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# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040727
Article Type:	Protocol
Date Submitted by the Author:	20-May-2020
Complete List of Authors:	Hansen, Rasmus; Aalborg Universitet, Health Science and Technology, Sport Sciences – Performance and Technology; Professionshøjskolen University College Nordjylland, Research and Innovation Samani, Afshin; Aalborg Universitet, Health Science and Technology, Sport Sciences – Performance and Technology Laessø, Uffe; Professionshøjskolen University College Nordjylland, Physiotherapy; Professionshøjskolen University College Nordjylland, Research and Innovation Handberg, Aase; Aalborg University Hospital, Clinical Biochemistry; Aalborg Universitet, Clinical Medicine Larsen, Ryan; Aalborg Universitet, Health Science and Technology, Sport Sciences – Performance and Technology
Keywords:	REHABILITATION MEDICINE, Physiology < NATURAL SCIENCE DISCIPLINES, Coronary heart disease < CARDIOLOGY, Neurological injury < NEUROLOGY, PUBLIC HEALTH, ULTRASONOGRAPHY

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4 1 **Cover Letter**

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6 2 **Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord injured**  
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8 3 **wheelchair users – Protocol for a randomized controlled trial**  
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10 4 Version: 1.0. Date: 20.05.2020.

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13 5 Dear Madam/Sir,

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15 6 We hereby submit this protocol manuscript for consideration for publication in BMJ Open because we think  
16 7 this study protocol is relevant to the focus of your journal.

17  
18 8 This research will determine if upper-body rowing, complying with the new exercise training guidelines (30  
19 9 minutes of moderate-to-vigorous intensity aerobic exercise, three times a week), is feasible and effective in  
20 10 reducing cardiometabolic risk in the spinal cord injured population. The results from this study will therefore  
21 11 provide novel information that can inform future intervention studies in spinal cord injured individuals.

22  
23 12 Recruitment of participants are planned to be commenced in September 2020.

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26 13 On behalf of all authors, I, as a corresponding author, hereby declare that 1) the submitted manuscript have  
27 14 not been published elsewhere or are not being considered for publication elsewhere; and 2) the research  
28 15 reported will not be submitted for publication elsewhere until a final decision has been made as to its  
29 16 acceptability in the BMJ Open.

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36 18 Yours sincerely

37 19 Rasmus Kopp Hansen, PhD student, MSc

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42 21 Rasmus Kopp Hansen, MSc<sup>1,2</sup> [rkopp@hst.aau.dk](mailto:rkopp@hst.aau.dk), <https://orcid.org/0000-0001-8515-8779>

43 22 Afshin Samani, PhD<sup>1</sup> [afsamani@hst.aau.dk](mailto:afsamani@hst.aau.dk), <https://orcid.org/0000-0001-6119-8231>

44 23 Uffe Laessoe, PhD<sup>2</sup> [ufl@ucn.dk](mailto:ufl@ucn.dk), <https://orcid.org/0000-0001-5388-1671>

45 24 Aase Handberg, DMSc, MD<sup>3,4</sup> [aaha@rn.dk](mailto:aaha@rn.dk), <https://orcid.org/0000-0001-5719-203X>

46 25 Ryan Godsk Larsen, PhD<sup>1</sup> [rl@hst.aau.dk](mailto:rl@hst.aau.dk), <https://orcid.org/0000-0002-4622-1453>

47  
48  
49  
50 26  
51 27 <sup>1</sup>Department of Health Science and Technology, Sport Sciences – Performance and Technology, Aalborg  
52 28 University, Aalborg, Denmark

53 29 <sup>2</sup>Department of Physiotherapy / Research and Innovation, University College of Northern Denmark,  
54 30 Aalborg, Denmark

55 31 <sup>3</sup>Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark  
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32 <sup>4</sup>*Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*

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34 **Keywords**

35 Spinal cord injuries; Exercise; Rowing; Cardiovascular; Risk factors; Metabolic health; Shoulder pain;  
36 Physical activity; Inflammation; Aerobic capacity

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39 Type of article: Protocol

40 Word count main text: 5881

41 Number of tables and figures: 1 figure.

42 Number of references: 104

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4 56 **Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord**  
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6 57 **injured wheelchair users – Protocol for a randomized controlled trial**  
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8 58 Rasmus Kopp Hansen, MSc<sup>1,2</sup>, Afshin Samani, PhD<sup>1</sup>, Uffe Laessoe, PhD<sup>2</sup>, Aase Handberg, DMSc, MD<sup>3,4</sup>,  
9  
10 59 Ryan Godsk Larsen, PhD<sup>1</sup>  
11  
12 60

13  
14 61 *<sup>1</sup>Department of Health Science and Technology, Sport Sciences – Performance and Technology, Aalborg*  
15 62 *University, Aalborg, Denmark*

16  
17 63 *<sup>2</sup>Department of Physiotherapy / Research and Innovation, University College of Northern Denmark,*  
18 64 *Aalborg, Denmark*

19  
20 65 *<sup>3</sup>Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark*

21  
22 66 *<sup>4</sup>Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*  
23

24 67 **Corresponding author:**

25 68 Rasmus Kopp Hansen, MSc.

26  
27 69 Department of Health Science and Technology, Sports Sciences – Performance and Technology

28  
29 70 Aalborg University

30 71 Niels Jernes Vej 12, A5-209

31  
32 72 DK-9220 Aalborg

33  
34 73 Denmark

35 74 Telephone: +4520892317  
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## 85 **ABSTRACT**

### 86 **Introduction**

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

### 97 **Methods and analysis**

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

### 105 **Ethics and dissemination**

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

### 111 **Trial registration number**

112 NCT04390087.

## 114 **ARTICLE SUMMARY**

### 115 **Strengths and limitations of this study**

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4 116 • The frequency, duration and intensity of the exercise intervention follows recently published  
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6 117 exercise recommendations for SCI individuals.  
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8 118 • This study uses a randomized controlled design to examine the effects of a novel exercise modality  
9 119 on both traditional and novel cardiometabolic risk factors.  
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11 120 • The exercise modality (upper-body rowing) includes not only an aerobic component, but also an  
12 121 element of resistance training for the posterior shoulder region, potentially ameliorating shoulder  
13 122 pain.  
14 123 • Lack of control of food intake is a study limitation.  
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- 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.

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## 1 2 3 4 143 **INTRODUCTION**

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6 144 Spinal cord injured (SCI) wheelchair users are placed at the lowest end of the fitness continuum <sup>1</sup>. Thus  
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8 145 cardiovascular disease and metabolic dysfunction is a growing concern in this population <sup>2,3</sup>. In recent years,  
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10 146 cardiovascular disease has emerged as the leading cause of mortality in chronic SCI individuals <sup>4</sup>. Factors  
11 147 contributing to high cardiometabolic morbidity and mortality in the SCI population are sedentary lifestyle  
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13 148 and low physical activity level <sup>5</sup>, and the ensuing negative influence on body composition, reflected by lower  
14 149 fat-free mass and larger amount of adipose tissue <sup>6</sup>. Explanations for the adoption of a sedentary lifestyle are  
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16 150 multifactorial, but studies have identified intrapersonal and socio-environmental physical activity barriers in  
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18 151 SCI wheelchair users <sup>7-9</sup>. Some barriers such as the intrapersonal barriers of lack of time<sup>10</sup> or energy<sup>11</sup>  
19 152 identified by individuals with mobility disabilities are consistent with those reported in the non-disabled  
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21 153 population. Other barriers are specific to the mobility disabled individuals, such as organizational or  
22 154 structural barriers (e.g. lack of accessible fitness centers<sup>7</sup> and adaptive exercise equipment<sup>8</sup>) and community  
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24 155 built environment barriers<sup>12</sup>. Consequently, new approaches to support the initiation and perseverance of  
25 156 physical activity in this population are required.

