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Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users – Protocol for a randomized controlled trial

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Cover Letter

Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users – Protocol for a randomized controlled trial

Version: 1.0. Date: 20.05.2020.

Dear Madam/Sir,

We hereby submit this protocol manuscript for consideration for publication in BMJ Open because we think this study protocol is relevant to the focus of your journal.
This research will determine if upper-body rowing, complying with the new exercise training guidelines (30 minutes of moderate-to-vigorous intensity aerobic exercise, three times a week), is feasible and effective in reducing cardiometabolic risk in the spinal cord injured population. The results from this study will therefore provide novel information that can inform future intervention studies in spinal cord injured individuals. Recruitment of participants are planned to be commenced in September 2020.

On behalf of all authors, I, as a corresponding author, hereby declare that 1) the submitted manuscript have not been published elsewhere or are not being considered for publication elsewhere; and 2) the research reported will not be submitted for publication elsewhere until a final decision has been made as to its acceptability in the BMJ Open.

Yours sincerely
Rasmus Kopp Hansen, PhD student, MSc

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Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users – Protocol for a randomized controlled trial

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ABSTRACT

Introduction

Cardiovascular and metabolic diseases are a growing concern for spinal cord injured (SCI) individuals. Physical inactivity contributes to cardiometabolic morbidity and mortality in the SCI population. However, previous studies have shown mixed results regarding the effects of exercise on cardiometabolic risk factors in SCI individuals. This discrepancy could be influenced by insufficient exercise stimuli. Recent guidelines recommend 30 minutes of moderate-to-vigorous intensity aerobic exercise, three times a week, for improvement in cardiometabolic health in SCI individuals. However, to date, no studies have implemented an exercise intervention matching the new recommendations to examine the effects on cardiometabolic risk factors. Therefore, the primary objective of this study is to determine the effects of 12-weeks of wheelchair user-modified upper-body rowing exercise on both traditional (constituents of the metabolic syndrome) and novel (e.g. vascular structure and function) cardiometabolic risk factors in SCI manual wheelchair users.

Methods and analysis

A randomized controlled trial will compare 12-weeks of upper-body rowing exercise, 30 minutes three times per week, with a control group continuing their normal lifestyle. Outcome measurements will be performed immediately before (baseline), after 12 weeks of training (post), and 6 months after the termination of the intervention period (follow up). Outcomes will include inflammatory and metabolic biomarkers determined from venous blood (with serum fasting insulin as primary outcome), body composition, arterial blood pressure, cardiorespiratory fitness level, brachial artery vascular structure and function, and autonomic nervous system function.

Ethics and dissemination

This trial is reported to the Danish Data Protection Agency (J.nr. 2019-899/10-0406) and approved by the Committees on Health Research Ethics in The North Denmark Region (Journal-nr. N-20190053). The principal investigator will collect written informed consent from all participants prior to inclusion. Irrespective of study outcomes, the results will be submitted to peer-reviewed scientific journals for publication.

Trial registration number

NCT04390087.

ARTICLE SUMMARY

Strengths and limitations of this study

- The frequency, duration and intensity of the exercise intervention follows recently published exercise recommendations for SCI individuals.
- This study uses a randomized controlled design to examine the effects of a novel exercise modality on both traditional and novel cardiometabolic risk factors.
- The exercise modality (upper-body rowing) includes not only an aerobic component, but also an element of resistance training for the posterior shoulder region, potentially ameliorating shoulder pain.
- Lack of control of food intake is a study limitation.

INTRODUCTION

Spinal cord injured (SCI) wheelchair users are placed at the lowest end of the fitness continuum [1]. Thus cardiovascular disease and metabolic dysfunction is a growing concern in this population [2,3]. In recent years, cardiovascular disease has emerged as the leading cause of mortality in chronic SCI individuals [4]. Factors contributing to high cardiometabolic morbidity and mortality in the SCI population are sedentary lifestyle and low physical activity level [5], and the ensuing negative influence on body composition, reflected by lower fat-free mass and larger amount of adipose tissue [6]. Explanations for the adoption of a sedentary lifestyle are multifactorial, but studies have identified intrapersonal and socio-environmental physical activity barriers in SCI wheelchair users [7–9]. Some barriers such as the intrapersonal barriers of lack of time[10] or energy[11] identified by individuals with mobility disabilities are consistent with those reported in the non-disabled population. Other barriers are specific to the mobility disabled individuals, such as organizational or structural barriers (e.g. lack of accessible fitness centers[7] and adaptive exercise equipment[8]) and community built environment barriers[12]. Consequently, new approaches to support the initiation and perseverance of physical activity in this population are required.

The majority of previous exercise intervention studies have used isolated aerobic exercise, often in the form of arm-cranking exercise [13]. These studies have demonstrated improvements in traditional risk factors for cardiometabolic diseases, such as high-density cholesterol (HDL-C) [14], fasting insulin [15], and indices of insulin resistance [16], whereas the effects on arterial blood pressure [17], blood lipids (e.g. low-density cholesterol (LDL-C) and triacylglycerol) are inconclusive [15,18,17]. Moreover, the effects of exercise interventions on body composition are generally lacking [19]. The explanation for the lack of an exercise effect on some of these risk factors is not clear, but could be related to insufficient volume [15,17] or intensity [19] of exercise, performed with limited amount of skeletal muscle mass.

Notably, in able-bodied individuals, the exercise-induced risk reduction in cardiovascular diseases cannot be fully explained by traditional risk factors (i.e. there is a risk factor gap) [20]. As a consequence, studies have started to focus on the effects of exercise on changes in the vascular wall [20]. It is known that dysfunction of the vascular endothelium occurs at the very early phases of atherosclerosis [21]. For instance, flow-mediated dilation (FMD), a non-invasive measure of nitric oxide (NO) dependent endothelial function [22], is a strong predictor of future cardiovascular events [23]. In addition, carotid intima media thickness (IMT), a measure of vessel wall thickness [24] has shown to be associated with future vascular events, such as the occurrence of stroke and myocardial infarction [24]. Accumulating evidence in able-bodied demonstrates beneficial effects of exercise on structural and functional adaptations of the vasculature [25]. However, little is known about the effects of exercise on the vasculature in the SCI population.

Reductions in femoral artery (lower body) diameter occurs rapidly in response to extreme inactivity, as observed within three weeks off acquiring a SCI [26]. De Groot et al. [27] found similar FMD in the brachial

artery among untrained SCI when compared to able-bodied individuals, however when FMD was normalized to the shear stress stimulus, the dilation response was reduced in the SCI group, indicating some degree of endothelial dysfunction in this population [28]. Other observational studies have demonstrated both larger conduit artery diameter and blood flow in the subclavian artery [29], and larger brachial diameter [27] in wheelchair athletes compared to non-athlete able-bodied controls. Together these findings indicate that remodeling of the vasculature also occurs in response to regular exercise in SCI wheelchair users. However, the causal link between adaptations of the upper body arteries and repetitive exercise stimulus in SCI is not fully established. Therefore, the relationship between exercise and vascular remodeling in wheelchair users needs to be determined through controlled exercise studies. A recent experimental study consisting of supervised aerobic exercise (20min, twice per week), adhering to the earlier exercise guidelines for SCI adults [30], was successful in improving measures of cardiorespiratory fitness and muscle strength [31]. Yet, Zepetnek et al. [17] demonstrated that this exercise paradigm (20min, twice per week) did not improve markers of cardiovascular disease risk, including carotid IMT and brachial FMD. Recent guidelines recommend at least 30 min of moderate-to-vigorous intensity aerobic exercise, three times per week in order to improve cardiometabolic health in SCI wheelchair users [32], suggesting that insufficient exercise stimuli may explain the lack of vascular adaptations in the study by Zepetnek et al. [17]. Notably, to date, no studies have examined the effects of the updated exercise guidelines (30 min of moderate-to-vigorous intensity aerobic exercise, three times per week) on vascular adaptations in SCI manual wheelchair users.

While isolated aerobic exercise, via arm-cranking or wheelchair ergometry, evokes positive effect on cardiorespiratory fitness, these modalities/types of exercises fail to address the importance of strengthening the posterior shoulder musculature of the upper-extremity [33]. In addition, these modalities use repetitive contractions of the shoulder musculature engaged in daily wheelchair propulsion activities, thereby increasing the risk of developing shoulder pain [34–36]. Studies have reported high prevalence of shoulder pain in long-term wheelchair users [37,38], which prevents these individuals from engaging in physical activity [39]. As wheelchair users rely on their upper-extremities for most daily activities, upper-extremity pain must be prevented or limited to preserve function, independence and quality of life (QOL) [16,40]. Indeed, health related QOL is lower in SCI adults compared with the able-bodied population [41,42]. The development of shoulder pain has been suggested to occur due to chronic overuse, shoulder strength imbalances between anterior and posterior musculature, postural changes and impingement syndrome [43–45]. Considering the general need for strong upper extremities to bear weight during different transfer tasks [46], to propel wheelchair [47], and to reach overhead levels [48], the inclusion of resistance training in exercise training paradigms seems prudent. One modality that combines aerobic and resistance components is rowing [49]. Specifically, it has been shown that wheelchair user-modified upper-body rowing ergometry challenges the cardiovascular system comparable to arm-cranking [34]. Additionally, upper-body rowing mirrors the muscle activation observed during traditional resistance training for the scapular retractors [50]. Earlier research has demonstrated beneficial effects of

resistance training of the posterior shoulder and scapular retractor musculature on shoulder pain [40,48,51]. Thus, the use of upper-body rowing ergometry may evoke positive effects on both cardiometabolic health and shoulder pain, the latter through alterations in posterior vs. anterior upper-body muscle strength balance. However, to date, no studies have implemented upper-body rowing ergometry as exercise modality in manual wheelchair users.

Objectives

The primary objective of this study is to determine the effects of 12-weeks of wheelchair user-modified upper-body rowing on both traditional (insulin resistance, obesity, dyslipidemia (including low HDL-C and elevated triglycerides, and blood pressure) and novel (inflammatory status, autonomic nervous system function, vascular structure and function, and cardiorespiratory fitness level) cardiometabolic risk factors in SCI manual wheelchair users. As secondary objectives, we will investigate the effects of the exercise intervention on free-living physical activity, shoulder pain, indices of QOL, and feasibility of the intervention.

METHODS AND ANALYSIS

Study design

A randomized controlled trial designed to determine the effects of 12 weeks of exercise training on cardiometabolic risk, indices of QOL, and shoulder pain, will be conducted in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [52]. The trial is registered as a controlled trial (NCT04390087). The study overview is presented in Figure 1. After giving written informed consent to participate in the study, participants will undergo baseline testing, after which they will be randomly assigned to either a control group or an exercise group (allocation ratio, 1:1), stratified for age and gender. Randomization will be conducted using a computer-generated random number sequence (https://www.randomizer.org/). Outcome measurements will be performed immediately before (baseline), after 12 weeks of training (post), and 6 months after the termination of the intervention period (follow up). This approach allows for assessment of the short term effects of exercise training as well as any residual effects from the training intervention on cardiometabolic risk, shoulder pain, indices of QOL, and free-living physical activity (i.e. leisure-time physical activity and activities of daily living [53]).

Participants

Inclusion criteria

Men and women; aged 18-65 years; chronic SCI (≥1 year since injury); individuals with sufficient sparing of arm function to participate in upper-body rowing (i.e. as a minimum excluding individuals with complete SCI at or above C5); using a manual wheelchair as a primary tool for mobility. Volunteers will be asked to

self-report SCI level and completeness and to provide a copy of the part of their medical records that confirm injury level and American Spinal Injury Association (ASIA) impairment scale classification before any measurements are commenced. As part of the screening, participants will also be asked to indicate smoking habits, known medical issues, diseases or use of medication that could affect metabolism (e.g. statins or metformin) or the cardiovascular system (e.g. diuretics, beta blockers, or angiotensin-converting enzyme inhibitors).

Exclusion criteria

Individuals who regularly engage in >150 min/week of moderate-to-vigorous intensity physical activity; have received a cortisone injection in the shoulder within the last four months; have had shoulder injury within the previous year; known medical issues (urinary tract infections, cardiovascular contraindications for exercise testing, and pressure sores); diagnosed diabetes or any other disease that may limit the ability to perform exercise.

Recruitment

Participants will be recruited through notices at Aalborg University, websites seeking volunteers for research studies (e.g., www.forsog.dk), organizations related to disability and SCI, including the Spinal Cord Injured in Denmark organization, physician clinics, wheelchair manufacturing company (Wolturnus A/S) and local community groups. Information on websites, social media, posters, flyers will be used to reach potential participants. This kind of participant recruitment can be considered passive since the participants have to choose to react on the study information[54]. This approach increases the risk of over representing individuals who are interested in the research area[54]. Considering this risk of selection bias, physician clinic visits from the principal investigator (i.e. active recruitment) will be used as an additional strategy to reach potential participants. For this study, 30 participants will be recruited. The sample size is based on the effect size (Cohen *d*: -0.69) for changes in fasting insulin after 6 weeks of arm-cycling exercise [15]. With a power of 0.9, and an alpha level of 0.05, 20 participants in total are required to detect a significant change. To account for drop-outs during the 12 week intervention, as well as potential drop-outs in the control group, 30 participants will be included in the project, with n=15 allocated to the control and exercise group, respectively.

Intervention

Exercise group

Volume, intensity and frequency of the intervention is based on recent exercise recommendations for SCI individuals [32]. Consequently, the training will be performed for 30 min, 3 times per week with moderate-to-vigorous intensity, with at least one rest day between sessions. Low compliance rate is a general issue in SCI exercise studies [55]. Compared with continuous exercise, interval-based exercise have been reported to elicit higher enjoyment in SCI individuals [56], which may increase exercise compliance. Considering this difference

between continuous and interval-based exercise, the target duration of 30 min will be reached through accumulation of 5-min bouts (up to 6 bouts), with 1-2 min of rest between each bout. Due to the training status of the participants, it is expected that some participants will not be able to exercise for 30 min with the intended intensity. Accordingly, exercise duration will be tailored to each participant's physical capacity [57] by gradually increasing the duration (i.e. the number of 5-min bouts) over the weeks towards the targeted 30 min (i.e. six * 5-min bouts). Exercise intensity will be prescribed based on rating of perceived exertion (RPE) corresponding to 12-15 on the 'Borg 6-20 RPE Scale [58,59]. The validity of using RPE to control moderate and vigorous exercise intensity has been demonstrated in SCI individuals [60]. During the first visit, participants will be familiarized with the RPE scale [61] and receive detailed instructions on the use of RPE and how to rate the overall exertion based on an integration of central and peripheral sensations of effort [60]. Some controversy exists about the validity of using overall RPE to monitor exercise intensity [61,62], as the relationships between overall RPE and objective physiological markers such as oxygen consumption (VO_2), heart rate (HR) and ventilation (VE) in SCI individuals have been questioned [62]. This have led some researchers to use a differentiated RPE scale that distinguishes between central (cardiorespiratory sensations) and peripheral (peripheral working limbs) sensations [63]. However, the current evidence does not indicate greater validity for differentiated RPE compared with overall RPE [61], and therefore overall RPE will be used to guide exercise intensity.

Each training session will consist of aerobic exercise performed on a wheelchair-modified upper-body rowing ergometer (Concept 2, Morrisville, Vermont, USA). Due to the pulling motion of the upper-body during rowing, this modality also includes a component of resistance exercise [49]. The modification of the ergometer is made by separating it into two parts using an Adapt2row[1], allowing the participants to sit in their wheelchair while performing upper-body rowing. Wedges will be positioned under the rear wheels to keep the wheelchair in place. Further, in case of SCI related insufficient innervation of torso musculature, straps will be wrapped around the back of the wheelchair and around the trunk of the participant, thereby securing the participant to the wheelchair. A pilot study [34] has provided promising results regarding the feasibility of using adaptive upper-body rowing exercise in the SCI population. Participants will be asked to empty their bladder before each training session. Average power output (W) will be recorded during each exercise session to monitor training load and quantify progress in work capacity.

