statistics and drawing survival curves, and the Cox proportional hazard model will be used for analysing confounders of survival and cardiovascular events. The long-term analysis will be explorative as we do not expect it to have adequate power as the study is not powered to detect differences on long-term outcome between treatment groups. Data from all included patients in the baseline assessment will be used, except from the patients lost to follow-up.

The analysis of the MRI scans will be performed with Statistical Parametric Mapping (SPM) with a paired design.

Before analysis, all variables will be controlled for normal distribution, and transformed if needed. Non-parametric testing will be used if data diverge from normal distribution after transformation. All tests will be two-sided and p-values < 0.05 will be considered significant. Data will be analysed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics 22 (Armonk, NY, USA) or a similar software. Statistical planning is conducted in cooperation with a biostatistician.

4.2. Ethics approval and consent to participate

The study has been approved by The Danish Data Protection Agency (ID: HGH-2015-021) and adhere to the Danish law of data protection. Furthermore, the study has been approved by the Research Ethics Committee in the Capital Region of Denmark (H-15012371) according to the Declaration of Helsinki of 1964, as revised in 2008. The study is registered at ClinicalTrials.gov (NCT02731235, registered Jan. 2016) and the reporting adheres to the SPIRIT 2013 statement [65]. All participants will provide written informed consent before enrolment. Results of this study will be published in peer-reviewed international journals and they will be presented at international and national conferences.

Protocol H-15012371 (version 4.0, June 2016) amendment 1 has been modified to allow an extended inclusion period from 0 to 21 days (previously 0–7 days). In addition, inclusion of patients with recurrent lacunar stroke, with clinical symptoms and a corresponding ischemic lesion on MRI will be allowed. Amendment 2 (version 5.0, June 2017) will be allowing inclusion from two other stroke units in the Capital Region of Copenhagen due to low recruitment rate. The article describes protocol version 5.0 from June 6th. 2017.

5. Discussion

The aim of this study will be to report results on an early aerobic exercise intervention carried out in the home environment of the patients. Firstly, this study will investigate whether it is possible to engage patients in physical activity early after stroke. Secondly, it will investigate whether it is feasible and safe for patients with lacunar stroke to do high-intensity interval training in their home environment and to explore their adherence to exercise on a regular basis for twelve weeks. Thirdly, we will monitor the long-term effects of the intervention on cerebrovascular events and death (5 year).

If the intervention turns out to be feasible and effective, this study will potentially contribute to establishing recommendations on exercise programs and guidelines for patients with lacunar stroke. It will also be interesting to explore whether there is a difference of having encouraging phone calls on a weekly basis (intervention group) or the physical assessments in itself at the post-intervention assessment (control group) are sufficient. Furthermore, it will be interesting to explore, at six and twelve-months follow-up, how many patients have kept doing exercise on regular basis. This will provide us with information on how easy/difficult it is to integrate physical activity as a routine in daily living after lacunar stroke.

A strength of this study will be that patients can choose their preferred modality of aerobic exercise, as long as they exercise with an intensity where they are unable to speak comfortably. With a self-chosen exercise modality, the chances of long-term adherence will potentially be higher. The home-based intervention will allow training to occur at times which are suitable for the patient, just as it eliminates limitations associated with transport to training facilities. As all patients will be assessed post-intervention using GCT-TT on a stationary bicycle, the free choice of exercise modality might be a potential bias. It has been suggested that submaximal exercise thresholds such as ventilatory threshold (VT) occur at a relatively lower exercise intensity during incremental exercise tests using unfamiliar exercise modalities – i.e. runners reach VT at a lower percentage of VO_{2max} during cycling than running [66]. Consequently, it could be expected that patients who choose to exercise on stationary bicycles might perform better on the GCT-TT compared with patients who choose to run.

To ensure a safe exercise intensity post stroke a continuous ECG-recording for 48 h will be performed during hospitalization. Furthermore, the patients will be completing their first aerobic exercise test at the hospital in a safe environment together with an experienced physiotherapist. Both actions should help making the patients feel safe when exercising at home. Another strength is the relatively large

sample size used which will allow the finding of the study to be generalized to other patients suffering from a lacunar stroke.