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28 157 The majority of previous exercise intervention studies have used isolated aerobic exercise, often in the form  
29 158 of arm-cranking exercise <sup>13</sup>. These studies have demonstrated improvements in traditional risk factors for  
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31 159 cardiometabolic diseases, such as high-density cholesterol (HDL-C) <sup>14</sup>, fasting insulin <sup>15</sup>, and indices of  
32 160 insulin resistance <sup>16</sup>, whereas the effects on arterial blood pressure <sup>17</sup>, blood lipids (e.g. low-density  
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34 161 cholesterol (LDL-C) and triacylglycerol) are inconclusive <sup>15,18,17</sup>. Moreover, the effects of exercise  
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36 162 interventions on body composition are generally lacking <sup>19</sup>. The explanation for the lack of an exercise effect  
37 163 on some of these risk factors is not clear, but could be related to insufficient volume <sup>15,17</sup> or intensity <sup>19</sup> of  
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39 164 exercise, performed with limited amount of skeletal muscle mass.

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41 165 Notably, in able-bodied individuals, the exercise-induced risk reduction in cardiovascular diseases cannot be  
42 166 fully explained by traditional risk factors (i.e. there is a risk factor gap) <sup>20</sup>. As a consequence, studies have  
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44 167 started to focus on the effects of exercise on changes in the vascular wall <sup>20</sup>. It is known that dysfunction of  
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46 168 the vascular endothelium occurs at the very early phases of atherosclerosis <sup>21</sup>. For instance, flow-mediated  
47 169 dilation (FMD), a non-invasive measure of nitric oxide (NO) dependent endothelial function <sup>22</sup>, is a strong  
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49 170 predictor of future cardiovascular events <sup>23</sup>. In addition, carotid intima media thickness (IMT), a measure of  
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51 171 vessel wall thickness <sup>24</sup> has shown to be associated with future vascular events, such as the occurrence of  
52 172 stroke and myocardial infarction <sup>24</sup>. Accumulating evidence in able-bodied demonstrates beneficial effects of  
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54 173 exercise on structural and functional adaptations of the vasculature <sup>25</sup>. However, little is known about the  
55 174 effects of exercise on the vasculature in the SCI population.

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57 175 Reductions in femoral artery (lower body) diameter occurs rapidly in response to extreme inactivity, as  
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59 176 observed within three weeks off acquiring a SCI <sup>26</sup>. De Groot et al. <sup>27</sup> found similar FMD in the brachial  
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4 177 artery among untrained SCI when compared to able-bodied individuals, however when FMD was normalized  
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6 178 to the shear stress stimulus, the dilation response was reduced in the SCI group, indicating some degree of  
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8 179 endothelial dysfunction in this population<sup>28</sup>. Other observational studies have demonstrated both larger  
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10 180 conduit artery diameter and blood flow in the subclavian artery<sup>29</sup>, and larger brachial diameter<sup>27</sup> in  
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12 181 wheelchair athletes compared to non-athlete able-bodied controls. Together these findings indicate that  
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14 182 remodeling of the vasculature also occurs in response to regular exercise in SCI wheelchair users. However,  
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16 183 the causal link between adaptations of the upper body arteries and repetitive exercise stimulus in SCI is not  
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18 184 fully established. Therefore, the relationship between exercise and vascular remodeling in wheelchair users  
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20 185 needs to be determined through controlled exercise studies. A recent experimental study consisting of  
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22 186 supervised aerobic exercise (20min, twice per week), adhering to the earlier exercise guidelines for SCI  
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24 187 adults<sup>30</sup>, was successful in improving measures of cardiorespiratory fitness and muscle strength<sup>31</sup>. Yet,  
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26 188 Zepetnek et al.<sup>17</sup> demonstrated that this exercise paradigm (20min, twice per week) did not improve markers  
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28 189 of cardiovascular disease risk, including carotid IMT and brachial FMD. Recent guidelines recommend at  
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30 190 least 30 min of moderate-to-vigorous intensity aerobic exercise, three times per week in order to improve  
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32 191 cardiometabolic health in SCI wheelchair users<sup>32</sup>, suggesting that insufficient exercise stimuli may explain  
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34 192 the lack of vascular adaptations in the study by Zepetnek et al.<sup>17</sup>. Notably, to date, no studies have examined  
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36 193 the effects of the updated exercise guidelines (30 min of moderate-to-vigorous intensity aerobic exercise,  
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38 194 three times per week) on vascular adaptations in SCI manual wheelchair users.

33 195 While isolated aerobic exercise, via arm-cranking or wheelchair ergometry, evokes positive effect on  
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35 196 cardiorespiratory fitness, these modalities/types of exercises fail to address the importance of strengthening  
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37 197 the posterior shoulder musculature of the upper-extremity<sup>33</sup>. In addition, these modalities use repetitive  
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39 198 contractions of the shoulder musculature engaged in daily wheelchair propulsion activities, thereby  
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41 199 increasing the risk of developing shoulder pain<sup>34-36</sup>. Studies have reported high prevalence of shoulder pain  
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43 200 in long-term wheelchair users<sup>37,38</sup>, which prevents these individuals from engaging in physical activity<sup>39</sup>. As  
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45 201 wheelchair users rely on their upper-extremities for most daily activities, upper-extremity pain must be  
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47 202 prevented or limited to preserve function, independence and quality of life (QOL)<sup>16,40</sup>. Indeed, health related  
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49 203 QOL is lower in SCI adults compared with the able-bodied population<sup>41,42</sup>. The development of shoulder  
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51 204 pain has been suggested to occur due to chronic overuse, shoulder strength imbalances between anterior and  
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53 205 posterior musculature, postural changes and impingement syndrome<sup>43-45</sup>. Considering the general need for  
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55 206 strong upper extremities to bear weight during different transfer tasks<sup>46</sup>, to propel wheelchair<sup>47</sup>, and to reach  
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57 207 overhead levels<sup>48</sup>, the inclusion of resistance training in exercise training paradigms seems prudent. One  
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59 208 modality that combines aerobic and resistance components is rowing<sup>49</sup>. Specifically, it has been shown that  
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209 wheelchair user-modified upper-body rowing ergometry challenges the cardiovascular system comparable to  
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211 arm-cranking<sup>34</sup>. Additionally, upper-body rowing mirrors the muscle activation observed during traditional  
resistance training for the scapular retractors<sup>50</sup>. Earlier research has demonstrated beneficial effects of

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resistance training of the posterior shoulder and scapular retractor musculature on shoulder pain<sup>40,48,51</sup>. 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<sup>52</sup>. 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<sup>53</sup>).

### Participants

#### *Inclusion criteria*

Men and women; aged 18-65 years; chronic SCI ( $\geq 1$  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

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4 245 self-report SCI level and completeness and to provide a copy of the part of their medical records that confirm  
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6 246 injury level and American Spinal Injury Association (ASIA) impairment scale classification before any  
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8 247 measurements are commenced. As part of the screening, participants will also be asked to indicate smoking  
9 248 habits, known medical issues, diseases or use of medication that could affect metabolism (e.g. statins or  
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11 249 metformin) or the cardiovascular system (e.g. diuretics, beta blockers, or angiotensin-converting enzyme  
12 250 inhibitors).

#### 14 251 *Exclusion criteria*

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17 252 Individuals who regularly engage in >150 min/week of moderate-to-vigorous intensity physical activity;  
18 253 have received a cortisone injection in the shoulder within the last four months; have had shoulder injury  
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20 254 within the previous year; known medical issues (urinary tract infections, cardiovascular contraindications for  
21 255 exercise testing, and pressure sores); diagnosed diabetes or any other disease that may limit the ability to  
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23 256 perform exercise.

#### 25 257 **Recruitment**

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27 258 Participants will be recruited through notices at Aalborg University, websites seeking volunteers for research  
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29 259 studies (e.g., [www.forsog.dk](http://www.forsog.dk)), organizations related to disability and SCI, including the Spinal Cord Injured  
30 260 in Denmark organization, physician clinics, wheelchair manufacturing company (Wolturnus A/S) and local  
31 261 community groups. Information on websites, social media, posters, flyers will be used to reach potential  
32 262 participants. This kind of participant recruitment can be considered passive since the participants have to  
33 263 choose to react on the study information<sup>54</sup>. This approach increases the risk of over representing individuals  
34 264 who are interested in the research area<sup>54</sup>. Considering this risk of selection bias, physician clinic visits from  
35 265 the principal investigator (i.e. active recruitment) will be used as an additional strategy to reach potential  
36 266 participants. For this study, 30 participants will be recruited. The sample size is based on the effect size  
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38 267 (Cohen *d*: -0.69) for changes in fasting insulin after 6 weeks of arm-cycling exercise<sup>15</sup>. With a power of 0.9,  
39 268 and an alpha level of 0.05, 20 participants in total are required to detect a significant change. To account for  
40 269 drop-outs during the 12 week intervention, as well as potential drop-outs in the control group, 30 participants  
41 270 will be included in the project, with n=15 allocated to the control and exercise group, respectively.