All exercise sessions will be supervised by the principal investigator, who is an exercise physiologist, or by sport science students to ensure proper assistance and guidance of the participants. Everyone involved in supervision will be thoroughly instructed in how to supervise correct exercise technique, and they will receive general knowledge about SCI and wheelchair use. To allow for some flexibility regarding scheduling conflicts, participants will have opportunity to exercise 2-4 days per week, with a target of 3 days per week.

[1] http://www.adapt2row.com/

That is, in case of a missing session one week, an additional training session can be included the following week. However, to secure adequate recovery, no more than four training days per week will be allowed. The intervention will be terminated after 12 weeks, irrespective of any missing training sessions.

Control group

The participants allocated to the control group will be asked to maintain their normal lifestyle throughout the intervention period. When the 6-months follow-up testing has been terminated, the control group will receive information about the exercise guidelines and the benefits of physical activity. Additionally, if requested, the principal investigator will organize contact to facilities where participants in the control group can perform adapted rowing.

Main trial day protocol

The experimental procedures will be similar at baseline, post intervention, and at follow-up 6 months later. To account for within-day variation, the procedures will be performed at the same time of day for each participant. Participants will arrive at the exercise laboratory at Aalborg University for testing. Participants will be asked to refrain from any strenuous exercise (>24 h), caffeine, alcohol, polyphenols, vitamin C, and supplements known to affect the cardiovascular system (>12 h), and attend in a fasted (>6 h) state. [64] Any smokers must abstain from smoking for >6 h prior to each visit [64]. If participants are taking medication, a wash-out period of at least 4-5 times the half-life of the drug (typically 24-48 h) will be used. If a drug cannot be withdrawn due to health issues, testing will be performed after a consistent time period after intake, as recommended for studies examining vascular function [64,65]. On trial days, participants will receive a standardized snack (energy bar) after completion of the FMD measurement. Participants will be asked to empty their bladder before any testing is commenced, and are allowed to drink water ad libitum during the test days.

INSERT FIGURE 1

Blood collection procedure

After an overnight fast (i.e. ≥ 10 hours of fasting), participants will have approximately 20 mL blood drawn from a peripheral vein. Blood samples will be aliquoted and stored at -80^0 at the Department of Clinical Biochemistry, Aalborg University Hospital, until analyses. Blood samples will be analyzed for indicators of cardiometabolic health (markers of glucose homeostasis, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and prothrombotic risk) as well as inflammatory markers (pro- and anti-inflammatory markers). Blood sampling will be conducted within a week prior to commencing the intervention (baseline), between 36 and 60 hours after the last exercise session (post) to minimize any effects from the last exercise session, and 6 month after the termination of the intervention (6-months follow-up).

Outcome measures

Primary outcome

The primary outcome is fasting insulin, since it is one of the hallmarks of the metabolic syndrome [66,67], and has shown to be modifiable with exercise training in SCI individuals [15].

Secondary key outcomes

Arterial blood pressure (BP) and resting heart rate (HR)

After resting for 10 min, participants will have their resting systolic and diastolic BP and HR measured with an automated BP monitoring device (OMRON M6, OMRON Healthcare, Hoofddorp, Netherlands). Measurements will be performed twice, with participants in sitting position. The lowest values will be used for further analyses.

Body composition

Participants will have their body mass measured while sitting in their wheelchair (wearing light clothing) using a platform wheelchair scale (Detecto ® 6550 wheelchair scale, Webb City, MO, USA). Body mass will be derived by subtracting the weight of the wheelchair from the total mass and rounded to the nearest 0.1 kg [68]. Supine height (cm) will be measured in supine position using non-elastic tape. For participants with contractures precluding stretching of the legs, length will be measured in segments from heel to top of the skull [69]. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (m^2). Waist circumference and waist-to-hip circumference ratio will be used as a surrogate for visceral adiposity [68–70]. Participants will have their waist and hip circumference measured in supine position following a deep expiration. Waist and hip circumference will be measured immediately below the lowest rib [69] and widest part of the trochanters [70], respectively. For all circumference measurements, the tape will be placed directly on the skin with the participants arms by the side [69]. Anthropometric measures will be taken in duplicate (height, waist and hip circumference), rounded to the nearest 0.1 cm and reported as the mean. If the difference between the first and second measure is >0.1 cm, a third measure will be obtained. [69]

Autonomic nervous system function

Increasing evidence suggest that autonomic dysfunction accentuates the risk for adverse cardiovascular events [71]. Individuals with SCI are prone to autonomic disturbances as a consequence of disruption to the spinal cord [72], placing them at increased risk for autonomic related cardiovascular diseases. Participants will be equipped with a 4-lead surface electrodes on their chest and have their electrocardiogram (ECG) recorded during 5 min of quiet rest. Heart rate variability analyses of the ECG will be used to assess autonomic function [71,73]..

Vascular structure and function

After a rest period of 10-15 min in a quiet and darkened room, vascular structure and function will be evaluated non-invasively using ultrasonography (LOGIQ S8 XDclear, GE Healthcare) following recent guidelines on assessment of conduit [64,74] and resistance [65] vessel function. Conduit artery structure will be determined in the common carotid artery (CCA) and brachial artery (BA) with B-mode echoes using a 10 MHz multifrequency linear assay ultrasound probe. Measures of CCA and BA structure will be reported as intima media thickness (IMT) (mm), lumen diameter (mm), and wall-to-lumen ratio. The B-mode image will be optimized by changing depth and resolution, and will be kept constant between study visits.

To assess BA and resistance vessel function, endothelial dependent flow-mediated dilation (FMD) and reactive hyperemia will be determined by cuff occlusion followed by re-perfusion [22]. First, participants will have their baseline BA diameter measured for a period of 30 s. Then, a cuff placed distally on the forearm (i.e. distal to the ultrasound probe) will be inflated for 5 min up to a pressure that exceeds systolic BP by >50 mmHg. After 5 min, the cuff will be deflated and post-deflation diameter and blood velocity will be continuously recorded for 3 min [64]. For determination of FMD, both absolute (mm) and relative (%) change in diameter from baseline to post-deflation will be calculated. Given the importance of shear stress as the stimulus for the FMD response [75], continuous and simultaneous measurement of pulse-wave velocity (Doppler) and diameter (B-mode) using duplex ultrasound will be performed. This allows for an estimation of the shear stress stimuli through the calculation of shear rate, which then can be used to normalize the FMD response [76]. Because the error of the insonation estimation increases exponentially with angles >60° [77], an insonation angle of ≤60° will be used, with the sample volume adjusted to cover the total width of the vessel.

Resistance vessel function will be determined by the magnitude of the reactive hyperemic response to cuff-induced ischemia. Several measures obtained from the reactive hyperemic response will be reported, including absolute blood flow (calculated based on the diameter derived cross sectional area and blood velocity) and velocity, peak change in blood flow, and blood flow area under the curve (AUC) across the post-deflation time period.

Although related, the measure of reactive hyperemia mirrors the magnitude of downstream resistance artery dilation, whereas FMD represent conduit artery dilation [65].

To ensure that the same part of the CCA and BA will be insonated across study visits, anatomical landmarks will be identified and recorded together with a photo of the insonation sites. All insonation settings (including sample volume, insonation angle, and recording time) and occlusion procedure (including cuff-position, pressure and duration) will be held consistent within participants across study visits. For standardization, the same investigator will perform all measurements and all analyses (blinded to the identity of the data).

Metabolic and inflammatory profile

The metabolic and inflammatory profile will be assessed via measures of glycemic control (fasting glucose, long-term blood glucose (HbA1c, glycosylated hemoglobin), homeostatic model assessment of insulin resistance (HOMA-IR)), lipid profile (HDL-c, LDL-c, total cholesterol and triglycerides (TG)), pro-inflammatory (C-reactive protein (CRP), interleukin (IL) 6, tumor necrosis factor-alpha), anti-inflammatory (IL-10, IL1RA)), prothrombotic (PAI-1), markers of NAFLD (hepatic enzymes (alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST)), growth differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21)).

Cardiorespiratory fitness level

Cardiorespiratory fitness level will be determined through an incremental arm-cranking test to exhaustion, with peak oxygen consumption (VO_{2peak}) as the outcome measure. The placement of the ergometer (Monark 881E, Vansbro, Sverige) will be adjusted such that the participants shoulder joint is aligned with the crank axis with the elbows slightly bend. Participants will be equipped with a HR monitoring belt (Suunto Ambit3 Run; Suunto, Vantaa, Finland) and a face mask, connected to an online open-circuit metabolic cart. The cart (JAEGER, Vyntus CPX, Carefusion) will be calibrated to known volumes and gas concentrations according to manufactural guidelines. After a 1-min warm-up with zero resistance, the test begins with an individualized starting load (5-90W) [78] with increases in work load (5 or 10W) every minute [79] until volitional fatigue, defined as an inability to maintain cadence above 55 rounds per minute (rpm) [78]. The individual starting load and increment size will be chosen based on training history and anticipated physical capacity, with the aim of reaching exhaustion within 8-12 minutes at a cadence of 60-70 rpm [79,80]. Breath-by-breath VO_2 and carbon dioxide output (VCO_2), and HR will be measured continuously throughout the test. VO_{2peak} will be reported in both absolute ($l\ O_2 \cdot min^{-1}$) and relative ($ml\ O_2 \cdot kg^{-1} \cdot min^{-1}$) terms, and defined as the highest 30-s average during the test, with the corresponding HR reported as HR_{peak}. The highest workload that is achieved for ≥30-s will be reported as PO_{peak}. Participants will be asked to indicate RPE (Borg 6-20 scale) during the last 15-s of each minute. On test cessation, participants will gradually cool-down for 5-min, while their BP will be measured immediately before and after this recovery period.

Other secondary outcomes

Shoulder pain

The prevalence and severity of shoulder pain will be assessed using the Danish version [81] of the Wheelchair Users Shoulder Pain Index (WUSPI)) [82]. WUSPI is a valid and reliable measure of shoulder pain in manual wheelchair users [44] The questionnaire utilizes a series of visual analog scales (VAS) ranging from "no pain" to "worst pain ever experienced", and it is a self-reported measure of the prevalence and severity of shoulder pain during different activities such as dressing, bathing, transfer, wheeling up, sleeping etc. [82]. Some participants may not perform all of the 15 activities. To account for that, a performance-corrected shoulder

pain score (PC-WUSPI) will be calculated by dividing the raw total WUSPI score by the number of performed activities, multiplied by 15 [83].

Health-related quality of life (HRQOL)

HRQOL will be monitored using the Danish translated version of the Short Form-36 (SF-36) [84], which is a reliable and validated questionnaire to assess HRQOL within both a physical and mental health domain [85]. Certain questions of the SF-36 will be adapted to wheelchair use. Specifically, the questions referring to 'walk' and 'stair-climbing' is substituted by the words 'climb' and 'go up', as previously recommended [86] . Construct validity stays acceptable with this modification [86]. Data will be scored using the RAND 36-item Health survey 1.0 method [87], in which original responses is transformed into a score from 0-100, with 100 representing the best possible health. Individual item scores is then averaged within domains to create eight subscales, four representing physical QOL and four representing mental QOL. For reporting of HRQOL, a physical component summary score (PCS) and a mental component summary score (MCS) will be created based on the average of each component subscales [88].

Free-living physical activity

To determine the effects of the exercise intervention on short-term (12-weeks follow-up) and long-term (6-months follow-up) habitual physical activity, free-living physical activity levels will be monitored objectively via accelerometry. Participants will be fitted with a triaxial wrist-worn accelerometer (Axivity, AX3, Newcastle, UK) placed on the non-dominant wrist using a standard rubber wristband, as recommended [89]. Participants will be asked to wear the accelerometer for the 7 days [90] preceding baseline and follow-up (12-weeks and 6-months) visits. The accelerometer (23 x 32.5 x 7.6 (mm)) will be worn continuously through this period (24 hours a day). To be considered a valid day, at least 80% of data for that 24-hour period is required [90]. The AX3 sensor records accelerations within the dynamic range of ± 8 g. Physical activity levels are derived by aggregating the raw acceleration (expressed as $g^1 \cdot min^{-1}$) using either Euclidian norm minus one (ENMO – expressed in mg), mean average deviation (MAD – expressed in mg), activity index (AI – expressed in mg) or Actigraph Counts (AG – expressed in counts) [91–94]. The most optimal aggregation, time interval or epoch, and data band-pass filtering to reduce noise has not been evaluated thoroughly in any previous study. Thus, the final selection of aggregation method, epoch length and band-pass filtering to be used is determined using the same study conducted to estimate the light, moderate and vigorous intensity thresholds (see below).

For determination of physical activity ($min \cdot day^{-1}$) with different intensities (i.e. light, moderate and vigorous physical activity), individual accelerometer cut-off points will be calculated. Individual calibration of wrist-worn accelerometers is recommended for valid estimates of physical activity level [95]. Previous studies [96,97] have established high internal-validity of wrist-worn accelerometer output when compared with energy

expenditure measured at fixed speeds during wheelchair propulsion on a motorized treadmill [96,97]. However, this approach may not have high external validity because physical activities outside the laboratory rarely occurs at fixed intensities. Indeed, SCI individuals perform a multitude of leisure-time physical activities and activities of daily living with varying intensity [98]. Therefore, AX3 sensor output will be individually calibrated based on five different standardized "real-life" mimicking activities, each performed for 6 min. Activities will include a folding clothes task, continuous wheelchair propulsion at three different self-paced tempi, and an intermittent wheelchair propulsion with wheeling and stopping at a self-paced tempo.

Feasibility and acceptability of the exercise intervention

Satisfaction with the exercise intervention will be evaluated with the Feasibility and Acceptability Questionnaire [99]. In brief, participants will be asked to rate how feasible and acceptable they consider the rowing exercise to be on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The questionnaire consists of six questions addressing issues such as how fun the exercise was perceived; the difficulty level of the exercise; and whether they received appropriate guidance in how to perform the exercise. A mean score of ≥3.0 will be used as a criterion to indicate that the intervention is acceptable [99]. Additionally, compliance to the exercise intervention will be recorded and presented as compliance rate (% participation). Compliance is defined as the number of exercise sessions completed out of the total number (36) of sessions.

Statistics

The between group difference in changes of outcome variables will be examined from baseline to post intervention (12-weeks follow-up) (primary endpoint) and again from post intervention to follow-up 6-months later (secondary endpoint).

Primary and secondary endpoint data are ratio and interval data and will therefore be treated as continuous variables. Between group comparisons on primary and secondary endpoint will be dependent on data distribution. We anticipate data to be approximately normally distributed, however before any analysis are commenced, distribution of the data will be assessed through visual inspection of Q-Q-plots and histograms, complemented by test of deviation from normality (Shapiro Wilk test). Assuming normality, descriptive data will be presented as mean ± standard deviation (SD), and a two-way analysis of variance (ANOVA) with repeated measurements will be used to evaluate any significant changes in outcomes between (control and exercise) and within (baseline and follow-up) groups from baseline to immediately after the 12-weeks intervention period. Same procedure will be done for secondary endpoint (factor 1: group (control and exercise), factor 2: time (follow-up at 12-weeks and 6-months)). Interactions between the factors will be included in the model. In case of significant F-values, post-hoc testing will be used for multiple comparisons. Effect size of change scores (Cohen's d) will be calculated in order to determine the magnitude of difference

between groups. P-values and 95% confidence intervals will be reported to facilitate interpretation of the results. Statistical significance will be accepted at $P < 0.05$.

Patient and public involvement

Neither participants nor public were involved with the conception of the research question, study design, or outcome measures, nor will they be involved with study conduction. The recruitment plan was partially planned based on feedback from the patient population. Each of the participants will receive a written summary of the study results after publication.