A limitation of the study will be the monitoring of physical activity for one week only rather than the entire exercise period. Another limitation is not being able to monitor the exercise intensity with heart rate monitors. A smaller pilot study has shown that when recording heart rate with ECG-electrodes for more than 3–5 days, the risk of developing eczema on the chest was high, rendering poor quality data. The use of commercially available heart rate monitors will be a challenge as the study population are elderly with potential cognitive deficits. Secondly, the current commercially available heart rate monitors have a limited battery life and a limited memory capacity. Therefore, we anticipate that the data quality will be too low if patients are unable to comply with correct use of equipment that needs frequent recharging. Instead, patients will record the amount of exercise in a diary. A possible bias may be that only patients intended to engage in exercise will choose to participate in the study. If this influences the activity of the control group, it could diminish the difference in outcome measures between the groups. This study will contribute information about the use of early high-intensity interval training in patients with lacunar stroke. Furthermore, we test the hypothesis that exercise can increase cardiovascular fitness and endothelial function and as a result, slow progression of vascular diseases and potentially prevent recurrent stroke.

Trial registration number

This study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02731235, registered January 2016).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All the authors contributed to the study conception and design. RSK and CK contributed to obtain funding. RSK, AV and CK drafted the manuscript. All authors reviewed the manuscript, provided comments and revisions as well as read and approved the final manuscript.