#### 48 271 **Intervention**

##### 49 272 *Exercise group*

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52 273 Volume, intensity and frequency of the intervention is based on recent exercise recommendations for SCI  
53 274 individuals<sup>32</sup>. Consequently, the training will be performed for 30 min, 3 times per week with moderate-to-  
54 275 vigorous intensity, with at least one rest day between sessions. Low compliance rate is a general issue in SCI  
55 276 exercise studies<sup>55</sup>. Compared with continuous exercise, interval-based exercise have been reported to elicit  
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4 278 between continuous and interval-based exercise, the target duration of 30 min will be reached through  
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6 279 accumulation of 5-min bouts (up to 6 bouts), with 1-2 min of rest between each bout. Due to the training  
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8 280 status of the participants, it is expected that some participants will not be able to exercise for 30 min with the  
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10 281 intended intensity. Accordingly, exercise duration will be tailored to each participant's physical capacity<sup>57</sup>  
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12 282 by gradually increasing the duration (i.e. the number of 5-min bouts) over the weeks towards the targeted 30  
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14 284 (RPE) corresponding to 12-15 on the 'Borg 6-20 RPE Scale'<sup>58,59</sup>. The validity of using RPE to control  
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16 285 moderate and vigorous exercise intensity has been demonstrated in SCI individuals<sup>60</sup>. During the first visit,  
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18 286 participants will be familiarized with the RPE scale<sup>61</sup> and receive detailed instructions on the use of RPE and  
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20 287 how to rate the overall exertion based on an integration of central and peripheral sensations of effort<sup>60</sup>. Some  
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22 288 controversy exists about the validity of using overall RPE to monitor exercise intensity<sup>61,62</sup>, as the  
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24 289 relationships between overall RPE and objective physiological markers such as oxygen consumption (VO<sub>2</sub>),  
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26 291 heart rate (HR) and ventilation (VE) in SCI individuals have been questioned<sup>62</sup>. This have led some  
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28 292 researchers to use a differentiated RPE scale that distinguishes between central (cardiorespiratory sensations)  
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30 294 and peripheral (peripheral working limbs) sensations<sup>63</sup>. However, the current evidence does not indicate  
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32 295 greater validity for differentiated RPE compared with overall RPE<sup>61</sup>, and therefore overall RPE will be used  
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34 296 to guide exercise intensity.

35  
36 297 Each training session will consist of aerobic exercise performed on a wheelchair-modified upper-body  
37  
38 298 rowing ergometer (Concept 2, Morrisville, Vermont, USA). Due to the pulling motion of the upper-body  
39  
40 300 during rowing, this modality also includes a component of resistance exercise<sup>49</sup>. The modification of the  
41  
42 301 ergometer is made by separating it into two parts using an Adapt2row<sup>1</sup>, allowing the participants to sit in  
43  
44 302 their wheelchair while performing upper-body rowing. Wedges will be positioned under the rear wheels to  
45  
46 303 keep the wheelchair in place. Further, in case of SCI related insufficient innervation of torso musculature,  
47  
48 305 straps will be wrapped around the back of the wheelchair and around the trunk of the participant, thereby  
49  
50 306 securing the participant to the wheelchair. A pilot study<sup>34</sup> has provided promising results regarding the  
51  
52 307 feasibility of using adaptive upper-body rowing exercise in the SCI population. Participants will be asked to  
53  
54 308 empty their bladder before each training session. Average power output (W) will be recorded during each  
55  
56 310 exercise session to monitor training load and quantify progress in work capacity.

57  
58  
59 306 All exercise sessions will be supervised by the principal investigator, who is an exercise physiologist, or by  
60  
307 sport science students to ensure proper assistance and guidance of the participants. Everyone involved in  
308 supervision will be thoroughly instructed in how to supervise correct exercise technique, and they will  
309 receive general knowledge about SCI and wheelchair use. To allow for some flexibility regarding scheduling  
310 conflicts, participants will have opportunity to exercise 2-4 days per week, with a target of 3 days per week.

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<sup>1</sup> <http://www.adapt2row.com/>

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4 311 That is, in case of a missing session one week, an additional training session can be included the following  
5  
6 312 week. However, to secure adequate recovery, no more than four training days per week will be allowed. The  
7  
8 313 intervention will be terminated after 12 weeks, irrespective of any missing training sessions.

#### 9 10 314 *Control group*

11  
12 315 The participants allocated to the control group will be asked to maintain their normal lifestyle throughout the  
13  
14 316 intervention period. When the 6-months follow-up testing has been terminated, the control group will receive  
15  
16 317 information about the exercise guidelines and the benefits of physical activity. Additionally, if requested, the  
17  
18 318 principal investigator will organize contact to facilities where participants in the control group can perform  
19  
20 319 adapted rowing.

#### 21 320 **Main trial day protocol**

22 321 The experimental procedures will be similar at baseline, post intervention, and at follow-up 6 months later.  
23  
24 322 To account for within-day variation, the procedures will be performed at the same time of day for each  
25  
26 323 participant. Participants will arrive at the exercise laboratory at Aalborg University for testing. Participants  
27  
28 324 will be asked to refrain from any strenuous exercise (>24 h), caffeine, alcohol, polyphenols, vitamin C, and  
29  
30 325 supplements known to affect the cardiovascular system (>12 h), and attend in a fasted (>6 h) state.<sup>64</sup> Any  
31  
32 326 smokers must abstain from smoking for >6 h prior to each visit<sup>64</sup>. If participants are taking medication, a  
33  
34 327 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  
35  
36 328 cannot be withdrawn due to health issues, testing will be performed after a consistent time period after  
37  
38 329 intake, as recommended for studies examining vascular function<sup>64,65</sup>. On trial days, participants will receive  
39  
40 330 a standardized snack (energy bar) after completion of the FMD measurement. Participants will be asked to  
41  
42 331 empty their bladder before any testing is commenced, and are allowed to drink water ad libitum during the  
43  
44 332 test days.

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46 333  
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48 334 INSERT FIGURE 1

#### 49 335 **Blood collection procedure**

50 336 After an overnight fast (i.e.  $\geq 10$  hours of fasting), participants will have approximately 20 mL blood drawn  
51  
52 337 from a peripheral vein. Blood samples will be aliquoted and stored at  $-80^{\circ}$  at the Department of Clinical  
53  
54 338 Biochemistry, Aalborg University Hospital, until analyses. Blood samples will be analyzed for indicators of  
55  
56 339 cardiometabolic health (markers of glucose homeostasis, dyslipidemia, non-alcoholic fatty liver disease  
57  
58 340 (NAFLD), and prothrombotic risk) as well as inflammatory markers (pro- and anti-inflammatory markers).  
59  
60 341 Blood sampling will be conducted within a week prior to commencing the intervention (baseline), between  
61  
62 342 36 and 60 hours after the last exercise session (post) to minimize any effects from the last exercise session,  
63  
64 343 and 6 month after the termination of the intervention (6-months follow-up).

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4 344 **Outcome measures**

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6 345 ***Primary outcome***

8 346 The primary outcome is fasting insulin, since it is one of the hallmarks of the metabolic syndrome<sup>66,67</sup>, and  
9  
10 347 has shown to be modifiable with exercise training in SCI individuals<sup>15</sup>.

11  
12 348 ***Secondary key outcomes***

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14 349 ***Arterial blood pressure (BP) and resting heart rate (HR)***

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16 350 After resting for 10 min, participants will have their resting systolic and diastolic BP and HR measured with  
17 351 an automated BP monitoring device (OMRON M6, OMRON Healthcare, Hoofddorp, Netherlands).