Ethics and dissemination

Considerations are made regarding the regulation of arterial BP in the participants [100 101]. BP instability does occur in cervical injured individuals (tetraplegics), who may suffer from pronounced autonomic disturbances [100,101]. During the VO_{2peak} test and exercise sessions, special attention is devoted towards potential symptoms of autonomic dysreflexia (AD) [102] in individuals with SCI ≥T6. Participants will be asked to empty their bladder before any testing or training is commenced. In case of AD, the exercise is stopped and the pertinent actions are made. Occurrences of post exercise hypotension [101] and orthostatic hypotension [100] are rather uncommon in individuals with thoracic injury (paraplegics). According to the inclusion criteria of the study, only individuals with a sparing of arm function (i.e. excluding individuals with a complete cervical injury ≥C5 participants) will be included in the study, presumably reducing the number of included individuals with impaired BP regulation. Nevertheless, in addition to reduced vasoconstrictor drive, the ability to increase cardiac output is limited in individuals with SCI ≥T5-T6 with interrupted cardiac sympathetic innervation, which could affect arterial BP stabilization during conditions in which peripheral vascular resistance is further reduced (i.e. during exercise). Therefore, to identify any participants that may be prone to experiencing post exercise hypotension, brachial artery BP will be monitored immediately after, and again 5 min after the first VO_{2peak} test. In such cases, and assuming the hypotension is well tolerated, the participants will be reminded to drink appropriately during and prior any future training and testing. Further, these participants will have their BP measured every second interval (i.e. every 10th min) during the training sessions. If hypotension develops, the training will be interrupted and hypotensive countermaneuvres (placement in a supine position, or legs up) will be applied. If the hypotension is not tolerated, such as if the participants exhibit signs of nausea, light-headedness, fatigue or presyncobal symptoms in response to either the VO_{2peak} test or the training, they will be excluded from further participation in the study.

Another consideration is that individuals with SCI suffer from impaired thermoregulation [103]. Although prolonged (60 min) moderate intensity exercise in warm conditions (>31°C) have been shown sustainable for some paraplegic and tetraplegic individuals [104], impaired thermoregulation makes SCI individuals more vulnerable to overheating compared to able-bodied [103]. This is especially the case during conditions of

increased environmental temperatures and metabolic heat production (such as when exercising in the heat). The degree of thermoregulatory impairment is closely related to the injury level, such that individuals with higher injury (tetraplegics) exhibit higher core temperatures during exercise compared to lower injury individuals (paraplegics) [104]. To diminish the risk for overheating during testing and training, a fan will be available for cooling of the participants and the room temperature and humidity will be continuously monitored to facilitate the conditions for dry and evaporative heat loss. Moreover, the participants will be asked to pay attention to proper hydration before and throughout each training session. However, if the participants demonstrate signs of any adverse response, the exercise session will be terminated immediately and further participation in the study will be reconsidered. Any adverse responses from the intervention will be reported to the regional health research committee. The trial is reported to the Danish Data Protection Agency (J.nr. 2019-899/10-0406), registered at Clinicaltrials.org, and approved by the Committees on Health Research Ethics in The North Denmark Region on 12 December 2019 (Journal-nr. N-20190053). Results will be submitted to scientific journals related to exercise and SCI for publication irrespective of study outcomes.

Data statement section

All participant data will be stored in a secure web-based database (Redcap) with restricted access and ID code, in accordance with data protection rules. Source documents including date, visit# and participant ID will be scanned and saved as electronic copies. Participant data will be transferred directly or by use of an encrypted USB stick. Each participant will be assigned an unique identification number, which will be the only identifier exported from Redcap upon data analysis. Except for the blood samples, which will be stored until analysis, or no more than 5 years, data will be stored for 5 years after the termination of the trial. After this period, paper material is shredded, data files are erased and the Redcap database is no longer accessible. The principal investigator will have access to all trial data.

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Author Contributions

RKH and RGL conceptualized the study. RKH, AS, UL, AH and RGL contributed to the study protocol design. RKH drafted the manuscript. RKH, AS, UL, AH and RGL commented and edited the manuscript and approved the final version.

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Competing interests

None declared.

Patient consent

Not required.

License statement

Figure 1. Study overview. PA = physical activity; INT = intervention; RPE = rating of perceived exertion; CON = control.

REFERENCES

1. LaPorte, R. *et al.* The Spectrum of Physical Activity, Cardiovascular Disease and Health: An Epidemiologic Perspective. *Am J Epidemiol.* **120**, 507–517 (1984).
2. Myers, J., Lee, M. & Kiratli, J. Cardiovascular disease in spinal cord injury: An overview of prevalence, risk, evaluation, and management. *Am. J. Phys. Med. Rehabil.* **86**, 142–152 (2007).
3. Nash, M. & Cowan, R. Cardiovascular disease, SCI and exercise: unique risks and focused countermeasures. *Disabil. Rehabil.* **32**, 2228–2236 (2010).
4. Garshick, E. *et al.* A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* **43**, 408–416 (2005).
5. Buchholz, A. C. *et al.* Greater daily leisure time physical activity is associated with lower chronic disease risk in adults with spinal cord injury. *Appl. Physiol. Nutr. Metab.* **34**, 640–647 (2009).
6. Gorgey, A., Dolbow, D., Dolbow, J., Khalil, R. & Gater, D. Effects of spinal cord injury on body composition and metabolic profile – Part I. *J. Spinal Cord Med.* **37**, 693–702 (2014).
7. Kehn, M. & Kroll, T. Staying physically active after spinal cord injury: A qualitative exploration of barriers and facilitators to exercise participation. *BMC Public Health* **9**, 1–11 (2009).
8. Rimmer, J. H., Riley, B., Wang, E., Rauworth, A. & Jurkowski, J. Physical activity participation among persons with disabilities: Barriers and facilitators. *Am. J. Prev. Med.* **26**, 419–425 (2004).
9. Hansen, R. K., Larsen, R. G., Læssøe, U., Samani, A. & Cowan, R. E. Perceived Physical Activity Barriers in Danish Manual Wheelchair Users. *Submitt. Manuscr.* (2020).
10. Cowan, R. E., Nash, M. S. & Anderson, K. D. Exercise participation barrier prevalence and association with exercise participation status in individuals with spinal cord injury. 27–32 (2013) doi:10.1038/sc.2012.53.
11. Rimmer, J. H., Rubin, S. S. & Braddock, D. Barriers to exercise in African American women with physical disabilities. *Arch. Phys. Med. Rehabil.* **81**, 182–188 (2000).
12. Rimmer, J. H., Wang, E. & Smith, D. Barriers associated with exercise and community access for individuals with stroke. *J. Rehabil. Res. Dev.* **45**, 315–322 (2008).
13. Van Der Scheer, J. W. *et al.* Effects of exercise on fitness and health of adults with spinal cord injury: A systematic review. *Neurology* **89**, 736–745 (2017).
14. El-Sayed, M. S. & Younesian, A. Lipid profiles are influenced by arm cranking exercise and training in individuals with spinal cord injury. *Spinal Cord* **43**, 299–305 (2005).
15. Nightingale, T. E., Walhin, J. P., Thompson, D. & Bilzon, J. L. J. Impact of Exercise on Cardiometabolic Component Risks in Spinal Cord-injured Humans. *Med. Sci. Sports Exerc.* **49**, 2469–2477 (2017).
16. Kim, D. Il, Lee, H., Lee, B. S., Kim, J. & Jeon, J. Y. Effects of a 6-Week Indoor Hand-Bike Exercise Program on Health and Fitness Levels in People With Spinal Cord Injury: A Randomized Controlled Trial Study. *Arch. Phys. Med. Rehabil.* **96**, 2033–2040 (2015).
17. Totosy de Zepetnek, J. O., Pelletier, C. A., Hicks, A. L. & MacDonald, M. J. Following the Physical Activity Guidelines for Adults With Spinal Cord Injury for 16 Weeks Does Not Improve Vascular Health: A Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* **96**, 1566–1575 (2015).

18. Wilt, T. J. *et al.* Carbohydrate and lipid disorders and relevant considerations in persons with spinal cord injury (Structured abstract). *Database Abstr. Rev. Eff.* 171 (2008).

19. Nightingale, T. E., Metcalfe, R. S., Vollaard, N. B. & Bilzon, J. L. Exercise Guidelines to Promote Cardiometabolic Health in Spinal Cord Injured Humans: Time to Raise the Intensity? *Arch. Phys. Med. Rehabil.* **98**, 1693–1704 (2017).

20. Green, D. J., Driscoll, G. O., Joyner, M. J. & Cable, N. T. Exercise and cardiovascular risk reduction : Time to update the rationale for exercise ? Exercise and cardiovascular risk reduction : Time to update the rationale for exercise ? 766–768 (2013) doi:10.1152/japplphysiol.01028.2007.

21. Gielen, S., Schuler, G. & Hambrecht, M. Exercise Training in Coronary Artery Disease and Coronary Vasomotion. *Circulation* **103**, 1–6 (2001).

22. Celermajer, D. *et al.* Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis Endothelial. *Lancet* **340**, 1111–1115 (1992).

23. J., Y. *et al.* Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: The multi-ethnic study of atherosclerosis. *Circulation* **120**, 502–509 (2009).

24. Lorenz, M. W., Markus, H. S., Bots, M. L., Rosvall, M. & Sitzer, M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation* **115**, 459–467 (2007).

25. Green, D. J., Hopman, M. T. E., Padilla, J., Laughlin, M. H. & Thijssen, D. H. J. Vascular adaptation to exercise in humans: Role of hemodynamic stimuli. *Physiol. Rev.* **97**, 495–528 (2017).

26. de Groot, P. C., Bleeker, M. W., van Kuppevelt, D. H., van der Woude, L. H. & Hopman, M. T. Rapid and Extensive Arterial Adaptations After Spinal Cord Injury. *Arch. Phys. Med. Rehabil.* **87**, 688–696 (2006).

27. Rowley, N. J. *et al.* Conduit diameter and wall remodeling in elite athletes and spinal cord injury. *Med. Sci. Sports Exerc.* **44**, 844–849 (2012).

28. de Groot, P. C. E., Poelkens, F., Kooijman, M. & Hopman, M. T. E. Preserved flow-mediated dilation in the inactive legs of spinal cord-injured individuals. *Am J Physiol Hear. Circ Physiol* **287**, 374–380 (2004).

29. Huonker, M., Schmid, A., Schmidt-Trucksäß, A., Grathwohl, D. & Keul, J. Size and blood flow of central and peripheral arteries in highly trained able-bodied and disabled athletes. *J. Appl. Physiol.* **95**, 685–691 (2003).

30. Ginis, K. A. M. *et al.* The development of evidence-informed physical activity guidelines for adults with spinal cord injury. *Spinal Cord* **49**, 1088–1096 (2011).

31. Pelletier, C. A., Totosy De Zepetnek, J. O., Macdonald, M. J. & Hicks, A. L. A 16-week randomized controlled trial evaluating the physical activity guidelines for adults with spinal cord injury. *Spinal Cord* **53**, 363–367 (2015).

32. Martin Ginis, K. A. *et al.* Evidence-based scientific exercise guidelines for adults with spinal cord injury: An update and a new guideline. *Spinal Cord* **56**, 308–321 (2018).

33. Cratsenberg, K. A. *et al.* Effectiveness of exercise programs for management of shoulder pain in manual wheelchair users with spinal cord injury. *J. Neurol. Phys. Ther.* **39**, 197–203 (2015).

34. Troy, K., Munce, T. & Longworth, J. An exercise trial targeting posterior shoulder strength in manual wheelchair users: Pilot results and lessons learned. *Disabil. Rehabil. Assist. Technol.* **10**, 415–420 (2015).

35. Nash, M. S. *et al.* A comparison of 2 circuit exercise training techniques for eliciting matched metabolic responses in persons with paraplegia. *Arch. Phys. Med. Rehabil.* **83**, 201–209 (2002).

36. Curtis, K. *et al.* Effect of a standard exercise protocol on shoulder pain in long-term wheelchair users. *Spinal Cord* **37**, 421–429 (1999).

37. Ballinger, D. A., Rintala, D. H. & Hart, K. A. The relation of shoulder pain and range-of-motion problems to functional limitations, disability, and perceived health of men with spinal cord injury: A multifaceted longitudinal study. *Arch. Phys. Med. Rehabil.* **81**, 1575–1581 (2000).

38. Nichols, P., Norman, P. & Ennis, J. Wheelchair user's shoulder? *Scand J Rehab Med* **11**, 29–32 (1979).

39. Gutierrez, D., Thompson, L., Kemp, B. & Mulroy, S. The relationship of shoulder pain intensity to quality of life, physical activity, and community participation in persons with paraplegia. *J. Spinal Cord Med.* **30**, 251–255 (2007).

40. Nash, M. S., van de Ven, I., van Elk, N. & Johnson, B. M. Effects of Circuit Resistance Training on Fitness Attributes and Upper-Extremity Pain in Middle-Aged Men With Paraplegia. *Arch. Phys. Med. Rehabil.* **88**, 70–75 (2007).

41. Leduc, B. & Lepage, Y. Health-related quality of life after spinal cord injury. *Disabil. Rehabil.* **24**, 196–202 (2002).

42. Lidal, I., Veenstra, M., Hjeltnes, N. & Biering-Sørensen, F. Health-related quality of life in persons with long-standing spinal cord injury. *Spinal Cord* **46**, 710–715 (2008).

43. Ambrosio, F. *et al.* Biomechanics and strength of manual wheelchair users. *J. Spinal Cord Med.* **28**, 407–414 (2005).

44. Curtis, K. *et al.* Reliability and validity of the Wheelchair User's Shoulder Pain Index (WUSPI). *Paraplegia* **33**, 595–601 (1995).

45. Burnham, R. S., May, L., Nelson, E., Steadward, R. & Reid, D. C. Shoulder pain in wheelchair athletes: The role of muscle imbalance. *Am. J. Sports Med.* **21**, 238–242 (1993).

46. Bayley, J., Cochran, T. & Sledge, C. The weight-bearing shoulder. The impingement syndrome in paraplegics. *J. Bone Jt. Surg.* **69**, 676–678 (1987).

47. Collinger, J. L. *et al.* Shoulder Biomechanics During the Push Phase of Wheelchair Propulsion: A Multisite Study of Persons With Paraplegia. *Arch. Phys. Med. Rehabil.* **89**, 667–676 (2008).

48. Mulroy, S. J. *et al.* Strengthening and Optimal Movements for Painful Shoulders (STOMPS) in Chronic Spinal Cord Injury: A Randomized Controlled Trial. *Phys. Ther.* **91**, 305–324 (2011).

49. Secher, N. The Physiology of Rowing. *J. Sports Sci.* **1**, 23–53 (1983).

50. Olenik, L., Laskin, J., Burnham, R., Wheeler, G. & Steadward, R. Efficacy of rowing, backward wheeling and isolated scapular retractor exercise as remedial strength activities for wheelchair users: Application of electromyography. *Paraplegia* **33**, 148–152 (1995).

51. Curtis, K. *et al.* Effect of a standard exercise protocol on shoulder pain in long-term wheelchair users. *Spinal Cord* **37**, 421–429 (1999).

52. Chan, A. *et al.* SPIRIT 2013 Statement : Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* **158**, 200–207 (2013).

53. Ginis, K. A. M., Phang, S. H., Latimer, A. E. & Arbour-Nicitopoulos, K. P. Reliability and Validity Tests of the Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury. *Arch.*

Phys. Med. Rehabil. **93**, 677–682 (2012).

54. Lee, R. *et al.* Active vs. passive methods of recruiting ethnic minority women to a health promotion program. *Ann. Behav. Med.* **19**, 378–384 (1997).

55. Ginis, K. a M. & Hicks, A. L. Exercise research issues in the spinal cord injured population. *Exerc. Sport Sci. Rev.* **33**, 49–53 (2005).