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References

- [1] M.S. Dhamoon, R.R. Sciacca, T. Rundek, R.L. Sacco, M.S. Elkind, Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study, *Neurology* 66 (5) (2006) 641–646.
- [2] S.E. Vermeer, T. Den Heijer, P.J. Koudstaal, M. Oudkerk, A. Hofman, M.M. Breteler, Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study, *Stroke* 34 (2) (2003) 392–396.
- [3] P.A. Nyquist, J.I. Barzilay, Really small vascular disease of the brain, *Neurology* 78 (2) (2012) 82–83.
- [4] G.P. Samsa, J. Bian, J. Lipscomb, D.B. Matchar, Epidemiology of recurrent cerebral infarction: a medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost, *Stroke* 30 (2) (1999) 338–349.
- [5] P. Amarenco, P.C. Lavallee, J. Labreuche, G.W. Albers, N.M. Bornstein, P. Canhaio, et al., One-year risk of stroke after transient ischemic attack or minor stroke, *N. Engl. J. Med.* 374 (16) (2016) 1533–1542.
- [6] S.C. Johnston, P. Amarenco, G.W. Albers, H. Denison, J.D. Easton, S.R. Evans, et al., Ticagrelor versus aspirin in acute stroke or transient ischemic attack, *N. Engl. J. Med.* 375 (1) (2016) 35–43.
- [7] J. Burn, M. Dennis, J. Bamford, P. Sandercock, D. Wade, C. Warlow, Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project, *Stroke* 25 (2) (1994) 333–337.
- [8] J. Chalmers, N. Chapman, Challenges for the prevention of primary and secondary stroke: the importance of lowering blood pressure and total cardiovascular risk, *Blood Press.* 10 (5–6) (2001) 344–351.
- [9] R.J. Adams, M.I. Chimowitz, J.S. Alpert, I.A. Awad, M.D. Cerqueria, P. Fayad, et al., Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: a scientific statement for healthcare professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association, *Circulation* 108 (10) (2003) 1278–1290.
- [10] B. Fuentes, J. Gallego, A. Gil-Nunez, A. Morales, F. Purroy, J. Roquer, et al., Guidelines for the preventive treatment of ischaemic stroke and TIA (I). Update on risk factors and life style, *Neurologia* 27 (9) (2012) 560–574.
- [11] S. Prabhakaran, J.Y. Chong, Risk factor management for stroke prevention, *Continuum* 20 (2) (2014) 296–308.
- [12] P. Duncan, S. Studenski, L. Richards, S. Gollub, S.M. Lai, D. Reker, et al., Randomized clinical trial of therapeutic exercise in subacute stroke, *Stroke* 34 (9) (2003) 2173–2180.
- [13] N. Gebruers, C. Vanroy, S. Truijen, S. Engelborghs, P.P. De Deyn, Monitoring of physical activity after stroke: a systematic review of accelerometry-based measures, *Arch. Phys. Med. Rehabil.* 91 (2) (2010) 288–297.
- [14] T. West, J. Bernhardt, Physical activity in hospitalised stroke patients, *Stroke Res. Treat.* 2012 (2012) 813765.
- [15] M.C. Ashe, W.C. Miller, J.J. Eng, L. Noreau, Older adults, chronic disease and leisure-time physical activity, *Gerontology* 55 (1) (2009) 64–72.
- [16] D. Rand, J.J. Eng, P.F. Tang, J.S. Jeng, C. Hung, How active are people with stroke?: use of accelerometers to assess physical activity, *Stroke* 40 (1) (2009) 163–168.
- [17] G. Banks, J. Bernhardt, L. Churilov, T.B. Cumming, Exercise preferences are different after stroke, *Stroke Res. Treat.* 2012 (2012) 890946.
- [18] WHO, Global Recommendations on Physical Activity for Health, © World Health Organization, Geneva, Switzerland, 2010, p. 60.
- [19] J. Crozier, M. Roig, J.J. Eng, M. MacKay-Lyons, J. Fung, M. Ploughman, et al., High-intensity interval training after stroke: an opportunity to promote functional recovery, cardiovascular health, and neuroplasticity, *Neurorehabilitation Neural Repair* 32 (6–7) (2018) 345–356.
- [20] H.P. Adams Jr., B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, 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* 24 (1) (1993) 35–41.
- [21] G.A. Rosenberg, A. Wallin, J.M. Wardlaw, H.S. Markus, J. Montaner, L. Wolfson, et al., Consensus statement for diagnosis of subcortical small vessel disease, *J. Cerebr. Blood Flow Metabol.* 36 (1) (2016) 6–25.
- [22] J.A. Rodriguez-Marroyo, J.G. Villa, J. Garcia-Lopez, C. Foster, Relationship between the talk test and ventilatory thresholds in well-trained cyclists, *J. Strength Condit Res.* 27 (7) (2013) 1942–1949.
- [23] P.T. Recalde, C. Foster, K. Skemp-Arit, et al., The “Talk Test” as a simple marker of ventilatory threshold, *SAJSM* 9 (2002) 5–8.
- [24] T.J. Quinn, B.A. Coons, The Talk Test and its relationship with the ventilatory and lactate thresholds, *J. Sports Sci.* 29 (11) (2011) 1175–1182.
- [25] C. Foster, J.P. Porcari, J. Anderson, M. Paulson, D. Smaczny, H. Webber, et al., The talk test as a marker of exercise training intensity, *J. Cardiopulm Rehabil Prev* 28 (1) (2008) 24–30 quiz 1–2.
- [26] R. Zanettini, P. Centeleghe, C. Franzelli, I. Mori, S. Benna, C. Penati, et al., Validity of the talk test for exercise prescription after myocardial revascularization, *Eur J Prev Cardiol* 20 (2) (2013) 376–382.
- [27] C.A. Brawner, M.A. Vanzant, J.K. Ehrman, C. Foster, J.P. Porcari, A.J. Kelso, et al., Guiding exercise using the talk test among patients with coronary artery disease, *J. Cardiopulm Rehabil* 26 (2) (2006) 72–75.
- [28] C. Cannon, C. Foster, J.P. Porcari, The talk test as a measure of exertional ischemia, *Am J Med Sports* 6 (2004) 52–57.
- [29] S.A. Voelker, C. Foster, J.P. Porcari, K.M. Skemp-Arlt, G. Brice, R. Backes, Relationship between the talk test and ventilatory threshold in cardiac patients, *Clin. Exerc. Physiol.* 4 (2) (2002) 120–123.
- [30] M. Dehart-Beverly, C. Foster, J. Porcari, D. Fater, R. Mikat, Relationship between the talk test and ventilatory threshold, *Clin. Exerc. Physiol.* 2 (2000) 3–38.
- [31] C. Foster, J.P. Porcari, M. Gibson, G. Wright, J. Greany, N. Talati, et al., Translation of submaximal exercise test responses to exercise prescription using the Talk Test, *J. Strength Condit Res.* 23 (9) (2009) 2425–2429.
- [32] R. Persinger, C. Foster, M. Gibson, D.C. Fater, J.P. Porcari, Consistency of the talk test for exercise prescription, *Med. Sci. Sports Exerc.* 36 (9) (2004) 1632–1636.