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19 352 Measurements will be performed twice, with participants in sitting position. The lowest values will be used  
20 353 for further analyses.

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23 354 ***Body composition***

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25 355 Participants will have their body mass measured while sitting in their wheelchair (wearing light clothing)  
26 356 using a platform wheelchair scale (Detecto® 6550 wheelchair scale, Webb City, MO, USA). Body mass will  
27 357 be derived by subtracting the weight of the wheelchair from the total mass and rounded to the nearest 0.1 kg

28 358<sup>68</sup>. Supine height (cm) will be measured in supine position using non-elastic tape. For participants with  
29 359 contractures precluding stretching of the legs, length will be measured in segments from heel to top of the  
30 360 skull<sup>69</sup>. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (m<sup>2</sup>). Waist  
31 361 circumference and waist-to-hip circumference ratio will be used as a surrogate for visceral adiposity<sup>68-70</sup>.

32 362 Participants will have their waist and hip circumference measured in supine position following a deep  
33 363 expiration. Waist and hip circumference will be measured immediately below the lowest rib<sup>69</sup> and widest  
34 364 part of the trochanters<sup>70</sup>, respectively. For all circumference measurements, the tape will be placed directly  
35 365 on the skin with the participants arms by the side<sup>69</sup>. Anthropometric measures will be taken in duplicate  
36 366 (height, waist and hip circumference), rounded to the nearest 0.1 cm and reported as the mean. If the  
37 367 difference between the first and second measure is >0.1 cm, a third measure will be obtained.<sup>69</sup>

38  
39 368 ***Autonomic nervous system function***

40 369 Increasing evidence suggest that autonomic dysfunction accentuates the risk for adverse cardiovascular  
41 370 events<sup>71</sup>. Individuals with SCI are prone to autonomic disturbances as a consequence of disruption to the  
42 371 spinal cord<sup>72</sup>, placing them at increased risk for autonomic related cardiovascular diseases. Participants will  
43 372 be equipped with a 4-lead surface electrodes on their chest and have their electrocardiogram (ECG) recorded  
44 373 during 5 min of quiet rest. Heart rate variability analyses of the ECG will be used to assess autonomic  
45 374 function<sup>71,73</sup>.

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47 375 ***Vascular structure and function***

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4 376 After a rest period of 10-15 min in a quiet and darkened room, vascular structure and function will be  
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6 377 evaluated non-invasively using ultrasonography (LOGIQ S8 XDclear, GE Healthcare) following recent  
7  
8 378 guidelines on assessment of conduit <sup>64,74</sup> and resistance <sup>65</sup> vessel function. Conduit artery structure will be  
9 379 determined in the common carotid artery (CCA) and brachial artery (BA) with B-mode echoes using a 10  
10  
11 380 MHz multifrequency linear assay ultrasound probe. Measures of CCA and BA structure will be reported as  
12 381 intima media thickness (IMT) (mm), lumen diameter (mm), and wall-to-lumen ratio. The B-mode image will  
13  
14 382 be optimized by changing depth and resolution, and will be kept constant between study visits.

15 383 To assess BA and resistance vessel function, endothelial dependent flow-mediated dilation (FMD) and  
16  
17 384 reactive hyperemia will be determined by cuff occlusion followed by re-perfusion <sup>22</sup>. First, participants will  
18  
19 385 have their baseline BA diameter measured for a period of 30 s. Then, a cuff placed distally on the forearm  
20 386 (i.e. distal to the ultrasound probe) will be inflated for 5 min up to a pressure that exceeds systolic BP by >50  
21  
22 387 mmHg. After 5 min, the cuff will be deflated and post-deflation diameter and blood velocity will be  
23 388 continuously recorded for 3 min <sup>64</sup>. For determination of FMD, both absolute (mm) and relative (%) change  
24  
25 389 in diameter from baseline to post-deflation will be calculated. Given the importance of shear stress as the  
26  
27 390 stimulus for the FMD response <sup>75</sup>, continuous and simultaneous measurement of pulse-wave velocity  
28 391 (Doppler) and diameter (B-mode) using duplex ultrasound will be performed. This allows for an estimation  
29  
30 392 of the shear stress stimuli through the calculation of shear rate, which then can be used to normalize the  
31 393 FMD response <sup>76</sup>. Because the error of the insonation estimation increases exponentially with angles >60° <sup>77</sup>,  
32  
33 394 an insonation angle of ≤60° will be used, with the sample volume adjusted to cover the total width of the  
34 395 vessel.

36 396 Resistance vessel function will be determined by the magnitude of the reactive hyperemic response to cuff-  
37 397 induced ischemia. Several measures obtained from the reactive hyperemic response will be reported,  
38 398 including absolute blood flow (calculated based on the diameter derived cross sectional area and blood  
39  
40 399 velocity) and velocity, peak change in blood flow, and blood flow area under the curve (AUC) across the  
41  
42 400 post-deflation time period.

45 401 Although related, the measure of reactive hyperemia mirrors the magnitude of downstream resistance artery  
46  
47 402 dilation, whereas FMD represent conduit artery dilation <sup>65</sup>.

49 403 To ensure that the same part of the CCA and BA will be insonated across study visits, anatomical landmarks  
50  
51 404 will be identified and recorded together with a photo of the insonation sites. All insonation settings  
52 405 (including sample volume, insonation angle, and recording time) and occlusion procedure (including cuff-  
53  
54 406 position, pressure and duration) will be held consistent within participants across study visits. For  
55 407 standardization, the same investigator will perform all measurements and all analyses (blinded to the identity  
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57 408 of the data).

59 409 *Metabolic and inflammatory profile*  
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410 The metabolic and inflammatory profile will be assessed via measures of glycemic control (fasting glucose,  
411 long-term blood glucose (HbA1c, glycosylated hemoglobin), homeostatic model assessment of insulin  
412 resistance (HOMA-IR)), lipid profile (HDL-c, LDL-c, total cholesterol and triglycerides (TG)), pro-  
413 inflammatory (C-reactive protein (CRP), interleukin (IL) 6, tumor necrosis factor-alpha), anti-inflammatory  
414 (IL-10, IL1RA)), prothrombotic (PAI-1), markers of NAFLD (hepatic enzymes (alanine-aminotransferase  
415 (ALT) and aspartate-aminotransferase (AST)), growth differentiation factor 15 (GDF15) and fibroblast  
416 growth factor 21 (FGF21)).

#### 417 *Cardiorespiratory fitness level*

418 Cardiorespiratory fitness level will be determined through an incremental arm-cranking test to exhaustion,  
419 with peak oxygen consumption ( $VO_{2peak}$ ) as the outcome measure. The placement of the ergometer (Monark  
420 881E, Vansbro, Sverige) will be adjusted such that the participants shoulder joint is aligned with the crank  
421 axis with the elbows slightly bend. Participants will be equipped with a HR monitoring belt (Suunto Ambit3  
422 Run; Suunto, Vantaa, Finland) and a face mask, connected to an online open-circuit metabolic cart. The cart  
423 (JAEGER, Vyntus CPX, Carefusion) will be calibrated to known volumes and gas concentrations according  
424 to manufactural guidelines. After a 1-min warm-up with zero resistance, the test begins with an  
425 individualized starting load (5-90W)<sup>78</sup> with increases in work load (5 or 10W) every minute<sup>79</sup> until  
426 volitional fatigue, defined as an inability to maintain cadence above 55 rounds per minute (rpm)<sup>78</sup>. The  
427 individual starting load and increment size will be chosen based on training history and anticipated physical  
428 capacity, with the aim of reaching exhaustion within 8-12 minutes at a cadence of 60-70 rpm<sup>79,80</sup>. Breath-by-  
429 breath  $VO_2$  and carbon dioxide output ( $VCO_2$ ), and HR will be measured continuously throughout the test.  
430  $VO_{2peak}$  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  
431 the highest 30-s average during the test, with the corresponding HR reported as  $HR_{peak}$ . The highest workload  
432 that is achieved for  $\geq 30$ -s will be reported as  $PO_{peak}$ . Participants will be asked to indicate RPE (Borg 6-20  
433 scale) during the last 15-s of each minute. On test cessation, participants will gradually cool-down for 5-min,  
434 while their BP will be measured immediately before and after this recovery period.