56. Astorino, T. A. & Thum, Jacob, S. Interval training elicits higher enjoyment versus moderate exercise in persons with spinal cord injury. *J. Spinal Cord Med.* **41**, 77–84 (2018).

57. Powell, K. E., Paluch, A. E. & Blair, S. N. Physical Activity for Health: What Kind? How Much? How Intense? On Top of What? *Annu. Rev. Public Health* **32**, 349–365 (2011).

58. Borg, G. Perceived exertion as an indicator of somatic stress. *Scand J Rehab Med* 92–98 (1970).

59. Birk, T. J. & Birk, C. A. Use of Ratings of Perceived Exertion for Exercise Prescription. *Sport. Med.* **4**, 1–8 (1987).

60. Goosey-Tolfrey, V. *et al.* Regulating intensity using perceived exertion in spinal cord-injured participants. *Med. Sci. Sports Exerc.* **42**, 608–613 (2010).

61. van der Scheer, J. W., Hutchinson, M. J., Paulson, T., Martin Ginis, K. A. & Goosey-Tolfrey, V. L. Reliability and Validity of Subjective Measures of Aerobic Intensity in Adults With Spinal Cord Injury: A Systematic Review. *PM R* **10**, 194–207 (2018).

62. Lewis, J. E., Nash, M. S., Hamm, L. F., Martins, S. C. & Groah, S. L. The Relationship Between Perceived Exertion and Physiologic Indicators of Stress During Graded Arm Exercise in Persons With Spinal Cord Injuries. *Arch. Phys. Med. Rehabil.* **88**, 1205–1211 (2007).

63. Noble, B. J., Borg, G. A. V., Jacobs, I., Ceci, R. & Kaiser, P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med. Sci. Sport. Exerc.* **16**, 523–528 (1983).

64. Thijssen, D. H. J. *et al.* Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur. Heart J.* **40**, 2534–2547 (2019).

65. Limberg, J. K. *et al.* Assessment of resistance vessel function in human skeletal muscle : guidelines for experimental design , Doppler ultrasound , and pharmacology. (2020) doi:10.1152/ajpheart.00649.2019.

66. Grundy, S. *et al.* Diagnosis and managment of the metabolic syndrome AHA / NHLBI Scientific Statement. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2735–2752 (2005) doi:10.1161/CIRCULATIONAHA.105.169404.

67. Nash, M. S. *et al.* Identification and Management of Cardiometabolic Risk after Spinal Cord Injury: Clinical Practice Guideline for Health Care Providers. *Top. Spinal Cord Inj. Rehabil.* **24**, 379–423 (2018).

68. McCauley, L. S., Sumrell, R. M. & Gorgey, A. S. Anthropometric Prediction of Visceral Adipose Tissue in Persons With Motor Complete Spinal Cord Injury. *PM R* **10**, 817–825 (2018).

69. Edwards, L. A., Bugaresti, J. M. & Buchholz, A. C. The amount of visceral adipose tissue and the ratio of visceral to subcutaneous adipose tissue is greater in adults with vs. without spinal cord injury. *Faseb J.* **21**, A7–A8 (2007).

70. Sumrell, R. M., Nightingale, T. E., McCauley, L. S. & Gorgey, A. S. Anthropometric cutoffs and associations with visceral adiposity and metabolic biomarkers after spinal cord injury. *PLoS One* **13**, e0203049 (2018).

71. Joyner, M. J. & Green, D. J. Exercise protects the cardiovascular system: Effects beyond traditional risk factors. *J. Physiol.* **587**, 5551–5558 (2009).

72. Ahuja, C. S. *et al.* Traumatic spinal cord injury. *Nat. Rev. Dis. Prim.* **3**, 1–21 (2017).

73. Otsuka, Y., Shima, N., Moritani, T., Okuda, K. & Yabe, K. Orthostatic influence on heart rate and blood pressure variability in trained persons with tetraplegia. *Eur. J. Appl. Physiol.* **104**, 75–78 (2008).

74. Thijssen, D. H. J. *et al.* Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *Am. J. Physiol. - Hear. Circ. Physiol.* **300**, 2–12 (2011).

75. Pyke, K. E. & Tschakovsky, M. E. Peak vs. total reactive hyperemia: Which determines the magnitude of flow-mediated dilation? *J. Appl. Physiol.* **102**, 1510–1519 (2007).

76. Padilla, J. *et al.* Normalization of flow-mediated dilation to shear stress area under the curve eliminates the impact of variable hyperemic stimulus. *Cardiovasc. Ultrasound* **6**, 1–10 (2008).

77. Thrush, A. & Hartshorne, T. *Vascular Ultrasound - How, When and Why*. *Churchill Livingstone* (2010). doi:10.1017/CBO9781107415324.004.

78. Maher, J. L. & Cowan, R. E. Comparison of 1- Versus 3-Minute Stage Duration During Arm Ergometry in Individuals With Spinal Cord Injury. *Arch. Phys. Med. Rehabil.* **97**, 1895–1900 (2016).

79. Eerden, S., Dekker, R. & Hettinga, F. J. Maximal and submaximal aerobic tests for wheelchair-dependent persons with spinal cord injury: a systematic review to summarize and identify useful applications for clinical rehabilitation. *Disabil. Rehabil.* **40**, 497–521 (2018).

80. Au, J. S., De Zepetnek, J. O. T. & MacDonald, M. J. Modeling perceived exertion during graded arm cycling exercise in spinal cord injury. *Med. Sci. Sports Exerc.* **49**, 1190–1196 (2017).

81. Larsen, C., Hansen, S., Hansen, L., P, B. & B, J.-K. Translation and Cross-Cultural Adaptation of the Danish Version: Wheelchair Users Shoulder Pain Index (WUSPI). in 1 (2015).

82. Curtis, K. *et al.* Development of the Wheelchair User's Shoulder Pain Index (WUSPI). *Paraplegia* **33**, 290–293 (1995).

83. Curtis, K. A. *et al.* Shoulder pain in wheelchair users with tetraplegia and paraplegia. *Arch. Phys. Med. Rehabil.* **80**, 453–457 (1999).

84. Bjorner, J. B., Thunedborg, K., Kristensen, T. S., Modvig, J. & Bech, P. The Danish SF-36 Health Survey: Translation and preliminary validity studies. *J. Clin. Epidemiol.* **51**, 991–999 (1998).

85. Ware, Jr., J. E. & Sherbourne, C. D. The MOS 36-Item Short-Form Health Survey (SF-36): I . Conceptual Framework and Item Selection Author. *Med. Care* **30**, 473–483 (1992).

86. Tate, D. G., Kalpakjian, C. Z. & Forchheimer, M. B. Quality of life issues in individuals with spinal cord injury. *Arch. Phys. Med. Rehabil.* **83**, 18–25 (2002).

87. RAND, H. C. 36-Item Short Form Survey (SF-36) Scoring Instructions. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html.

88. Nightingale, T. E., Rouse, P. C., Walhin, J. P., Thompson, D. & Bilzon, J. L. J. Home-Based Exercise Enhances Health-Related Quality of Life in Persons With Spinal Cord Injury: A Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* **99**, 1998-2006.e1 (2018).

89. Nightingale, T. E., Rouse, P. C., Thompson, D. & Bilzon, J. L. J. Measurement of Physical Activity and Energy Expenditure in Wheelchair Users: Methods, Considerations and Future Directions. *Sport. Med. - Open* **3**, (2017).

90. Nightingale, T. E., Walhin, J. P., Turner, J. E., Thompson, D. & Bilzon, J. L. J. The influence of a home-based exercise intervention on human health indices in individuals with chronic spinal cord injury (HOMEX-SCI): Study protocol for a randomised controlled trial. *Trials* **17**, 1–12 (2016).

91. Brønd, J. C., Andersen, L. B. & Arvidsson, D. Generating ActiGraph Counts from Raw Acceleration Recorded by an Alternative Monitor. *Med. Sci. Sports Exerc.* **49**, 2351–2360 (2017).

92. van Hees, V. T. *et al.* Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity. *PLoS One* **8**, 1–10 (2013).

93. Aittasalo, M. *et al.* Mean amplitude deviation calculated from raw acceleration data: a novel method for classifying the intensity of adolescents' physical activity irrespective of accelerometer brand. *BMC Sports Sci. Med. Rehabil.* **7**, 1–7 (2015).

94. Bai, J. *et al.* An Activity Index for Raw Accelerometry Data and Its Comparison with Other Activity Metrics. *PLoS One* **11**, 1–14 (2016).

95. McCracken, L. A. *et al.* Wrist Accelerometry for Physical Activity Measurement in Individuals with Spinal Cord Injury - A Need for Individually Calibrated Cut-Points. *Arch. Phys. Med. Rehabil.* **99**, 684–689 (2018).

96. Learmonth, Y. C., Kinnett-Hopkins, D., Rice, I. M., Dysterheft, J. L. & Motl, R. W. Accelerometer output and its association with energy expenditure during manual wheelchair propulsion. *Spinal Cord* **54**, 110–114 (2016).

97. Nightingale, T. E., Walhin, J. P., Thompson, D. & Bilzon, J. L. J. Influence of accelerometer type and placement on physical activity energy expenditure prediction in manual wheelchair users. *PLoS One* **10**, 1–15 (2015).

98. Hetz, S. P., Latimer, A. E. & Martin Ginis, K. A. Activities of daily living performed by individuals with SCI: Relationships with physical fitness and leisure time physical activity. *Spinal Cord* **47**, 550–554 (2009).

99. Visovsky, C. & Corripio, J. Feasibility and Acceptability of a Resistance Exercise Intervention: For Women Undergoing Chemotherapy for Breast Cancer. *Nurs. Heal.* **3**, 110–119 (2015).

100. Claydon, V. E. & Krassioukov, A. V. Orthostatic Hypotension and Autonomic Pathways after Spinal Cord Injury. *J. Neurotrauma* **23**, 1713–1725 (2006).

101. Claydon, V. E., Hol, A. T., Eng, J. J. & Krassioukov, A. V. Cardiovascular Responses and Postexercise Hypotension After Arm Cycling Exercise in Subjects With Spinal Cord Injury. *Arch. Phys. Med. Rehabil.* **87**, 1106–1114 (2006).

102. Phillips, A. A. & Krassioukov, A. V. Contemporary Cardiovascular Concerns after Spinal Cord Injury: Mechanisms, Maladaptations, and Management. *J. Neurotrauma* **32**, 1927–1942 (2015).

103. Sawka, M., Latzka, W. & Pandolf, K. Temperature Regulation During Upper Body Exercise: Able Bodied And Spinal Cord Injured. *Med. Eng. Phys.* **21**, 132–40 (1989).

104. Price, M. & Campbell, I. Effects of spinal cord lesion level upon thermoregulation during exercise in the heat. *Med. Sci. Sports Exerc.* **35**, 1100–1107 (2003).

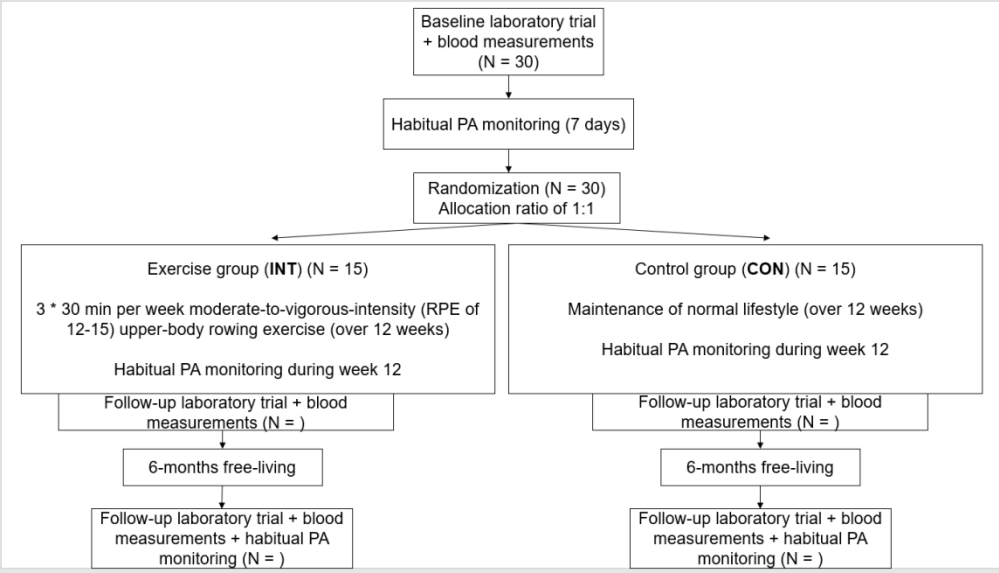

Figure 1. Study overview. PA = physical activity; INT = intervention; RPE = rating of perceived exertion; CON = control.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4,8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a. The trial has been registered with details provided at Clinicaltrials.gov
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,2,18
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	18
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether	18

		they will have ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a. No such committee has been established.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio,	8

		and framework (eg, superiority, equivalence, non-inferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9,11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	9-11, 17,18

		response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	16
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a. Participants allocated to the exercise and control group cannot be blinded to the PI, because PI is responsible for conducting the study. Parts of data analysis will be blinded to the PI.
Methods: Data collection,			

management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17-18
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,	18

		REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to	n/a

		those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for	11

future use in ancillary studies, if applicable

BMJ Open

Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users – Protocol for a randomized controlled trial

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Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users – Protocol for a randomized controlled trial

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ABSTRACT

Introduction

Cardiovascular and metabolic diseases are a growing concern for individuals with spinal cord injury (SCI). Physical inactivity contributes to cardiometabolic morbidity and mortality in the SCI population. However, previous studies have shown mixed results regarding the effects of exercise on cardiometabolic risk factors in individuals with SCI. This discrepancy could be influenced by insufficient exercise stimuli. Recent guidelines recommend 30 minutes of moderate-to-vigorous intensity aerobic exercise, three times a week, for improvement in cardiometabolic health in individuals with SCI. However, to date, no studies have implemented an exercise intervention matching the new recommendations to examine the effects on cardiometabolic risk factors. Therefore, the primary objective of this study is to determine the effects of 12-weeks of wheelchair user-modified upper-body rowing exercise on both traditional (constituents of the metabolic syndrome) and novel (e.g. vascular structure and function) cardiometabolic risk factors in manual wheelchair users with SCI.

Methods and analysis

A randomized controlled trial will compare 12-weeks of upper-body rowing exercise, 30 minutes three times per week, with a control group continuing their normal lifestyle. Outcome measurements will be performed immediately before (baseline), after 6 weeks (halfway), 12 weeks of training (post), and 6 months after the termination of the intervention period (follow up). Outcomes will include inflammatory (e.g. C-reactive protein) and metabolic biomarkers determined from venous blood (with serum fasting insulin as primary outcome), body composition, arterial blood pressure, cardiorespiratory fitness level, brachial artery vascular structure and function, and autonomic nervous system function.

Ethics and dissemination

This trial is reported to the Danish Data Protection Agency (J.nr. 2019-899/10-0406) and approved by the Committees on Health Research Ethics in The North Denmark Region on 12 December 2019 (Journal-nr. N-20190053). The principal investigator will collect written informed consent from all participants prior to inclusion. Irrespective of study outcomes, the results will be submitted to peer-reviewed scientific journals for publication.

Trial registration number

NCT04390087.