- [33] T. Okura, K. Tanaka, A unique method for predicting cardiorespiratory fitness using rating of perceived exertion, *J. Physiol. Anthropol. Appl. Hum. Sci.* 20 (5) (2001) 255–261.
- [34] R. Steen Krawczyk, A. Vinther, N. Caesar Petersen, C. Kruuse, “Graded cycling test with talk test” is a reliable test to monitor cardiovascular fitness in patients with minor stroke, *J. Stroke Cerebrovasc. Dis.* 26 (3) (2017) 494–499.
- [35] S.G. Nielsen, L. Buus, T. Hage, H. Olsen, M. Walsoe, A. Vinther, The graded cycling test combined with the talk test is reliable for patients with ischemic heart disease, *J. Cardiopulm Rehabil Prev* 34 (4) (2014) 276–280.
- [36] T. Heitzer, T. Schlinzig, K. Krohn, T. Meinertz, T. Munzel, Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease, *Circulation* 104 (22) (2001) 2673–2678.
- [37] N.M. Hamburg, J. Palmisano, M.G. Larson, L.M. Sullivan, B.T. Lehman, R.S. Vasan, et al., Relation of brachial and digital measures of vascular function in the community: the Framingham heart study, *Hypertension* 57 (3) (2011) 390–396.
- [38] J.P. Cooke, The endothelium: a new target for therapy, *Vasc. Med.* 5 (1) (2000) 49–53.
- [39] A.S. Hansen, J.H. Butt, S. Holm-Yildiz, W. Karlsson, C. Kruuse, Validation of repeated endothelial function measurements using EndoPAT in stroke, *Front. Neurol.* 8 (2017) 178.
- [40] N.M. Hamburg, M.J. Keyes, M.G. Larson, R.S. Vasan, R. Schnabel, M.M. Pryde, et al., Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study, *Circulation* 117 (19) (2008) 2467–2474.
- [41] M.J. O'Donnell, S.L. Chin, S. Rangarajan, D. Xavier, L. Liu, H. Zhang, et al., Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study, *Lancet* 388 (10046) (2016) 761–775.
- [42] L.G. Andersen, M. Groenvold, T. Jorgensen, M. Aadahl, Construct validity of a revised Physical Activity Scale and testing by cognitive interviewing, *Scand. J. Publ. Health* 38 (7) (2010) 707–714.
- [43] B.E. Ainsworth, W.L. Haskell, M.C. Whitt, M.L. Irwin, A.M. Swartz, S.J. Strath, et al., Compendium of physical activities: an update of activity codes and MET intensities, *Med. Sci. Sports Exerc.* 32 (9 Suppl) (2000) S498–S504.
- [44] J. Skotte, M. Korshoj, J. Kristiansen, C. Hanisch, A. Holtermann, Detection of physical activity types using triaxial accelerometers, *J. Phys. Activ. Health* 11 (1) (2014) 76–84.
- [45] J.S.I. Ingebrigtsen, C. Christiansen, S. Jorgen, C. Hanisch, et al., Validation of a commercial and custom made accelerometer-based software for step count and frequency during walking and running, *J. Ergon.* 3 (Issue 2) (2013).
- [46] C.W. Topp, S.D. Ostergaard, S. Sondergaard, P. Bech, The WHO-5 Well-Being Index: a systematic review of the literature, *Psychother. Psychosom.* 84 (3) (2015) 167–176.
- [47] P. Bech, L.R. Olsen, M. Kjoller, N.K. Rasmussen, 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.* 12 (2) (2003) 85–91.
- [48] J.E. Ware Jr., The status of health assessment 1994, *Annu. Rev. Public Health* 16 (1995) 327–354.
- [49] S. Awata, P. Bech, S. Yoshida, M. Hirai, S. Suzuki, M. Yamashita, 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, *Psychiatr. Clin. Neurosci.* 61 (1) (2007) 112–119.
- [50] Z.S. Nasreddine, N.A. Phillips, V. Bedirian, S. Charbonneau, V. Whitehead, I. Collin, et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, *J. Am. Geriatr. Soc.* 53 (4) (2005) 695–699.