#### 435 *Other secondary outcomes*

##### 436 *Shoulder pain*

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

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4 443 pain score (PC-WUSPI) will be calculated by dividing the raw total WUSPI score by the number of  
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6 444 performed activities, multiplied by 15<sup>83</sup>.

#### 8 445 *Health-related quality of life (HRQOL)*

9  
10 446 HRQOL will be monitored using the Danish translated version of the Short Form-36 (SF-36)<sup>84</sup>, which is a  
11 447 reliable and validated questionnaire to assess HRQOL within both a physical and mental health domain<sup>85</sup>.  
12  
13 448 Certain questions of the SF-36 will be adapted to wheelchair use. Specifically, the questions referring to  
14  
15 449 'walk' and 'stair-climbing' is substituted by the words 'climb' and 'go up', as previously recommended<sup>86</sup>.  
16 450 Construct validity stays acceptable with this modification<sup>86</sup>. Data will be scored using the RAND 36-item  
17  
18 451 Health survey 1.0 method<sup>87</sup>, in which original responses is transformed into a score from 0-100, with 100  
19 452 representing the best possible health. Individual item scores is then averaged within domains to create eight  
20  
21 453 subscales, four representing physical QOL and four representing mental QOL. For reporting of HRQOL, a  
22  
23 454 physical component summary score (PCS) and a mental component summary score (MCS) will be created  
24 455 based on the average of each component subscales<sup>88</sup>.

#### 26 456 *Free-living physical activity*

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29 457 To determine the effects of the exercise intervention on short-term (12-weeks follow-up) and long-term (6-  
30 458 months follow-up) habitual physical activity, free-living physical activity levels will be monitored  
31  
32 459 objectively via accelerometry. Participants will be fitted with a triaxial wrist-worn accelerometer (Axivity,  
33 460 AX3, Newcastle, UK) placed on the non-dominant wrist using a standard rubber wristband, as recommended  
34  
35 461<sup>89</sup>. Participants will be asked to wear the accelerometer for the 7 days<sup>90</sup> preceding baseline and follow-up  
36 462 (12-weeks and 6-months) visits. The accelerometer (23 x 32.5 x 7.6 (mm)) will be worn continuously  
37  
38 463 through this period (24 hours a day). To be considered a valid day, at least 80% of data for that 24-hour  
39  
40 464 period is required<sup>90</sup>. The AX3 sensor records accelerations within the dynamic range of  $\pm 8$  g. Physical  
41 465 activity levels are derived by aggregating the raw acceleration (expressed as  $\text{g}^1 \cdot \text{min}^{-1}$ ) using either Euclidian  
42  
43 466 norm minus one (ENMO – expressed in mg), mean average deviation (MAD – expressed in mg), activity  
44 467 index (AI – expressed in mg) or Actigraph Counts (AG – expressed in counts)<sup>91–94</sup>. The most optimal  
45  
46 468 aggregation, time interval or epoch, and data band-pass filtering to reduce noise has not been evaluated  
47  
48 469 thoroughly in any previous study. Thus, the final selection of aggregation method, epoch length and band-  
49 470 pass filtering to be used is determined using the same study conducted to estimate the light, moderate and  
50  
51 471 vigorous intensity thresholds (see below).

52  
53 472 For determination of physical activity ( $\text{min} \cdot \text{day}^{-1}$ ) with different intensities (i.e. light, moderate and vigorous  
54 473 physical activity), individual accelerometer cut-off points will be calculated. Individual calibration of wrist-  
55  
56 474 worn accelerometers is recommended for valid estimates of physical activity level<sup>95</sup>. Previous studies<sup>96,97</sup>  
57  
58 475 have established high internal-validity of wrist-worn accelerometer output when compared with energy  
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expenditure measured at fixed speeds during wheelchair propulsion on a motorized treadmill <sup>96,97</sup>. 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 <sup>98</sup>. 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 <sup>99</sup>. 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  $\geq 3.0$  will be used as a criterion to indicate that the intervention is acceptable <sup>99</sup>. 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  $\pm$  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

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4 509 between groups. P-values and 95% confidence intervals will be reported to facilitate interpretation of the  
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6 510 results. Statistical significance will be accepted at  $P < 0.05$ .

### 8 511 **Patient and public involvement**

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10 512 Neither participants nor public were involved with the conception of the research question, study design, or  
11 513 outcome measures, nor will they be involved with study conduction. The recruitment plan was partially  
12  
13 514 planned based on feedback from the patient population. Each of the participants will receive a written  
14  
15 515 summary of the study results after publication.

### 17 517 **Ethics and dissemination**

19 518 Considerations are made regarding the regulation of arterial BP in the participants<sup>100 101</sup>. BP instability does  
20 519 occur in cervical injured individuals (tetraplegics), who may suffer from pronounced autonomic disturbances  
21 520<sup>100,101</sup>. During the  $VO_{2peak}$  test and exercise sessions, special attention is devoted towards potential symptoms  
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23 521 of autonomic dysreflexia (AD)<sup>102</sup> in individuals with  $SCI \geq T6$ . Participants will be asked to empty their  
24  
25 522 bladder before any testing or training is commenced. In case of AD, the exercise is stopped and the pertinent  
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27 523 actions are made. Occurrences of post exercise hypotension<sup>101</sup> and orthostatic hypotension<sup>100</sup> are rather  
28  
29 524 uncommon in individuals with thoracic injury (paraplegics). According to the inclusion criteria of the study,  
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31 525 only individuals with a sparing of arm function (i.e. excluding individuals with a complete cervical injury  
32 526  $\geq C5$  participants) will be included in the study, presumably reducing the number of included individuals with  
33  
34 527 impaired BP regulation. Nevertheless, in addition to reduced vasoconstrictor drive, the ability to increase  
35 528 cardiac output is limited in individuals with  $SCI \geq T5-T6$  with interrupted cardiac sympathetic innervation,  
36  
37 529 which could affect arterial BP stabilization during conditions in which peripheral vascular resistance is  
38  
39 530 further reduced (i.e. during exercise). Therefore, to identify any participants that may be prone to  
40 531 experiencing post exercise hypotension, brachial artery BP will be monitored immediately after, and again 5  
41 532 min after the first  $VO_{2peak}$  test. In such cases, and assuming the hypotension is well tolerated, the participants  
42  
43 533 will be reminded to drink appropriately during and prior any future training and testing. Further, these  
44  
45 534 participants will have their BP measured every second interval (i.e. every 10<sup>th</sup> min) during the training  
46 535 sessions. If hypotension develops, the training will be interrupted and hypotensive countermeasures  
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48 536 (placement in a supine position, or legs up) will be applied. If the hypotension is not tolerated, such as if the  
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50 537 participants exhibit signs of nausea, light-headedness, fatigue or presyncopal symptoms in response to either  
51 538 the  $VO_{2peak}$  test or the training, they will be excluded from further participation in the study.

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53 539 Another consideration is that individuals with SCI suffer from impaired thermoregulation<sup>103</sup>. Although  
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55 540 prolonged (60 min) moderate intensity exercise in warm conditions ( $>31^{\circ}C$ ) have been shown sustainable for  
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57 541 some paraplegic and tetraplegic individuals<sup>104</sup>, impaired thermoregulation makes SCI individuals more  
58 542 vulnerable to overheating compared to able-bodied<sup>103</sup>. This is especially the case during conditions of  
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4 543 increased environmental temperatures and metabolic heat production (such as when exercising in the heat).  
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6 544 The degree of thermoregulatory impairment is closely related to the injury level, such that individuals with  
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8 545 higher injury (tetraplegics) exhibit higher core temperatures during exercise compared to lower injury  
9 546 individuals (paraplegics) <sup>104</sup>. To diminish the risk for overheating during testing and training, a fan will be  
10  
11 547 available for cooling of the participants and the room temperature and humidity will be continuously  
12 548 monitored to facilitate the conditions for dry and evaporative heat loss. Moreover, the participants will be  
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14 549 asked to pay attention to proper hydration before and throughout each training session. However, if the  
15 550 participants demonstrate signs of any adverse response, the exercise session will be terminated immediately  
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17 551 and further participation in the study will be reconsidered. Any adverse responses from the intervention will  
18  
19 552 be reported to the regional health research committee. The trial is reported to the Danish Data Protection  
20 553 Agency (J.nr. 2019-899/10-0406), registered at Clinicaltrials.org, and approved by the Committees on Health  
21  
22 554 Research Ethics in The North Denmark Region on 12 December 2019 (Journal-nr. N-20190053). Results  
23 555 will be submitted to scientific journals related to exercise and SCI for publication irrespective of study  
24  
25 556 outcomes.