ARTICLE SUMMARY

Strengths and limitations of this study

- The frequency, duration and intensity of the exercise intervention follows recently published exercise recommendations for individuals with SCI.
- This study uses a randomized controlled design to examine the effects of a novel exercise modality on both traditional and novel cardiometabolic risk factors.
- The exercise modality (upper-body rowing) includes not only an aerobic component, but also an element of resistance training for the posterior shoulder region, potentially ameliorating shoulder pain.
- Lack of control of food intake is a study limitation as altered energy intake could influence the interpretation of the effects of exercise on body mass and body composition

INTRODUCTION

Individuals with spinal cord injury (SCI) are placed at the lowest end of the fitness continuum [1]. Thus cardiovascular disease and metabolic dysfunction is a growing concern in this population [2,3]. In recent years, cardiovascular disease has emerged as the leading cause of mortality in individuals with chronic SCI [4]. Factors contributing to high cardiometabolic morbidity and mortality in individuals with SCI are sedentary lifestyle and low physical activity level [5], and the ensuing negative influence on body composition, reflected by lower fat-free mass and larger amount of adipose tissue [6].

The clinical manifestations of SCI rely on the level of neurological injury and the completeness of injury [7]. SCI can result in complete or partial loss of sensorimotor function below the level of injury. In general, a cervical injury leads to impairment of all four extremities (i.e. both arms and legs) as well as the trunk and pelvic organs (tetraplegia), whereas an injury to the thoracic, lumbar or sacral spine preserves functioning of the arms (paraplegia) [8]. In addition to the impairment of sensorimotor function, SCI can disrupt sympathetic nervous system function as preganglionic sympathetic neurons are located between the T1 and L2 spinal segment [7]. Due to an increased amount of paralyzed muscle mass and larger disruption of the autonomic nervous system, lower physical capacity [9] and heightened cardiovascular risk [10] are generally observed among individuals with a high (tetraplegic) and complete SCI. The loss of sensorimotor function in the lower extremities forces many individuals with SCI to rely on a wheelchair for mobility. For those wheelchair users with sufficient strength and movement control in the arms, a manual wheelchair (i.e. a wheelchair that can be propelled by the user) is typical used for mobility [11].

Besides the obvious limitation to physical activities requiring ambulation, explanations for the adoption of a sedentary lifestyle are multifactorial, but studies have identified intrapersonal and socio-environmental physical activity barriers in manual wheelchair users with SCI [12–14]. Some barriers such as the intrapersonal barriers of lack of time[15] or energy[16] identified by individuals with mobility disabilities are consistent with those reported in the non-disabled population. Other barriers are specific to the mobility of individuals with disability, such as organizational or structural barriers (e.g. lack of accessible fitness centers[12] and adaptive exercise equipment[13]) and community built environment barriers[17]. Consequently, new approaches to support the initiation and perseverance of physical activity in this population are required.

The majority of previous exercise intervention studies have used isolated aerobic exercise, often in the form of arm-cranking exercise [18]. These studies have demonstrated improvements in traditional risk factors for cardiometabolic diseases, such as high-density cholesterol (HDL-C) [19], fasting insulin [20], and indices of insulin resistance [21], whereas the effects on arterial blood pressure [22], blood lipids (e.g. low-density cholesterol (LDL-C) and triacylglycerol) are inconclusive [20,23,22]. Moreover, although evidence from cross-sectional studies suggests an association between increased participation in moderate-to-vigorous intensity leisure time physical activity and a reduction in visceral adipose tissue [24], there is insufficient evidence for

the effects of upper-body aerobic exercise on changes in body mass and body composition, such as a reduction in total and visceral adipose tissue [18,25,26]. The explanation for the lack of an exercise effect on some of these above mentioned risk factors is not clear, but could be related to insufficient volume [20,22] or intensity [25] of exercise, performed with limited amount of skeletal muscle mass.

Notably, in able-bodied individuals, the exercise-induced risk reduction in cardiovascular diseases cannot be fully explained by traditional risk factors (constituents of the metabolic syndrome), i.e. there is a risk factor gap [27]. As a consequence, studies have started to focus on the effects of exercise on changes in the vascular wall [27]. It is known that dysfunction of the vascular endothelium occurs at the very early phases of atherosclerosis [28]. For instance, flow-mediated dilation (FMD), a non-invasive measure of nitric oxide (NO) dependent endothelial function [29], is a strong predictor of future cardiovascular events [30]. In addition, carotid intima media thickness (IMT), a measure of vessel wall thickness [31] has shown to be associated with future vascular events, such as the occurrence of stroke and myocardial infarction [31]. Accumulating evidence in able-bodied individuals demonstrates beneficial effects of exercise on structural and functional adaptations of the vasculature [32]. However, little is known about the effects of exercise on the vasculature in individuals with SCI.

Reductions in femoral artery (lower body) diameter occurs rapidly in response to extreme inactivity, as observed within three weeks off acquiring a SCI [33]. De Groot et al. [34] found similar FMD in the brachial artery among untrained SCI when compared to able-bodied individuals, however when FMD was normalized to the shear stress stimulus, the dilation response was reduced in the SCI group, indicating some degree of endothelial dysfunction in this population [35]. Other observational studies have demonstrated both larger conduit artery diameter and blood flow in the subclavian artery [36], and larger brachial diameter [34] in wheelchair athletes compared to non-athlete able-bodied controls. Together these findings indicate that remodeling of the vasculature also occurs in response to regular exercise in wheelchair users with SCI. However, the causal link between adaptations of the upper body arteries and repetitive exercise stimulus in SCI is not fully established. Therefore, the relationship between exercise and vascular remodeling in manual wheelchair users needs to be determined through controlled exercise studies. A recent experimental study consisting of supervised aerobic exercise (20min, twice per week), adhering to the earlier (2011) exercise guidelines for adults with SCI [37], was successful in improving measures of cardiorespiratory fitness and muscle strength [38]. Yet, Zepetnek et al. [22] demonstrated that this exercise paradigm (20min, twice per week) did not improve markers of cardiovascular disease risk, including carotid IMT and brachial FMD. Recent (2018) guidelines recommend at least 30 min of moderate-to-vigorous intensity aerobic exercise, three times per week in order to improve cardiometabolic health in individuals with SCI [39], suggesting that insufficient exercise stimuli may explain the lack of vascular adaptations in the study by Zepetnek et al. [22]. Notably, to date, no studies have examined the effects of the updated exercise guidelines (30 min of moderate-to-

vigorous intensity aerobic exercise, three times per week) on vascular adaptations in manual wheelchair users with SCI.

While isolated aerobic exercise, via arm-cranking or wheelchair ergometry, evokes positive effects on cardiorespiratory fitness, these modalities/types of exercises fail to address the importance of strengthening the posterior shoulder musculature of the upper-extremity for individuals with SCI relying on a manual wheelchair for mobility [40]. In addition, these modalities use repetitive contractions of the shoulder musculature engaged in daily wheelchair propulsion activities, thereby increasing the risk of developing shoulder pain [41–43]. Studies have reported high prevalence of shoulder pain in long-term wheelchair users [44,45], which prevents these individuals from engaging in physical activity [46]. As wheelchair users rely on their upper-extremities for most daily activities, upper-extremity pain must be prevented or limited to preserve function, independence and quality of life (QOL) [21,47]. Indeed, health related QOL is lower in adults with SCI compared with the able-bodied population [48,49]. The development of shoulder pain has been suggested to occur due to chronic overuse, shoulder strength imbalances between anterior and posterior musculature, postural changes and impingement syndrome [50–52]. Considering the general need for strong upper extremities to bear weight during different transfer tasks [53], to propel wheelchair [54], and to reach overhead levels [55], the inclusion of resistance training in exercise training paradigms seems prudent. One modality that combines aerobic and resistance components is rowing [56]. Specifically, it has been shown that wheelchair user-modified upper-body rowing ergometry challenges the cardiovascular system comparable to arm-cranking [41]. Additionally, upper-body rowing mirrors the muscle activation observed during traditional resistance training for the scapular retractors [57]. Earlier research has demonstrated beneficial effects of resistance training of the posterior shoulder and scapular retractor musculature on shoulder pain [47,55,58]. Thus, the use of upper-body rowing ergometry may evoke positive effects on both cardiometabolic health and shoulder pain in manual wheelchair users, the latter through alterations in posterior vs. anterior upper-body muscle strength balance. However, to date, no studies have implemented upper-body rowing ergometry as exercise modality in this population.

Objectives

The primary objective of this study is to determine the effects of 12-weeks of wheelchair user-modified upper-body rowing on both traditional (insulin resistance, obesity, dyslipidemia (including low HDL-C and elevated triglycerides, and blood pressure) and novel (inflammatory status, autonomic nervous system function, vascular structure and function, and cardiorespiratory fitness level) cardiometabolic risk factors in manual wheelchair users with SCI. As secondary objectives, we will investigate the effects of the exercise intervention on leisure time physical activity, shoulder pain, indices of QOL, and feasibility of the intervention.

METHODS AND ANALYSIS

Study design

A randomized controlled trial designed to determine the effects of 12 weeks of exercise training on cardiometabolic risk, indices of QOL, and shoulder pain, will be conducted in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [59]. The trial is registered as a controlled trial on 15 May 2020 (NCT04390087) with first enrolment beginning in November 2020. The study overview is presented in Figure 1. After giving written informed consent to participate in the study (see online supplementary appendix for details about the model consent form), participants will undergo baseline testing, after which they will be randomly assigned to either a control group or an exercise group (allocation ratio, 1:1), stratified for age, self-reported leisure time physical activity level, and SCI level. Randomization will be conducted using a computer-generated random number sequence (https://www.randomizer.org/). Outcome measurements will be performed immediately before (baseline), after 6 weeks (halfway), 12 weeks of training (post), and 6 months after the termination of the intervention period (follow up). This approach allows for assessment of the short term effects of exercise training as well as any residual effects from the training intervention on cardiometabolic risk, shoulder pain, indices of QOL, and self-reported leisure time physical activity. Participants will be asked to maintain their normal dietary habits throughout the study period.

Participants

Inclusion criteria

Men and women; aged 18-65 years; chronic SCI (≥1 year since injury); individuals with sufficient sparing of arm flexor function to participate in upper-body rowing (i.e. as a minimum excluding individuals with complete SCI at or above C5); using a manual wheelchair as a primary tool for mobility. Volunteers will be asked to self-report SCI level and completeness and to provide a copy of the part of their medical records that confirm injury level and American Spinal Injury Association (ASIA) impairment scale classification before any measurements are commenced. In addition, volunteers will be asked to briefly perform the rowing exercise during the first laboratory visit to ensure that the individual is able to perform the exercise intervention. As part of the screening, volunteers will also be asked to indicate smoking habits, known medical issues, diseases or use of medication that could affect metabolism (e.g. statins or metformin) or the cardiovascular system (e.g. diuretics, beta blockers, or angiotensin-converting enzyme inhibitors).

Exclusion criteria

Individuals who regularly engage in >90 min/week of moderate-to-vigorous intensity physical activity; have received a cortisone injection in the shoulder within the last four months; have had shoulder injury within the previous year; known medical issues (urinary tract infections, cardiovascular contraindications for exercise

testing, and pressure sores); diagnosed diabetes or any other disease that may limit the ability to perform exercise.

Recruitment

Starting from September 2020, participants will be recruited through notices at Aalborg University, websites seeking volunteers for research studies (e.g., www.forsog.dk), organizations related to disability and SCI, including the Spinal Cord Injured in Denmark organization, physician clinics, wheelchair manufacturing company (Wolturnus A/S) and local community groups. Information on websites, social media, posters, flyers will be used to reach potential participants. This kind of participant recruitment can be considered passive since the participants have to choose to react on the study information[60]. This approach increases the risk of over representing individuals who are interested in the research area[60]. Considering this risk of selection bias, physician clinic visits from the principal investigator (i.e. active recruitment) will be used as an additional strategy to reach potential participants. For this study, 30 participants will be recruited. The sample size is based on the effect size (Cohen *d*: -0.69) for changes in fasting insulin after 6 weeks of arm-cycling exercise [20]. With a power of 0.9, and an alpha level of 0.05, 20 participants in total are required to detect a significant change. To account for drop-outs during the 12 week intervention, as well as potential drop-outs in the control group, 30 participants will be included in the project, with n=15 allocated to the control and exercise group, respectively.

Intervention

Exercise group

Volume, intensity and frequency of the intervention is based on recent exercise recommendations for individuals with SCI [39]. Consequently, the training will be performed for 30 min, 3 times per week with moderate-to-vigorous intensity, with at least one rest day between sessions. Low compliance rate is a general issue in SCI exercise studies [61]. Compared with continuous exercise, interval-based exercise have been reported to elicit higher enjoyment in individuals with SCI [62], which may increase exercise compliance. Considering this difference between continuous and interval-based exercise, the target duration of 30 min will be reached through accumulation of 5-min bouts (up to 6 bouts), with 1-2 min of rest between each bout. It is possible that some participants will not be able to exercise for 30 min with the intended intensity. Accordingly, exercise duration will be tailored to each participant's physical capacity [63] by gradually increasing the duration (i.e. the number of 5-min bouts) over the weeks towards the targeted 30 min (i.e. six * 5-min bouts). Exercise intensity will be prescribed based on rating of perceived exertion (RPE) corresponding to 12-15 on the 'Borg 6-20 RPE Scale [64,65]. The validity of using RPE to control moderate and vigorous exercise intensity has been demonstrated in individuals with SCI [66]. During the first visit, participants will be familiarized with the RPE scale [67] and receive detailed instructions on the use of RPE and how to rate the overall exertion based on an integration of central and peripheral sensations of effort [66]. Some

controversy exists about the validity of using overall RPE to monitor exercise intensity [67,68], as the relationships between overall RPE and objective physiological markers such as oxygen consumption (VO_2), heart rate (HR) and ventilation (VE) in individuals with SCI have been questioned [68]. This have led some researchers to use a differentiated RPE scale that distinguishes between central (cardiorespiratory sensations) and peripheral (peripheral working limbs) sensations [69]. However, the current evidence does not indicate greater validity for differentiated RPE compared with overall RPE [67], and therefore overall RPE will be used to guide exercise intensity.

Each training session will consist of aerobic exercise performed on a wheelchair-modified upper-body rowing ergometer (Concept 2, Morrisville, Vermont, USA). Due to the pulling motion of the upper-body during rowing, this modality also includes a component of resistance exercise [56]. The modification of the ergometer is made by separating it into two parts using an Adapt2row[1], allowing the participants to sit in their wheelchair while performing upper-body rowing. Wedges will be positioned under the rear wheels to keep the wheelchair in place. Further, in case of SCI related insufficient innervation of torso musculature, straps will be wrapped around the back of the wheelchair and around the trunk of the participant, thereby securing the participant to the wheelchair. A pilot study [41] has provided promising results regarding the feasibility of using adaptive upper-body rowing exercise in the SCI population. Participants will be asked to empty their bladder before each training session. Average power output (W) will be recorded during each exercise session to monitor training load and quantify progress in work capacity.

All exercise sessions will be supervised by the principal investigator, who is an exercise physiologist, or by sport science students to ensure proper assistance and guidance of the participants. Everyone involved in supervision will be thoroughly instructed in how to supervise correct exercise technique, and they will receive general knowledge about SCI and wheelchair use. To allow for some flexibility regarding scheduling conflicts, participants will have opportunity to exercise 2-4 days per week, with a target of 3 days per week. That is, in case of a missing session one week, an additional training session can be included the following week. However, to secure adequate recovery, no more than four training days per week will be allowed. The intervention will be terminated after 12 weeks, irrespective of any missing training sessions. An adherence rate threshold of 75% will be used (≥27 exercise sessions out of the maximum 36) [70]. However, there are no previous reports of adherence rates for this type of exercise intervention (12 weeks of wheelchair-modified rowing) in individuals with SCI. Therefore, if some participants show low (<75%) adherence rates, we intend to do a sensitivity analyses in order to determine how sensitive the exercise responses are to reaching (≥75%) or not reaching (<75%) the *a priori* set adherence rate. If adherence rate influences the exercise response, we will consider to include adherence rate as a covariate in the statistical analyses.

[1] http://www.adapt2row.com/

Control group

The participants allocated to the control group will be asked to maintain their normal lifestyle throughout the intervention period. When the 6-months follow-up testing has been terminated, the control group will receive information about the exercise guidelines and the benefits of physical activity. Additionally, if requested, the principal investigator will organize contact to facilities where participants in the control group can perform adapted rowing.