- [51] A. Wong, Y.Y. Xiong, P.W. Kwan, A.Y. Chan, W.W. Lam, K. Wang, et al., The validity, reliability and clinical utility of the Hong Kong Montreal Cognitive Assessment (HK-MoCA) in patients with cerebral small vessel disease, *Dement. Geriatr. Cognit. Disord.* 28 (1) (2009) 81–87.
- [52] P. Bech, N.A. Rasmussen, L.R. Olsen, V. Noerholm, W. Abildgaard, The sensitivity and specificity of the major depression inventory, using the present state examination as the index of diagnostic validity, *J. Affect. Disord.* 66 (2–3) (2001) 159–164.
- [53] P. Bech, *Clinical Psychometrics*, 2nd ed., Wiley-Blackwell, 2012, p. 216.
- [54] E.M. Smets, B. Garssen, B. Bonke, J.C. De Haes, The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue, *J. Psychosom. Res.* 39 (3) (1995) 315–325.
- [55] T. Watt, M. Groenvold, J.B. Bjorner, V. Noerholm, N.A. Rasmussen, P. Bech, Fatigue in the Danish general population. Influence of sociodemographic factors and disease, *J. Epidemiol. Community Health* 54 (11) (2000) 827–833.
- [56] N. Bergmann, S. Ballegaard, P. Holmager, J. Kristiansen, F. Gyntelberg, L.J. Andersen, et al., Pressure pain sensitivity: a new method of stress measurement in patients with ischemic heart disease, *Scand. J. Clin. Lab. Invest.* 73 (5) (2013) 373–379.
- [57] S. Ballegaard, P.B. Petersen, F. Gyntelberg, J. Faber, The association between pressure pain sensitivity, and answers to questionnaires estimating psychological stress level in the workplace. A feasibility study, *Scand. J. Clin. Lab. Invest.* 72 (6) (2012) 459–466.
- [58] S. Ballegaard, B. Karpatschof, W. Trojaborg, A.M. Hansen, G. Magnusson, P.B. Petersen, A simple and objective marker for stress, *Scand. J. Clin. Lab. Invest.* 69 (6) (2009) 713–721.
- [59] S. Ballegaard, P.B. Petersen, G.S. Harboe, B. Karpatschof, F. Gyntelberg, J. Faber, The association between changes in pressure pain sensitivity and changes in cardiovascular physiological factors associated with persistent stress, *Scand. J. Clin. Lab. Invest.* 74 (2) (2014) 116–125.
- [60] N. Bergmann, S. Ballegaard, P. Bech, A. Hjalmarsen, J. Krogh, F. Gyntelberg, et al., The effect of daily self-measurement of pressure pain sensitivity followed by acupuncture on depression and quality of life versus treatment as usual in ischemic heart disease: a randomized clinical trial, *PLoS One* 9 (5) (2014) e97553.
- [61] S.C. Slade, C.E. Dionne, M. Underwood, R. Buchbinder, B. Beck, K. Bennell, et al., Consensus on exercise reporting template (CERT): modified Delphi study, *Phys. Ther.* 96 (10) (2016) 1514–1524.
- [62] M. Buchheit, P.B. Laursen, High-intensity interval training, solutions to the programming puzzle. Part II: anaerobic energy, neuromuscular load and practical applications, *Sports Med.* 43 (10) (2013) 927–954.
- [63] M. Kolmos, R.S. Krawczyk, C. Kruuse, Effect of high-intensity training on endothelial function in patients with cardiovascular and cerebrovascular disease: a systematic review, *SAGE Open Med* 4 (2016) 2050312116682253.
- [64] C.J. Coffman, D. Edelman, R.F. Woolson, To condition or not condition? Analysing ‘change’ in longitudinal randomised controlled trials, *BMJ Open* 6 (12) (2016) e013096.
- [65] A.W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gotsche, K. Krleza-Jeric, et al., SPIRIT 2013 statement: defining standard protocol items for clinical trials, *Ann. Intern. Med.* 158 (3) (2013) 200–207.
- [66] G.P. Millet, V.E. Vleck, D.J. Bentley, Physiological differences between cycling and running: lessons from triathletes, *Sports Med.* 39 (3) (2009) 179–206.