#### 27 557 **Data statement section**

29 558 All participant data will be stored in a secure web-based database (Redcap) with restricted access and ID  
30  
31 559 code, in accordance with data protection rules. Source documents including date, visit# and participant ID  
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33 560 will be scanned and saved as electronic copies. Participant data will be transferred directly or by use of an  
34 561 encrypted USB stick. Each participant will be assigned an unique identification number, which will be the  
35  
36 562 only identifier exported from Redcap upon data analysis. Except for the blood samples, which will be stored  
37 563 until analysis, or no more than 5 years, data will be stored for 5 years after the termination of the trial. After  
38  
39 564 this period, paper material is shredded, data files are erased and the Redcap database is no longer accessible.  
40 565 The principal investigator will have access to all trial data.

#### 43 566 **Acknowledgement**

44 567 The authors would like to thank Dr. Rachel E. Cowan for valuable discussions regarding the study protocol,  
45  
46 568 and Dr. Jan Christian Brønd for assistance with the section related to accelerometer data.

#### 48 569 **Author Contributions**

49  
50 570 RKH and RGL conceptualized the study. RKH, AS, UL, AH and RGL contributed to the study protocol  
51 571 design. RKH drafted the manuscript. RKH, AS, UL, AH and RGL commented and edited the manuscript and  
52  
53 572 approved the final version.

#### 56 574 **Funding**

57  
58 575 This work is supported by Aage and Johanne Louis-Hansens Fond, grant number 20-2B-5947, and by  
59 576 Wolturnus A/S. Aage and Johanne Louis-Hansens Fond and Wolturnus A/S will have no influence on any  
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1  
2  
3  
4 577 part of the project design, data collection, data analysis, data interpretation or the disclosure of the results.

5  
6 578 Thus, their support is solely economical.  
7

8 579 **Competing interests**

9  
10 580 None declared.  
11 581

12  
13 582 **Patient consent**

14 583 Not required.  
15  
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17 584 **License statement**

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32 593 **Figure 1.** Study overview. PA = physical activity; INT = intervention; RPE = rating of perceived exertion;  
33 594 CON = control.  
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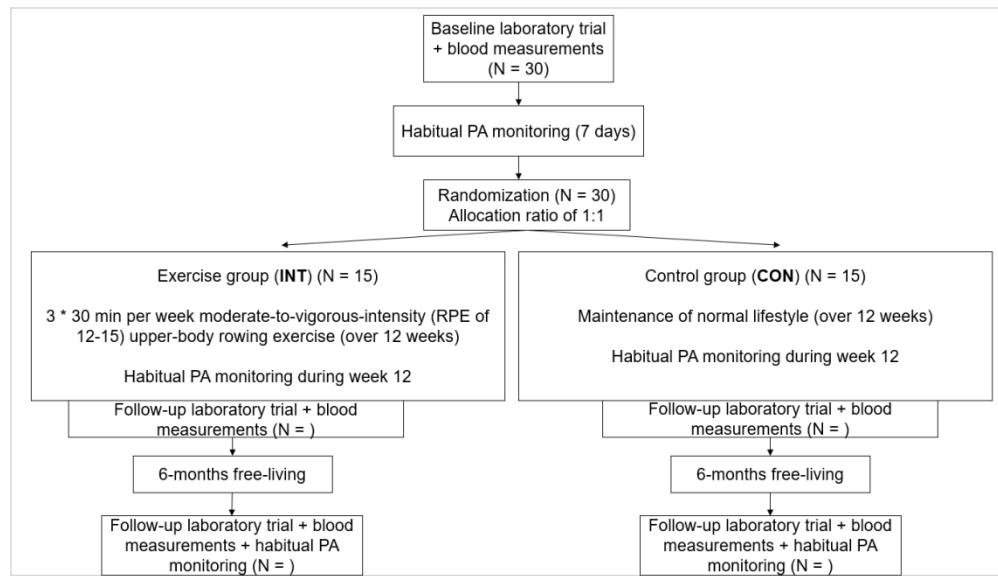


Figure 1. Study overview. PA = physical activity; INT = intervention; RPE = rating of perceived exertion; CON = control.

# 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.

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.

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	Reporting Item	Page Number
<b>Administrative information</b>		
Title	<a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3

1	Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not	4,8
2			yet registered, name of intended	
3			registry	
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8				
9	Trial registration:	<a href="#">#2b</a>	All items from the World Health	n/a. The trial has been
10			Organization Trial Registration Data	registered with details
11	data set		Set	provided at Clinicaltrials.gov
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16	Protocol version	<a href="#">#3</a>	Date and version identifier	1
17				
18				
19	Funding	<a href="#">#4</a>	Sources and types of financial,	18
20			material, and other support	
21				
22				
23				
24				
25	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of	1,2,18
26			protocol contributors	
27	responsibilities:			
28				
29	contributorship			
30				
31				
32	Roles and	<a href="#">#5b</a>	Name and contact information for the	18
33			trial sponsor	
34	responsibilities:			
35				
36	sponsor contact			
37				
38	information			
39				
40				
41				
42	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if	18
43			any, in study design; collection,	
44	responsibilities:		management, analysis, and	
45			interpretation of data; writing of the	
46	sponsor and		report; and the decision to submit the	
47			report for publication, including whether	
48	funder			
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1 they will have ultimate authority over  
 2  
 3 any of these activities  
 4

5  
 6 Roles and [#5d](#) Composition, roles, and responsibilities n/a. No such committee has  
 7 responsibilities: of the coordinating centre, steering been established.  
 8 committees committee, endpoint adjudication  
 9 committee, data management team,  
 10 and other individuals or groups  
 11 overseeing the trial, if applicable (see  
 12 Item 21a for data monitoring  
 13 committee)  
 14  
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 16  
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## 25 Introduction

26  
 27  
 28 Background and [#6a](#) Description of research question and 6-8  
 29 rationale justification for undertaking the trial,  
 30 including summary of relevant studies  
 31 (published and unpublished) examining  
 32 benefits and harms for each  
 33 intervention  
 34  
 35  
 36  
 37  
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 41

42 Background and [#6b](#) Explanation for choice of comparators 6-8  
 43 rationale: choice  
 44 of comparators  
 45  
 46  
 47  
 48  
 49

50 Objectives [#7](#) Specific objectives or hypotheses 8  
 51  
 52

53 Trial design [#8](#) Description of trial design including type 8  
 54 of trial (eg, parallel group, crossover,  
 55 factorial, single group), allocation ratio,  
 56  
 57  
 58  
 59  
 60



and framework (eg, superiority,  
equivalence, non-inferiority,  
exploratory)

## Methods:

### Participants, interventions, and outcomes

Study setting	<a href="#">#9</a>	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	<a href="#">#10</a>	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	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
Interventions: modifications	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	9-11, 17,18