Main trial day protocol

The experimental procedures will be similar at baseline, halfway, post intervention, and at follow-up 6 months later. To account for within-day variation, the procedures will be performed at the same time of day for each participant. Participants will arrive at the exercise laboratory at Aalborg University for testing. Participants will be asked to refrain from any strenuous exercise (>24 h), caffeine, alcohol, polyphenols, vitamin C, and supplements known to affect the cardiovascular system (>12 h), and attend in a fasted (>6 h) state. [71] Any smokers must abstain from smoking for >6 h prior to each visit [71]. If participants are taking medication, a wash-out period of at least 4-5 times the half-life of the drug (typically 24-48 h) will be used. If a drug cannot be withdrawn due to health issues, testing will be performed after a consistent time period after intake, as recommended for studies examining vascular function [71,72]. On trial days, participants will receive a standardized snack (energy bar) after completion of the FMD measurement. Participants will be asked to empty their bladder before any testing is commenced, and are allowed to drink water ad libitum during the test days.

INSERT FIGURE 1

Blood collection procedure

On a separate day, after an overnight fast (i.e. ≥10 hours of fasting), participants will have approximately 20 mL blood drawn from a peripheral vein. Blood samples will be aliquoted and stored at -80^0 at the Department of Clinical Biochemistry, Aalborg University Hospital, until analyses. Blood samples will be analyzed for indicators of cardiometabolic health (markers of glucose homeostasis, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and prothrombotic risk) as well as inflammatory markers (pro- and anti-inflammatory markers). Blood sampling will be conducted within a week prior to commencing the intervention (baseline), between 36 and 60 hours after the last exercise session in week 6 (halfway) and week 12 (post) to minimize any effects from the last exercise session, and 6 months after the termination of the intervention (6-months follow-up).

Outcome measures

Primary outcome

The primary outcome is fasting insulin, since it is one of the hallmarks of the metabolic syndrome [73,74], and has shown to be modifiable with exercise training in individuals with SCI [20].

Secondary key outcomes

Arterial blood pressure (BP) and resting heart rate (HR)

After resting for 10 min, participants will have their resting systolic and diastolic BP and HR measured with an automated BP monitoring device (OMRON M3, OMRON Healthcare, Hoofddorp, Netherlands). Measurements will be performed twice, with participants in sitting position. If these measurements deviate >5 %, a third measurement will be performed. The lowest values will be used for further analyses.

Body composition

Participants will have their body mass measured while sitting in their wheelchair (wearing light clothing) using a platform wheelchair scale (Detecto ® 6550 wheelchair scale, Webb City, MO, USA). Body mass will be derived by subtracting the weight of the wheelchair from the total mass and rounded to the nearest 0.1 kg [75]. Supine height (cm) will be measured in supine position using non-elastic tape. For participants with contractures precluding stretching of the legs, length will be measured in segments from heel to top of the skull [76]. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (m^2). Waist circumference and waist-to-hip circumference ratio will be used as a surrogate for visceral adiposity [75–77]. Participants will have their waist and hip circumference measured in supine position following a deep expiration. Waist and hip circumference will be measured immediately below the lowest rib [76] and widest part of the trochanters [77], respectively. For all circumference measurements, the tape will be placed directly on the skin with the participants arms by the side [76]. Anthropometric measures will be taken in duplicate (height, waist and hip circumference), rounded to the nearest 0.1 cm and reported as the mean. If the difference between the first and second measure is >0.1 cm, a third measure will be obtained. [76]

Autonomic nervous system function

Increasing evidence suggest that autonomic dysfunction accentuates the risk for adverse cardiovascular events [78]. Individuals with SCI are prone to autonomic disturbances as a consequence of disruption to the spinal cord [7], placing them at increased risk for autonomic related cardiovascular diseases. It is generally accepted that the heart in individuals with SCI below T6 is innervated by both sympathetic and parasympathetic neurons. In contrast, due to disruption of sympathetic outflow, parasympathetic innervation dominates in individuals with complete cervical and upper thoracic injuries, thereby resulting in bradycardia, reduced cardiac output and arterial BP [7]. Recently, it has been shown, however, that sympathetic control can be partially preserved in athletes with a cervical motor complete injury, with the degree of preservation being an important determinant of exercise performance [79]. Yet, whether exercise training can alter autonomic

nervous system function (e.g. balance between sympathetic and parasympathetic activity) in individuals with SCI is uncertain. Thus, as assessment of autonomic nervous system function, HR variability (HRV) [78,80] and arterial BP changes in response to an orthostatic challenge (sit-up tilt test) [79] will be measured as exploratory aims. For HRV measurements, participants will be equipped with a 4-lead surface electrodes on their chest and have their electrocardiogram (ECG) recorded (LabScribe v4, iWorx, Dover, NH, US) during 5 min of quiet rest. ECG data will be exported to dedicated software (Kubios HRV Standard 3.2.0; Kuopio, Finland) for analyses of frequency-domain parameters (low frequency power, high frequency power and total power) and time-domain parameters (HR and the root mean square of successive RR interval differences) in accordance with guidelines from The European Society of Cardiology and Heart Rhythm Society [81,82]. For the sit-up tilt test, participants will be equipped with a finger plethysmograph (Finometer, Finapres Medical Systems BV, Enschede, the Nederlands) for continuous and non-invasive measurement of arterial BP and HR during a 10 min orthostatic challenge (sit-up test). Briefly, after 10-15 min of supine rest with baseline recordings, participants will be moved (i.e. without assistance from the participant) to an upright seating position with their legs hanging free of the bed at an angle of 90° [79]. Changes in systolic BP and diastolic BP will be calculated as the difference between mean seated and supine BPs [83]. The presence of orthostatic hypotension will be defined as a ≥20 mm Hg drop in systolic BP or a ≥10 mm Hg drop in diastolic BP when moving to an upright position [84].

Vascular structure and function

After a rest period of 10-15 min in a quiet and darkened room, vascular structure and function will be evaluated non-invasively using ultrasonography (LOGIQ S8 XDclear, GE Healthcare) following recent guidelines on assessment of conduit [71,85] and resistance [72] vessel function. Conduit artery structure will be determined in the common carotid artery (CCA) and brachial artery (BA) with B-mode echoes using a 10 MHz multifrequency linear assay ultrasound probe. Measures of CCA and BA structure will be reported as intima media thickness (IMT) (mm), lumen diameter (mm), and wall-to-lumen ratio. The B-mode image will be optimized by changing depth and resolution, and will be kept constant between study visits.

To assess BA and resistance vessel function, endothelial dependent flow-mediated dilation (FMD) and reactive hyperemia will be determined by cuff occlusion followed by re-perfusion [29]. First, participants will have their baseline BA diameter measured for a period of 30 s. Then, a cuff placed distally on the forearm (i.e. distal to the ultrasound probe) will be inflated for 5 min up to a pressure that exceeds systolic BP by >50 mmHg. After 5 min, the cuff will be deflated and post-deflation diameter and blood velocity will be continuously recorded for 3 min [71]. For determination of FMD, both absolute (mm) and relative (%) change in diameter from baseline to post-deflation will be calculated. Given the importance of shear stress as the stimulus for the FMD response [86], continuous and simultaneous measurement of pulse-wave velocity (Doppler) and diameter (B-mode) using duplex ultrasound will be performed. This allows for an estimation

of the shear stress stimuli through the calculation of shear rate, which then can be used to normalize the FMD response [87]. Because the error of the insonation estimation increases exponentially with angles >60° [88], an insonation angle of ≤60° will be used, with the sample volume adjusted to cover the total width of the vessel.

Resistance vessel function will be determined by the magnitude of the reactive hyperemic response to cuff-induced ischemia. Several measures obtained from the reactive hyperemic response will be reported, including absolute blood flow (calculated based on the diameter derived cross sectional area and blood velocity) and velocity, peak change in blood flow, and blood flow area under the curve (AUC) across the post-deflation time period.

Although related, the measure of reactive hyperemia mirrors the magnitude of downstream resistance artery dilation, whereas FMD represents conduit artery dilation [72].

To ensure that the same part of the CCA and BA will be insonated across study visits, anatomical landmarks will be identified and recorded together with a photo of the insonation sites. All insonation settings (including sample volume, insonation angle, and recording time) and occlusion procedure (including cuff-position, pressure and duration) will be held consistent within participants across study visits. For standardization, the same investigator will perform all measurements and all analyses (blinded to the identity of the data).

Metabolic and inflammatory profile

The metabolic and inflammatory profile will be assessed via measures of glycemic control (fasting glucose, long-term blood glucose (HbA1c, glycosylated hemoglobin), homeostatic model assessment of insulin resistance (HOMA-IR)), lipid profile (HDL-c, LDL-c, total cholesterol and triglycerides (TG)), pro-inflammatory (C-reactive protein (CRP), interleukin (IL) 6, tumor necrosis factor-alpha), anti-inflammatory (IL-10, IL1RA)), prothrombotic (PAI-1), markers of NAFLD (hepatic enzymes (alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST)), growth differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21)).

Cardiorespiratory fitness level

Cardiorespiratory fitness level will be determined through an incremental arm-cranking test to exhaustion, with peak oxygen consumption (VO_{2peak}) and ventilatory thresholds as the outcome measures. The placement of the ergometer (Monark 881E, Vansbro, Sverige) will be adjusted such that the participants shoulder joint is aligned with the crank axis with the elbows slightly bend. Participants will be equipped with a HR monitoring belt (Suunto Ambit3 Run; Suunto, Vantaa, Finland) and a face mask, connected to an online open-circuit metabolic cart. The cart (JAEGER, Vyntus CPX, Carefusion) will be calibrated to known volumes and gas concentrations according to manufactural guidelines. After a 1-min warm-up with zero

resistance, the test begins with an individualized starting load (5-90W) [89] with increases in work load (5 or 10W) every minute [90] until volitional fatigue, defined as an inability to maintain cadence above 55 rounds per minute (rpm) [89]. The individual starting load and increment size will be chosen based on training history and anticipated physical capacity, with the aim of reaching exhaustion within 8-12 minutes at a cadence of 60-70 rpm [90,91]. Breath-by-breath VO_2 and carbon dioxide output (VCO_2), and HR will be measured continuously throughout the test. VO_{2peak} will be reported in both absolute (l $O_2 \cdot min^{-1}$) and relative (ml $O_2 \cdot kg^{-1} \cdot min^{-1}$) terms, and defined as the highest 30-s average during the test, with the corresponding HR reported as HR_{peak}. The highest workload that is achieved for ≥30-s will be reported as PO_{peak}. Participants will be asked to indicate RPE (Borg 6-20 scale) during the last 15-s of each minute. On test cessation, participants will gradually cool-down for 5-min, while their BP will be measured immediately before and after this recovery period.

As part of the cardiorespiratory fitness assessment, the first ventilatory threshold (VT1) and the second ventilatory threshold (VT2) will be determined during the incremental arm-cranking test. V1 and V2 represents distinct physiological events, but are both related to an increase in blood lactate and a subsequent increase in VCO_2 in response to increased exercise intensity [92]. Each VT will be defined according to the V-slope method or the ventilatory equivalent method, depending on which plot most clearly illustrates the particular VT [92]. In addition, a plot showing the respiratory exchange ratio (RER) will be used as extra reference in order to support the recognition of individual thresholds [92]. Thresholds will be determined independently by two researchers, with the average value used for analysis [93]. In case of deviation of >5 % for individual thresholds, the disparity will be discussed and a mutual agreement will be found [93]. Although 1-min stages seems short for the attainment of steady state, the usage of 1-min stages have previously shown to be efficient for the detection of VTs on a group level, especially in paraplegics [92].

Other secondary outcomes

Shoulder pain

The prevalence and severity of shoulder pain will be assessed using the Danish version [94] of the Wheelchair Users Shoulder Pain Index (WUSPI)) [95]. WUSPI is a valid and reliable measure of shoulder pain in manual wheelchair users [51] The questionnaire utilizes a series of visual analog scales (VAS) ranging from “no pain” to “worst pain ever experienced”, and it is a self-reported measure of the prevalence and severity of shoulder pain during different activities such as dressing, bathing, transfer, wheeling up, sleeping etc. [95]. Some participants may not perform all of the 15 activities. To account for that, a performance-corrected shoulder pain score (PC-WUSPI) will be calculated by dividing the raw total WUSPI score by the number of performed activities, multiplied by 15 [96].

Health-related quality of life (HRQOL)

HRQOL will be monitored using the Danish translated version of the Short Form-36 (SF-36) [97], which is a reliable and validated questionnaire to assess HRQOL within both a physical and mental health domain [98]. Certain questions of the SF-36 will be adapted to wheelchair use. Specifically, the questions referring to 'walk' and 'stair-climbing' is substituted by the words 'climb' and 'go up', as previously recommended [99] . Construct validity stays acceptable with this modification [99]. Data will be scored using the RAND 36-item Health survey 1.0 method [100], in which original responses is transformed into a score from 0-100, with 100 representing the best possible health. Individual item scores is then averaged within domains to create eight subscales, four representing physical QOL and four representing mental QOL. For reporting of HRQOL, a physical component summary score (PCS) and a mental component summary score (MCS) will be created based on the average of each component subscales [101].

Leisure time physical activity

To determine the effects of the exercise intervention on short-term (6 and 12-weeks follow-up) and long-term (6-months follow-up) habitual physical activity, leisure time physical activity levels will be monitored using the Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury (LTPAQ-SCI) [102]. In brief, the LTPAQ-SCI is a valid and reliable self-reported measure of leisure time physical activity that assesses minutes of mild, moderate, and heavy intensity leisure time physical activity performed over the previous 7 days [102]. Participants in both the intervention and the control group will be asked to complete the LTPAQ-SCI once every week throughout the 12-weeks intervention period and again once during the week leading up to the 6-months follow-up. In addition, completion of the LTPAQ-SCI will work as a training diary for the intervention group, allowing us to monitor leisure time physical activity performed beyond the amount related to the exercise intervention, which will strengthen our ability to interpret the results from the intervention.

Feasibility and acceptability of the exercise intervention

Satisfaction with the exercise intervention will be evaluated with the Feasibility and Acceptability Questionnaire [103]. In brief, participants will be asked to rate how feasible and acceptable they consider the rowing exercise to be on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). The questionnaire consists of six questions addressing issues such as how fun the exercise was perceived; the difficulty level of the exercise; and whether they received appropriate guidance in how to perform the exercise. A mean score of ≥3.0 will be used as a criterion to indicate that the intervention is acceptable [103]. Additionally, compliance to the exercise intervention will be recorded and presented as compliance rate (% participation). Compliance is defined as the number of exercise sessions completed out of the total number (36) of sessions.

Statistics

The between group difference in changes of outcome variables will be examined from baseline to 6-weeks follow-up (secondary endpoint), from baseline to post intervention (12-weeks follow-up; primary endpoint) and again from post intervention to follow-up 6-months later (secondary endpoint).

Primary and secondary endpoint data are ratio and interval data and will therefore be treated as continuous variables. Between group comparisons on primary and secondary endpoint will be dependent on data distribution. We anticipate data to be approximately normally distributed, however before any analysis are commenced, distribution of the data will be assessed through visual inspection of Q-Q-plots and histograms, complemented by test of deviation from normality (Shapiro Wilk test). Assuming normality, descriptive data will be presented as mean ± standard deviation (SD), and a two-way analysis of variance (ANOVA) with repeated measurements will be used to evaluate any significant changes in outcomes between (control and exercise) and within (baseline, 6-weeks, and 12-weeks follow-up) groups from baseline to immediately after the 12-weeks intervention period. Same procedure will be done for the 6-months follow-up (factor 1: group (control and exercise), factor 2: time (baseline, 12-weeks and 6-months follow-up). Interactions between the factors will be included in the model. In case of significant F-values, post-hoc testing will be used for multiple comparisons. Effect size of change scores (Cohen's d) will be calculated in order to determine the magnitude of difference between groups. P-values and 95% confidence intervals will be reported to facilitate interpretation of the results. Statistical significance will be accepted at $P < 0.05$.

Patient and public involvement

Neither participants nor public were involved with the conception of the research question, study design, or outcome measures, nor will they be involved with study conduction. The recruitment plan was partially planned based on feedback from the patient population. Each of the participants will receive a written summary of the study results after publication.

Ethics and dissemination

Considerations are made regarding the regulation of arterial BP in the participants [104 105]. BP instability does occur in cervical injured individuals (tetraplegics), who may suffer from pronounced autonomic disturbances [104,105]. During the VO_{2peak} test and exercise sessions, special attention is devoted towards potential symptoms of autonomic dysreflexia (AD) [106] in individuals with SCI ≥T6. Participants will be asked to empty their bladder before any testing or training is commenced. In case of AD, the exercise is stopped and the pertinent actions are made. Occurrences of post exercise hypotension [105] and orthostatic hypotension [104] are rather uncommon in individuals with thoracic injury (paraplegics). According to the inclusion criteria of the study, only individuals with a sparing of arm flexor function (i.e. excluding individuals with a complete cervical injury ≥C5 participants) will be included in the study, presumably reducing the number of included individuals with impaired BP regulation. Nevertheless, in addition to reduced vasoconstrictor drive, the ability to increase cardiac output is limited in individuals with SCI ≥T5-T6 with interrupted cardiac

sympathetic innervation, which could affect arterial BP stabilization during conditions in which peripheral vascular resistance is further reduced (i.e. during exercise). Therefore, to identify any participants that may be prone to experiencing post exercise hypotension, brachial artery BP will be monitored immediately after, and again 5 min after the first VO_{2peak} test. In such cases, and assuming the hypotension is well tolerated, the participants will be reminded to drink appropriately during and prior any future training and testing. Further, these participants will have their BP measured every second interval (i.e. every 10th min) during the training sessions. If hypotension develops, the training will be interrupted and hypotensive countermaneuvres (placement in a supine position, or legs up) will be applied. If the hypotension is not tolerated, such as if the participants exhibit signs of nausea, light-headedness, fatigue or presyncobal symptoms in response to either the VO_{2peak} test or the training, they will be excluded from further participation in the study.

Another consideration is that individuals with SCI suffer from impaired thermoregulation [107]. Although prolonged (60 min) moderate intensity exercise in warm conditions (>31°C) have been shown sustainable for some paraplegic and tetraplegic individuals [108], impaired thermoregulation makes individuals with SCI more vulnerable to overheating compared to able-bodied [107]. This is especially the case during conditions of increased environmental temperatures and metabolic heat production (such as when exercising in the heat). The degree of thermoregulatory impairment is closely related to the injury level, such that individuals with higher injury (tetraplegics) exhibit higher core temperatures during exercise compared to lower injury individuals (paraplegics) [108]. To diminish the risk for overheating during testing and training, a fan will be available for cooling of the participants and the room temperature and humidity will be continuously monitored to facilitate the conditions for dry and evaporative heat loss. Moreover, the participants will be asked to pay attention to proper hydration before and throughout each training session. However, if the participants demonstrate signs of any adverse response, the exercise session will be terminated immediately and further participation in the study will be reconsidered. Any adverse responses from the intervention will be reported to the regional health research committee. The trial is reported to the Danish Data Protection Agency (J.nr. 2019-899/10-0406), registered at ClinicalTrials.gov on 15 May 2020, and approved by the Committees on Health Research Ethics in The North Denmark Region on 12 December 2019 (Journal-nr. N-20190053). Results will be submitted to scientific journals related to exercise and SCI for publication irrespective of study outcomes.

Data statement section

All participant data will be stored in a secure web-based database (Redcap) with restricted access and ID code, in accordance with data protection rules. Source documents including date, visit# and participant ID will be scanned and saved as electronic copies. Participant data will be transferred directly or by use of an encrypted USB stick. Each participant will be assigned an unique identification number, which will be the only identifier exported from Redcap upon data analysis. Except for the blood samples, which will be stored

until analysis, or no more than 5 years, data will be stored for 5 years after the termination of the trial. After this period, paper material is shredded, data files are erased and the Redcap database is no longer accessible. The principal investigator will have access to all trial data.

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Author Contributions

RKH and RGL conceptualized the study. RKH, AS, UL, AH and RGL contributed to the study protocol design. RKH drafted the manuscript. RKH, AS, UL, AH and RGL commented and edited the manuscript and approved the final version.

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Competing interests

None declared.

Patient consent

Not required.

Figure 1. Study overview. INT = intervention; CON = control; RPE = rating of perceived exertion; LTPA = leisure time physical activity.

REFERENCES

1. LaPorte, R. *et al.* The Spectrum of Physical Activity, Cardiovascular Disease and Health: An Epidemiologic Perspective. *Am J Epidemiol.* **120**, 507–517 (1984).
2. Myers, J., Lee, M. & Kiratli, J. Cardiovascular disease in spinal cord injury: An overview of prevalence, risk, evaluation, and management. *Am. J. Phys. Med. Rehabil.* **86**, 142–152 (2007).
3. Nash, M. & Cowan, R. Cardiovascular disease, SCI and exercise: unique risks and focused countermeasures. *Disabil. Rehabil.* **32**, 2228–2236 (2010).
4. Garshick, E. *et al.* A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* **43**, 408–416 (2005).
5. Buchholz, A. C. *et al.* Greater daily leisure time physical activity is associated with lower chronic disease risk in adults with spinal cord injury. *Appl. Physiol. Nutr. Metab.* **34**, 640–647 (2009).
6. Gorgey, A., Dolbow, D., Dolbow, J., Khalil, R. & Gater, D. Effects of spinal cord injury on body composition and metabolic profile – Part I. *J. Spinal Cord Med.* **37**, 693–702 (2014).
7. Ahuja, C. S. *et al.* Traumatic spinal cord injury. *Nat. Rev. Dis. Prim.* **3**, 1–21 (2017).
8. Kirshblum, S. C. *et al.* International standards for neurological classification of spinal cord injury (Revised 2011). *J. Spinal Cord Med.* **34**, 535–546 (2011).
9. Haisma, J. A. *et al.* Physical capacity in wheelchair-dependent persons with a spinal cord injury: A critical review of the literature. *Spinal Cord* **44**, 642–652 (2006).
10. Groah, S. L., Weitzenkamp, D., Sett, P., Soni, B. & Savic, G. The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. *Spinal Cord* **39**, 310–317 (2001).
11. Spinal Cord Injury Research Evidence (SCIRE) Community. *Manual Wheelchairs*. *Practitioner* www.scireproject.com/community/topic/manual-wheelchairs/%0AManual (2020) doi:10.29085/9781783304509.002.
12. Kehn, M. & Kroll, T. Staying physically active after spinal cord injury: A qualitative exploration of barriers and facilitators to exercise participation. *BMC Public Health* **9**, 1–11 (2009).
13. Rimmer, J. H., Riley, B., Wang, E., Rauworth, A. & Jurkowski, J. Physical activity participation among persons with disabilities: Barriers and facilitators. *Am. J. Prev. Med.* **26**, 419–425 (2004).
14. Hansen, R. K., Larsen, R. G., Læssøe, U., Samani, A. & Cowan, R. E. Physical Activity Barriers in Danish Manual Wheelchair Users - A Cross-sectional Study. *Submitt. Manuscr.* (2020).
15. Cowan, R. E., Nash, M. S. & Anderson, K. D. Exercise participation barrier prevalence and association with exercise participation status in individuals with spinal cord injury. 27–32 (2013) doi:10.1038/sc.2012.53.
16. Rimmer, J. H., Rubin, S. S. & Braddock, D. Barriers to exercise in African American women with physical disabilities. *Arch. Phys. Med. Rehabil.* **81**, 182–188 (2000).
17. Rimmer, J. H., Wang, E. & Smith, D. Barriers associated with exercise and community access for individuals with stroke. *J. Rehabil. Res. Dev.* **45**, 315–322 (2008).
18. Van Der Scheer, J. W. *et al.* Effects of exercise on fitness and health of adults with spinal cord injury: A systematic review. *Neurology* **89**, 736–745 (2017).

19. El-Sayed, M. S. & Younesian, A. Lipid profiles are influenced by arm cranking exercise and training in individuals with spinal cord injury. *Spinal Cord* **43**, 299–305 (2005).

20. Nightingale, T. E., Walhin, J. P., Thompson, D. & Bilzon, J. L. J. Impact of Exercise on Cardiometabolic Component Risks in Spinal Cord-injured Humans. *Med. Sci. Sports Exerc.* **49**, 2469–2477 (2017).

21. Kim, D. Il, Lee, H., Lee, B. S., Kim, J. & Jeon, J. Y. Effects of a 6-Week Indoor Hand-Bike Exercise Program on Health and Fitness Levels in People With Spinal Cord Injury: A Randomized Controlled Trial Study. *Arch. Phys. Med. Rehabil.* **96**, 2033–2040 (2015).

22. Totosy de Zepetnek, J. O., Pelletier, C. A., Hicks, A. L. & MacDonald, M. J. Following the Physical Activity Guidelines for Adults With Spinal Cord Injury for 16 Weeks Does Not Improve Vascular Health: A Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* **96**, 1566–1575 (2015).

23. Wilt, T. J. *et al.* Carbohydrate and lipid disorders and relevant considerations in persons with spinal cord injury (Structured abstract). *Database Abstr. Rev. Eff.* 171 (2008).

24. Pelletier, C. A., Omidvar, M., Miyatani, M., Giangregorio, L. & Craven, B. C. Participation in moderate-to-vigorous leisure time physical activity is related to decreased visceral adipose tissue in adults with spinal cord injury. *Appl. Physiol. Nutr. Metab.* **43**, 139–144 (2018).

25. Nightingale, T. E., Metcalfe, R. S., Vollaard, N. B. & Bilzon, J. L. Exercise Guidelines to Promote Cardiometabolic Health in Spinal Cord Injured Humans: Time to Raise the Intensity? *Arch. Phys. Med. Rehabil.* **98**, 1693–1704 (2017).

26. Hicks, A. L. *et al.* The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: A systematic review. *Spinal Cord* **49**, 1103–1127 (2011).

27. Green, D. J., Driscoll, G. O., Joyner, M. J. & Cable, N. T. Exercise and cardiovascular risk reduction : Time to update the rationale for exercise ? Exercise and cardiovascular risk reduction : Time to update the rationale for exercise ? 766–768 (2013) doi:10.1152/japplphysiol.01028.2007.

28. Gielen, S., Schuler, G. & Hambrecht, M. Exercise Training in Coronary Artery Disease and Coronary Vasomotion. *Circulation* **103**, 1–6 (2001).

29. Celermajer, D. *et al.* Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis Endothelial. *Lancet* **340**, 1111–1115 (1992).

30. Yeboah, J. *et al.* Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: The multi-ethnic study of atherosclerosis. *Circulation* **120**, 502–509 (2009).

31. Lorenz, M. W., Markus, H. S., Bots, M. L., Rosvall, M. & Sitzer, M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation* **115**, 459–467 (2007).

32. Green, D. J., Hopman, M. T. E., Padilla, J., Laughlin, M. H. & Thijssen, D. H. J. Vascular adaptation to exercise in humans: Role of hemodynamic stimuli. *Physiol. Rev.* **97**, 495–528 (2017).

33. de Groot, P. C., Bleeker, M. W., van Kuppevelt, D. H., van der Woude, L. H. & Hopman, M. T. Rapid and Extensive Arterial Adaptations After Spinal Cord Injury. *Arch. Phys. Med. Rehabil.* **87**, 688–696 (2006).

34. Rowley, N. J. *et al.* Conduit diameter and wall remodeling in elite athletes and spinal cord injury. *Med. Sci. Sports Exerc.* **44**, 844–849 (2012).

35. de Groot, P. C. E., Poelkens, F., Kooijman, M. & Hopman, M. T. E. Preserved flow-mediated dilation in the inactive legs of spinal cord-injured individuals. *Am J Physiol Hear. Circ Physiol* **287**, 374–380 (2004).

36. Huonker, M., Schmid, A., Schmidt-Trucksäß, A., Grathwohl, D. & Keul, J. Size and blood flow of central and peripheral arteries in highly trained able-bodied and disabled athletes. *J. Appl. Physiol.* **95**, 685–691 (2003).

37. Ginis, K. A. M. *et al.* The development of evidence-informed physical activity guidelines for adults with spinal cord injury. *Spinal Cord* **49**, 1088–1096 (2011).

38. Pelletier, C. A., Totosy De Zepetnek, J. O., Macdonald, M. J. & Hicks, A. L. A 16-week randomized controlled trial evaluating the physical activity guidelines for adults with spinal cord injury. *Spinal Cord* **53**, 363–367 (2015).

39. Martin Ginis, K. A. *et al.* Evidence-based scientific exercise guidelines for adults with spinal cord injury: An update and a new guideline. *Spinal Cord* **56**, 308–321 (2018).

40. Cratsenberg, K. A. *et al.* Effectiveness of exercise programs for management of shoulder pain in manual wheelchair users with spinal cord injury. *J. Neurol. Phys. Ther.* **39**, 197–203 (2015).

41. Troy, K., Munce, T. & Longworth, J. An exercise trial targeting posterior shoulder strength in manual wheelchair users: Pilot results and lessons learned. *Disabil. Rehabil. Assist. Technol.* **10**, 415–420 (2015).

42. Nash, M. S. *et al.* A comparison of 2 circuit exercise training techniques for eliciting matched metabolic responses in persons with paraplegia. *Arch. Phys. Med. Rehabil.* **83**, 201–209 (2002).

43. Curtis, K. *et al.* Effect of a standard exercise protocol on shoulder pain in long-term wheelchair users. *Spinal Cord* **37**, 421–429 (1999).

44. Ballinger, D. A., Rintala, D. H. & Hart, K. A. The relation of shoulder pain and range-of-motion problems to functional limitations, disability, and perceived health of men with spinal cord injury: A multifaceted longitudinal study. *Arch. Phys. Med. Rehabil.* **81**, 1575–1581 (2000).

45. Nichols, P., Norman, P. & Ennis, J. Wheelchair user's shoulder? *Scand J Rehab Med* **11**, 29–32 (1979).

46. Gutierrez, D., Thompson, L., Kemp, B. & Mulroy, S. The relationship of shoulder pain intensity to quality of life, physical activity, and community participation in persons with paraplegia. *J. Spinal Cord Med.* **30**, 251–255 (2007).

47. Nash, M. S., van de Ven, I., van Elk, N. & Johnson, B. M. Effects of Circuit Resistance Training on Fitness Attributes and Upper-Extremity Pain in Middle-Aged Men With Paraplegia. *Arch. Phys. Med. Rehabil.* **88**, 70–75 (2007).

48. Leduc, B. & Lepage, Y. Health-related quality of life after spinal cord injury. *Disabil. Rehabil.* **24**, 196–202 (2002).

49. Lidal, I., Veenstra, M., Hjeltnes, N. & Biering-Sørensen, F. Health-related quality of life in persons with long-standing spinal cord injury. *Spinal Cord* **46**, 710–715 (2008).

50. Ambrosio, F. *et al.* Biomechanics and strength of manual wheelchair users. *J. Spinal Cord Med.* **28**, 407–414 (2005).

51. Curtis, K. *et al.* Reliability and validity of the Wheelchair User's Shoulder Pain Index (WUSPI). *Paraplegia* **33**, 595–601 (1995).

52. Burnham, R. S., May, L., Nelson, E., Steadward, R. & Reid, D. C. Shoulder pain in wheelchair

athletes: The role of muscle imbalance. *Am. J. Sports Med.* **21**, 238–242 (1993).