1		response to harms, participant request,	
2		or improving / worsening disease)	
3			
4			
5			
6	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to	16
7			
8	adherence	intervention protocols, and any	
9			
10		procedures for monitoring adherence	
11			
12		(eg, drug tablet return; laboratory tests)	
13			
14			
15			
16	Interventions:	<a href="#">#11d</a> Relevant concomitant care and	9-11
17			
18	concomitant care	interventions that are permitted or	
19			
20		prohibited during the trial	
21			
22			
23	Outcomes	<a href="#">#12</a> Primary, secondary, and other	12-17
24			
25		outcomes, including the specific	
26			
27		measurement variable (eg, systolic	
28			
29		blood pressure), analysis metric (eg,	
30			
31		change from baseline, final value, time	
32			
33		to event), method of aggregation (eg,	
34			
35		median, proportion), and time point for	
36			
37		each outcome. Explanation of the	
38			
39		clinical relevance of chosen efficacy	
40			
41		and harm outcomes is strongly	
42			
43		recommended	
44			
45			
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47			
48			
49	Participant	<a href="#">#13</a> Time schedule of enrolment,	11
50			
51	timeline	interventions (including any run-ins and	
52			
53		washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is	
56			
57		highly recommended (see Figure)	
58			
59			
60			

1	Sample size	<a href="#">#14</a>	Estimated number of participants	9
2				
3			needed to achieve study objectives and	
4			how it was determined, including	
5			clinical and statistical assumptions	
6			supporting any sample size calculations	
7				
8				
9				
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11				
12				
13	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate	9
14			participant enrolment to reach target	
15			sample size	
16				
17				
18				
19				
20				
21	<b>Methods:</b>			
22				
23	<b>Assignment of</b>			
24				
25	<b>interventions (for</b>			
26				
27	<b>controlled trials)</b>			
28				
29				
30				
31	Allocation:	<a href="#">#16a</a>	Method of generating the allocation	8
32			sequence (eg, computer-generated	
33	sequence		random numbers), and list of any	
34			factors for stratification. To reduce	
35	generation		predictability of a random sequence,	
36			details of any planned restriction (eg,	
37			blocking) should be provided in a	
38			separate document that is unavailable	
39			to those who enrol participants or	
40			assign interventions	
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1	Allocation	<a href="#">#16b</a>	Mechanism of implementing the	8
2				
3	concealment		allocation sequence (eg, central	
4			telephone; sequentially numbered,	
5	mechanism		opaque, sealed envelopes), describing	
6			any steps to conceal the sequence until	
7			interventions are assigned	
8				
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14				
15	Allocation:	<a href="#">#16c</a>	Who will generate the allocation	8-9
16				
17	implementation		sequence, who will enrol participants,	
18			and who will assign participants to	
19			interventions	
20				
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23				
24				
25	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to	13
26			interventions (eg, trial participants, care	
27			providers, outcome assessors, data	
28			analysts), and how	
29				
30				
31				
32				
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34				
35	Blinding	<a href="#">#17b</a>	If blinded, circumstances under which	n/a. Participants allocated to
36				
37	(masking):		unblinding is permissible, and	the exercise and control
38			procedure for revealing a participant's	group cannot be blinded to
39	emergency		allocated intervention during the trial	the PI, because PI is
40				responsible for conducting
41	unblinding			the study. Parts of data
42				analysis will be blinded to the
43				PI.
44				
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54	<b>Methods: Data</b>			
55				
56	<b>collection,</b>			
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**management, and****analysis**

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5			
6	Data collection	<a href="#">#18a</a>	Plans for assessment and collection of 10-16
7			
8	plan		outcome, baseline, and other trial data,
9			
10			including any related processes to
11			
12			promote data quality (eg, duplicate
13			
14			measurements, training of assessors)
15			
16			and a description of study instruments
17			
18			(eg, questionnaires, laboratory tests)
19			
20			along with their reliability and validity, if
21			
22			known. Reference to where data
23			
24			collection forms can be found, if not in
25			
26			the protocol
27			
28			
29			
30			
31	Data collection	<a href="#">#18b</a>	Plans to promote participant retention 16
32			
33	plan: retention		and complete follow-up, including list of
34			
35			any outcome data to be collected for
36			
37			participants who discontinue or deviate
38			
39			from intervention protocols
40			
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42			
43	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, 18
44			
45			and storage, including any related
46			
47			processes to promote data quality (eg,
48			
49			double data entry; range checks for
50			
51			data values). Reference to where
52			
53			details of data management procedures
54			
55			can be found, if not in the protocol
56			
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1	Statistics:	<a href="#">#20a</a>	Statistical methods for analysing	16
2				
3	outcomes		primary and secondary outcomes.	
4				
5			Reference to where other details of the	
6			statistical analysis plan can be found, if	
7				
8			not in the protocol	
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10				
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12				
13	Statistics:	<a href="#">#20b</a>	Methods for any additional analyses	16
14				
15	additional		(eg, subgroup and adjusted analyses)	
16				
17	analyses			
18				
19				
20				
21	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating	16
22				
23	population and		to protocol non-adherence (eg, as	
24				
25	missing data		randomised analysis), and any	
26				
27			statistical methods to handle missing	
28				
29			data (eg, multiple imputation)	
30				
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33	<b>Methods:</b>			
34				
35	<b>Monitoring</b>			
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38	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring	n/a
39				
40	formal committee		committee (DMC); summary of its role	
41				
42			and reporting structure; statement of	
43				
44			whether it is independent from the	
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46			sponsor and competing interests; and	
47				
48			reference to where further details about	
49				
50			its charter can be found, if not in the	
51				
52			protocol. Alternatively, an explanation	
53				
54			of why a DMC is not needed	
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1	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and	n/a
2				
3	interim analysis		stopping guidelines, including who will	
4				
5			have access to these interim results	
6				
7			and make the final decision to	
8				
9			terminate the trial	
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12				
13	Harms	<a href="#">#22</a>	Plans for collecting, assessing,	17-18
14				
15			reporting, and managing solicited and	
16				
17			spontaneously reported adverse events	
18				
19			and other unintended effects of trial	
20				
21			interventions or trial conduct	
22				
23				
24				
25	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing	17-18
26				
27			trial conduct, if any, and whether the	
28				
29			process will be independent from	
30				
31			investigators and the sponsor	
32				
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35	<b>Ethics and</b>			
36				
37	<b>dissemination</b>			
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41	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics	18
42				
43	approval		committee / institutional review board	
44				
45			(REC / IRB) approval	
46				
47				
48	Protocol	<a href="#">#25</a>	Plans for communicating important	18
49				
50	amendments		protocol modifications (eg, changes to	
51				
52			eligibility criteria, outcomes, analyses)	
53				
54			to relevant parties (eg, investigators,	
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1		REC / IRBs, trial participants, trial	
2		registries, journals, regulators)	
3			
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5			
6	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or	8
7		assent from potential trial participants	
8		or authorised surrogates, and how (see	
9		Item 32)	
10			
11			
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15	Consent or	<a href="#">#26b</a> Additional consent provisions for	n/a
16		collection and use of participant data	
17	assent: ancillary	and biological specimens in ancillary	
18		studies, if applicable	
19	studies		
20			
21			
22			
23			
24			
25	Confidentiality	<a href="#">#27</a> How personal information about	18
26		potential and enrolled participants will	
27		be collected, shared, and maintained in	
28		order to protect confidentiality before,	
29		during, and after the trial	
30			
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37	Declaration of	<a href="#">#28</a> Financial and other competing interests	18
38		for principal investigators for the overall	
39	interests	trial and each study site	
40			
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44			
45	Data access	<a href="#">#29</a> Statement of who will have access to	18
46		the final trial dataset, and disclosure of	
47		contractual agreements that limit such	
48		access for investigators	
49			
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55	Ancillary and post	<a href="#">#30</a> Provisions, if any, for ancillary and	n/a
56		post-trial care, and for compensation to	
57	trial care		
58			
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1			those who suffer harm from trial	
2				
3			participation	
4				
5				
6	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to	18
7				
8	policy: trial results		communicate trial results to	
9				
10			participants, healthcare professionals,	
11				
12			the public, and other relevant groups	
13				
14			(eg, via publication, reporting in results	
15			databases, or other data sharing	
16			arrangements), including any	
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18			publication restrictions	
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24				
25	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any	18
26				
27	policy: authorship		intended use of professional writers	
28				
29				
30	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access	n/a
31				
32	policy:		to the full protocol, participant-level	
33				
34	reproducible		dataset, and statistical code	
35				
36				
37	research			
38				
39				
40	<b>Appendices</b>			
41				
42				
43	Informed consent	<a href="#">#32</a>	Model consent form and other related	
44				
45	materials		documentation given to participants	
46				
47			and authorised surrogates	
48				
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50				
51	Biological	<a href="#">#33</a>	Plans for collection, laboratory	11
52				
53	specimens		evaluation, and storage of biological	
54				
55			specimens for genetic or molecular	
56				
57			analysis in the current trial and for	
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1 future use in ancillary studies, if