53. Bayley, J., Cochran, T. & Sledge, C. The weight-bearing shoulder. The impingement syndrome in paraplegics. *J. Bone Jt. Surg.* **69**, 676–678 (1987).

54. Collinger, J. L. *et al.* Shoulder Biomechanics During the Push Phase of Wheelchair Propulsion: A Multisite Study of Persons With Paraplegia. *Arch. Phys. Med. Rehabil.* **89**, 667–676 (2008).

55. Mulroy, S. J. *et al.* Strengthening and Optimal Movements for Painful Shoulders (STOMPS) in Chronic Spinal Cord Injury: A Randomized Controlled Trial. *Phys. Ther.* **91**, 305–324 (2011).

56. Secher, N. The Physiology of Rowing. *J. Sports Sci.* **1**, 23–53 (1983).

57. Olenik, L., Laskin, J., Burnham, R., Wheeler, G. & Steadward, R. Efficacy of rowing, backward wheeling and isolated scapular retractor exercise as remedial strength activities for wheelchair users: Application of electromyography. *Paraplegia* **33**, 148–152 (1995).

58. Curtis, K. *et al.* Effect of a standard exercise protocol on shoulder pain in long-term wheelchair users. *Spinal Cord* **37**, 421–429 (1999).

59. Chan, A. *et al.* SPIRIT 2013 Statement : Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med* **158**, 200–207 (2013).

60. Lee, R. *et al.* Active vs. passive methods of recruiting ethnic minority women to a health promotion program. *Ann. Behav. Med.* **19**, 378–384 (1997).

61. Ginis, K. a M. & Hicks, A. L. Exercise research issues in the spinal cord injured population. *Exerc. Sport Sci. Rev.* **33**, 49–53 (2005).

62. Astorino, T. A. & Thum, Jacob, S. Interval training elicits higher enjoyment versus moderate exercise in persons with spinal cord injury. *J. Spinal Cord Med.* **41**, 77–84 (2018).

63. Powell, K. E., Paluch, A. E. & Blair, S. N. Physical Activity for Health: What Kind? How Much? How Intense? On Top of What? *Annu. Rev. Public Health* **32**, 349–365 (2011).

64. Borg, G. Perceived exertion as an indicator of somatic stress. *Scand J Rehab Med* 92–98 (1970).

65. Birk, T. J. & Birk, C. A. Use of Ratings of Perceived Exertion for Exercise Prescription. *Sport. Med.* **4**, 1–8 (1987).

66. Goosey-Tolfrey, V. *et al.* Regulating intensity using perceived exertion in spinal cord-injured participants. *Med. Sci. Sports Exerc.* **42**, 608–613 (2010).

67. van der Scheer, J. W., Hutchinson, M. J., Paulson, T., Martin Ginis, K. A. & Goosey-Tolfrey, V. L. Reliability and Validity of Subjective Measures of Aerobic Intensity in Adults With Spinal Cord Injury: A Systematic Review. *PM R* **10**, 194–207 (2018).

68. Lewis, J. E., Nash, M. S., Hamm, L. F., Martins, S. C. & Groah, S. L. The Relationship Between Perceived Exertion and Physiologic Indicators of Stress During Graded Arm Exercise in Persons With Spinal Cord Injuries. *Arch. Phys. Med. Rehabil.* **88**, 1205–1211 (2007).

69. Noble, B. J., Borg, G. A. V., Jacobs, I., Ceci, R. & Kaiser, P. A category-ratio perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med. Sci. Sport. Exerc.* **16**, 523–528 (1983).

70. Krassioukov, A. V. *et al.* Effects of exercise interventions on cardiovascular health in individuals with chronic, motor complete spinal cord injury: protocol for a randomised controlled trial [Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (C. *BMJ Open* **9**, (2019).

71. Thijssen, D. H. J. *et al.* Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur. Heart J.* **40**, 2534–2547 (2019).

72. Limberg, J. K. *et al.* Assessment of resistance vessel function in human skeletal muscle : guidelines for experimental design , Doppler ultrasound , and pharmacology. (2020) doi:10.1152/ajpheart.00649.2019.

73. Grundy, S. *et al.* Diagnosis and managment of the metabolic syndrome AHA / NHLBI Scientific Statement. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2735–2752 (2005) doi:10.1161/CIRCULATIONAHA.105.169404.

74. Nash, M. S. *et al.* Identification and Management of Cardiometabolic Risk after Spinal Cord Injury: Clinical Practice Guideline for Health Care Providers. *Top. Spinal Cord Inj. Rehabil.* **24**, 379–423 (2018).

75. McCauley, L. S., Sumrell, R. M. & Gorgey, A. S. Anthropometric Prediction of Visceral Adipose Tissue in Persons With Motor Complete Spinal Cord Injury. *PM R* **10**, 817–825 (2018).

76. Edwards, L. A., Bugaresti, J. M. & Buchholz, A. C. The amount of visceral adipose tissue and the ratio of visceral to subcutaneous adipose tissue is greater in adults with vs. without spinal cord injury. *Faseb J.* **21**, A7–A8 (2007).

77. Sumrell, R. M., Nightingale, T. E., McCauley, L. S. & Gorgey, A. S. Anthropometric cutoffs and associations with visceral adiposity and metabolic biomarkers after spinal cord injury. *PLoS One* **13**, e0203049 (2018).

78. Joyner, M. J. & Green, D. J. Exercise protects the cardiovascular system: Effects beyond traditional risk factors. *J. Physiol.* **587**, 5551–5558 (2009).

79. West, C. R., Romer, L. M. & Krassioukov, A. Autonomic Function and Exercise Performance in Elite Athletes with Cervical Spinal Cord Injury. *Med. Sci. Sports Exerc.* **45**, 261–267 (2013).

80. Otsuka, Y., Shima, N., Moritani, T., Okuda, K. & Yabe, K. Orthostatic influence on heart rate and blood pressure variability in trained persons with tetraplegia. *Eur. J. Appl. Physiol.* **104**, 75–78 (2008).

81. Malik, M. et al. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur. Heart J.* **17**, 354–381 (1996).

82. Shaffer, F. & Ginsberg, J. P. An Overview of Heart Rate Variability Metrics and Norms. *Front. Public Heal.* **5**, 1–17 (2017).

83. Pelletier, C. A., Jones, G., Latimer-Cheung, A. E., Warburton, D. E. & Hicks, A. L. Aerobic capacity, orthostatic tolerance, and exercise perceptions at discharge from inpatient spinal cord injury rehabilitation. *Arch. Phys. Med. Rehabil.* **94**, 2013–2019 (2013).

84. American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* **46**, 1470 (1996).

85. Thijssen, D. H. J. *et al.* Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *Am. J. Physiol. - Hear. Circ. Physiol.* **300**, 2–12 (2011).

86. Pyke, K. E. & Tschakovsky, M. E. Peak vs. total reactive hyperemia: Which determines the magnitude of flow-mediated dilation? *J. Appl. Physiol.* **102**, 1510–1519 (2007).

87. Padilla, J. *et al.* Normalization of flow-mediated dilation to shear stress area under the curve

eliminates the impact of variable hyperemic stimulus. *Cardiovasc. Ultrasound* **6**, 1–10 (2008).

88. Thrush, A. & Hartshorne, T. *Vascular Ultrasound - How, When and Why*. *Churchill Livingstone* (2010). doi:10.1017/CBO9781107415324.004.

89. Maher, J. L. & Cowan, R. E. Comparison of 1- Versus 3-Minute Stage Duration During Arm Ergometry in Individuals With Spinal Cord Injury. *Arch. Phys. Med. Rehabil.* **97**, 1895–1900 (2016).

90. Eerden, S., Dekker, R. & Hettinga, F. J. Maximal and submaximal aerobic tests for wheelchair-dependent persons with spinal cord injury: a systematic review to summarize and identify useful applications for clinical rehabilitation. *Disabil. Rehabil.* **40**, 497–521 (2018).

91. Au, J. S., De Zepetnek, J. O. T. & MacDonald, M. J. Modeling perceived exertion during graded arm cycling exercise in spinal cord injury. *Med. Sci. Sports Exerc.* **49**, 1190–1196 (2017).

92. Kouwijzer, I. *et al.* Interrater and intrarater reliability of ventilatory thresholds determined in individuals with spinal cord injury. *Spinal Cord* **57**, 669–678 (2019).

93. Leicht, C. A., Griggs, K. E., Lavin, J., Tolfrey, K. & Goosey-Tolfrey, V. L. Blood lactate and ventilatory thresholds in wheelchair athletes with tetraplegia and paraplegia. *Eur. J. Appl. Physiol.* **114**, 1635–1643 (2014).

94. Larsen, C., Hansen, S., Hansen, L., P, B. & B, J.-K. Translation and Cross-Cultural Adaptation of the Danish Version: Wheelchair Users Shoulder Pain Index (WUSPI). in 1 (2015).

95. Curtis, K. *et al.* Development of the Wheelchair User's Shoulder Pain Index (WUSPI). *Paraplegia* **33**, 290–293 (1995).

96. Curtis, K. A. *et al.* Shoulder pain in wheelchair users with tetraplegia and paraplegia. *Arch. Phys. Med. Rehabil.* **80**, 453–457 (1999).

97. Bjorner, J. B., Thunedborg, K., Kristensen, T. S., Modvig, J. & Bech, P. The Danish SF-36 Health Survey: Translation and preliminary validity studies. *J. Clin. Epidemiol.* **51**, 991–999 (1998).

98. Ware, Jr., J. E. & Sherbourne, C. D. The MOS 36-Item Short-Form Health Survey (SF-36): I . Conceptual Framework and Item Selection Author. *Med. Care* **30**, 473–483 (1992).

99. Tate, D. G., Kalpakjian, C. Z. & Forchheimer, M. B. Quality of life issues in individuals with spinal cord injury. *Arch. Phys. Med. Rehabil.* **83**, 18–25 (2002).

100. RAND, H. C. 36-Item Short Form Survey (SF-36) Scoring Instructions. https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html.

101. Nightingale, T. E., Rouse, P. C., Walhin, J. P., Thompson, D. & Bilzon, J. L. J. Home-Based Exercise Enhances Health-Related Quality of Life in Persons With Spinal Cord Injury: A Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* **99**, 1998-2006.e1 (2018).

102. Ginis, K. A. M., Phang, S. H., Latimer, A. E. & Arbour-Nicitopoulos, K. P. Reliability and Validity Tests of the Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury. *Arch. Phys. Med. Rehabil.* **93**, 677–682 (2012).

103. Visovsky, C. & Corripio, J. Feasibility and Acceptability of a Resistance Exercise Intervention: For Women Undergoing Chemotherapy for Breast Cancer. *Nurs. Heal.* **3**, 110–119 (2015).

104. Claydon, V. E. & Krassioukov, A. V. Orthostatic Hypotension and Autonomic Pathways after Spinal Cord Injury. *J. Neurotrauma* **23**, 1713–1725 (2006).

105. Claydon, V. E., Hol, A. T., Eng, J. J. & Krassioukov, A. V. Cardiovascular Responses and Postexercise Hypotension After Arm Cycling Exercise in Subjects With Spinal Cord Injury. *Arch.*

Phys. Med. Rehabil. **87**, 1106–1114 (2006).

106. Phillips, A. A. & Krassioukov, A. V. Contemporary Cardiovascular Concerns after Spinal Cord Injury: Mechanisms, Maladaptations, and Management. *J. Neurotrauma* **32**, 1927–1942 (2015).

107. Sawka, M., Latzka, W. & Pandolf, K. Temperature Regulation During Upper Body Exercise: Able Bodied And Spinal Cord Injured. *Med. Eng. Phys.* **21**, 132–40 (1989).

108. Price, M. & Campbell, I. Effects of spinal cord lesion level upon thermoregulation during exercise in the heat. *Med. Sci. Sports Exerc.* **35**, 1100–1107 (2003).

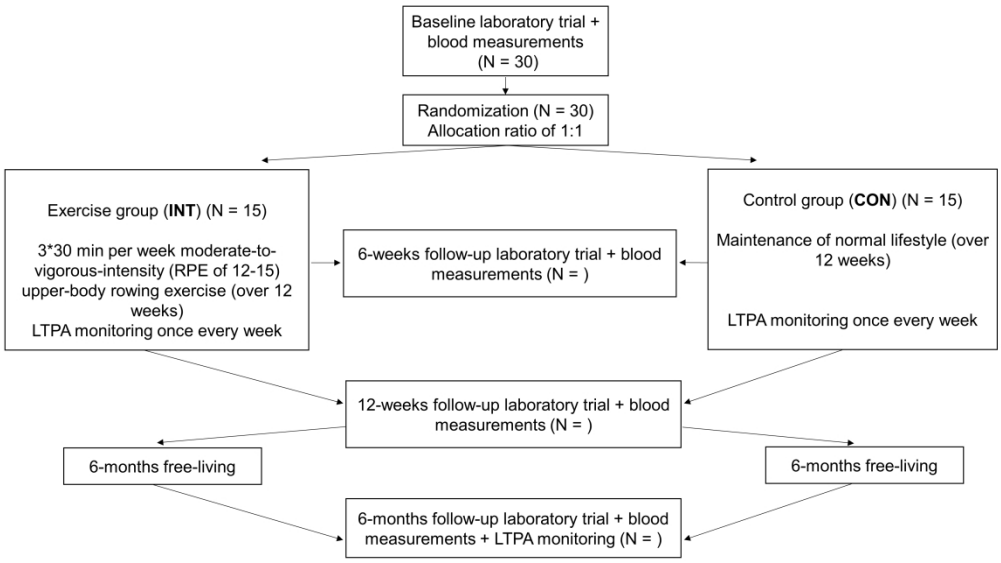

Figure 1. Study overview. INT = intervention; CON = control; RPE = rating of perceived exertion; LTPA = leisure time physical activity.

338x190mm (300 x 300 DPI)

Project title: Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users

Informed Consent to Participation in a Health Scientific Research Project

Title of the research project: Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured wheelchair users

Declaration by the Volunteer

I have received information about the research project both in writing and orally, and I have sufficient knowledge of the objective, method, advantages and disadvantages to confirm my participation.

I know that participation is voluntary and that I can always withdraw my consent without losing my present or future rights to treatment.

I hereby give my consent to participation in the research project and to taking out samples of my biological material for storage in a research bio-bank. I have received a copy of this form and of all written information about the project for my own use.

Name of the Volunteer: _____

Date: _____ Signature: _____

If new, significant health information appears during the research project, you will be informed. If you wish to **decline** receipt of this information, please tick here: __

Would you like to be informed of the results of the research project and of the consequences for you, if any?

Yes_____ No _____ (tick the appropriate field)

Declaration by the Person giving Information

I hereby declare that the Volunteer has received information both in writing and orally about the research project.

I believe that the information given is sufficient for making a decision on participation in the research project.

Name of the person giving the information: _____

Date: _____ Signature: _____

Project identification: N-20190053

Standard declaration of consent issued by Den Nationale Videnskabsetiske Komité, December 2011.
Translation into English made by Center for Sensory-Motor Interaction, Aalborg University

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4,9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a. The trial has been registered with details provided at Clinicaltrials.gov
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,2,20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether	20

		they will have ultimate authority over any of these activities	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a. No such committee has been established.
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6-8
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio,	9

		and framework (eg, superiority, equivalence, non-inferiority, exploratory)	
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10,12
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	10-11, 18-19

		response to harms, participant request, or improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-17
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a. Participants allocated to the exercise and control group cannot be blinded to the PI, because PI is responsible for conducting the study. Parts of data analysis will be blinded to the PI.
Methods: Data collection,			

management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-17
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19-20

Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-19
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	19
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators,	19

		REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19-20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19-20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to	n/a

		those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18-19
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	9
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for	12

	future use in ancillary studies, if applicable