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3 applicable

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6 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution

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For peer review only

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-040727.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Sep-2020
Complete List of Authors:	Hansen, Rasmus; Aalborg Universitet, Health Science and Technology, Sport Sciences – Performance and Technology; Professionshøjskolen University College Nordjylland, Research and Innovation Samani, Afshin; Aalborg Universitet, Health Science and Technology, Sport Sciences – Performance and Technology Laessoe, Uffe; Professionshøjskolen University College Nordjylland, Physiotherapy; Professionshøjskolen University College Nordjylland, Research and Innovation Handberg, Aase; Aalborg University Hospital, Clinical Biochemistry; Aalborg Universitet, Clinical Medicine Larsen, Ryan; Aalborg Universitet, Health Science and Technology, Sport Sciences – Performance and Technology
<b>Primary Subject Heading</b>:	Rehabilitation medicine
Secondary Subject Heading:	Cardiovascular medicine, Sports and exercise medicine, Public health
Keywords:	REHABILITATION MEDICINE, Physiology < NATURAL SCIENCE DISCIPLINES, Coronary heart disease < CARDIOLOGY, Neurological injury < NEUROLOGY, PUBLIC HEALTH, ULTRASONOGRAPHY

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4 1 **Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord**  
5 **injured wheelchair users – Protocol for a randomized controlled trial**  
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8 3 Rasmus Kopp Hansen, MSc<sup>1,2</sup>, Afshin Samani, PhD<sup>1</sup>, Uffe Laessoe, PhD<sup>2</sup>, Aase Handberg, DMSc, MD<sup>3,4</sup>,  
9 4 Ryan Godsk Larsen, PhD<sup>1</sup>  
10  
11

12 5  
13  
14 6 *<sup>1</sup>Department of Health Science and Technology, Sport Sciences – Performance and Technology, Aalborg*  
15 *University, Aalborg, Denmark*  
16 7

17 8 *<sup>2</sup>Department of Physiotherapy / Research and Innovation, University College of Northern Denmark,*  
18 *Aalborg, Denmark*  
19 9

20 10 *<sup>3</sup>Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark*  
21

22 11 *<sup>4</sup>Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*  
23

24 12 **Corresponding author:**

25 13 Rasmus Kopp Hansen, MSc.

26 14 Department of Health Science and Technology, Sports Sciences – Performance and Technology

27 15 Aalborg University

28 16 Niels Jernes Vej 12, A5-209

29 17 DK-9220 Aalborg

30 18 Denmark

31 19 Telephone: +4520892317

32 20 Email [rkopp@hst.aau.dk](mailto:rkopp@hst.aau.dk)  
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## 30 **ABSTRACT**

### 31 **Introduction**

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

### 43 **Methods and analysis**

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

### 51 **Ethics and dissemination**

52 This trial is reported to the Danish Data Protection Agency (J.nr. 2019-899/10-0406) and approved by the  
53 Committees on Health Research Ethics in The North Denmark Region on 12 December 2019 (Journal-nr. N-  
54 20190053). The principal investigator will collect written informed consent from all participants prior to  
55 inclusion. Irrespective of study outcomes, the results will be submitted to peer-reviewed scientific journals  
56 for publication.

### 57 **Trial registration number**

58 NCT04390087.

## 60 **ARTICLE SUMMARY**

### 61 **Strengths and limitations of this study**

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4 62 • The frequency, duration and intensity of the exercise intervention follows recently published  
5 exercise recommendations for individuals with SCI.  
6 63  
7 64 • This study uses a randomized controlled design to examine the effects of a novel exercise modality  
8 on both traditional and novel cardiometabolic risk factors.  
9 65  
10 66 • The exercise modality (upper-body rowing) includes not only an aerobic component, but also an  
11 element of resistance training for the posterior shoulder region, potentially ameliorating shoulder  
12 pain.  
13 67  
14 68  
15 69 • Lack of control of food intake is a study limitation as altered energy intake could influence the  
16 interpretation of the effects of exercise on body mass and body composition  
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## 89 INTRODUCTION

90 Individuals with spinal cord injury (SCI) are placed at the lowest end of the fitness continuum<sup>1</sup>. Thus  
91 cardiovascular disease and metabolic dysfunction is a growing concern in this population<sup>2,3</sup>. In recent years,  
92 cardiovascular disease has emerged as the leading cause of mortality in individuals with chronic SCI<sup>4</sup>.

93 Factors contributing to high cardiometabolic morbidity and mortality in individuals with SCI are sedentary  
94 lifestyle and low physical activity level<sup>5</sup>, and the ensuing negative influence on body composition, reflected  
95 by lower fat-free mass and larger amount of adipose tissue<sup>6</sup>.

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

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

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



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4 123 the effects of upper-body aerobic exercise on changes in body mass and body composition, such as a  
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6 124 reduction in total and visceral adipose tissue<sup>18,25,26</sup>. The explanation for the lack of an exercise effect on  
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8 125 some of these above mentioned risk factors is not clear, but could be related to insufficient volume<sup>20,22</sup> or  
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10 126 intensity<sup>25</sup> of exercise, performed with limited amount of skeletal muscle mass.

11 127 Notably, in able-bodied individuals, the exercise-induced risk reduction in cardiovascular diseases cannot be  
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13 128 fully explained by traditional risk factors (constituents of the metabolic syndrome), i.e. there is a risk factor  
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15 129 gap<sup>27</sup>. As a consequence, studies have started to focus on the effects of exercise on changes in the vascular  
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17 130 wall<sup>27</sup>. It is known that dysfunction of the vascular endothelium occurs at the very early phases of  
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19 131 atherosclerosis<sup>28</sup>. For instance, flow-mediated dilation (FMD), a non-invasive measure of nitric oxide (NO)  
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21 132 dependent endothelial function<sup>29</sup>, is a strong predictor of future cardiovascular events<sup>30</sup>. In addition, carotid  
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23 133 intima media thickness (IMT), a measure of vessel wall thickness<sup>31</sup> has shown to be associated with future  
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25 134 vascular events, such as the occurrence of stroke and myocardial infarction<sup>31</sup>. Accumulating evidence in  
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27 135 able-bodied individuals demonstrates beneficial effects of exercise on structural and functional adaptations  
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29 136 of the vasculature<sup>32</sup>. However, little is known about the effects of exercise on the vasculature in individuals  
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31 137 with SCI.

32 138 Reductions in femoral artery (lower body) diameter occurs rapidly in response to extreme inactivity, as  
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34 139 observed within three weeks off acquiring a SCI<sup>33</sup>. De Groot et al.<sup>34</sup> found similar FMD in the brachial  
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36 140 artery among untrained SCI when compared to able-bodied individuals, however when FMD was normalized  
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38 141 to the shear stress stimulus, the dilation response was reduced in the SCI group, indicating some degree of  
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40 142 endothelial dysfunction in this population<sup>35</sup>. Other observational studies have demonstrated both larger  
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42 143 conduit artery diameter and blood flow in the subclavian artery<sup>36</sup>, and larger brachial diameter<sup>34</sup> in  
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44 144 wheelchair athletes compared to non-athlete able-bodied controls. Together these findings indicate that  
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46 145 remodeling of the vasculature also occurs in response to regular exercise in wheelchair users with SCI.  
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48 146 However, the causal link between adaptations of the upper body arteries and repetitive exercise stimulus in  
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50 147 SCI is not fully established. Therefore, the relationship between exercise and vascular remodeling in manual  
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52 148 wheelchair users needs to be determined through controlled exercise studies. A recent experimental study  
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54 149 consisting of supervised aerobic exercise (20min, twice per week), adhering to the earlier (2011) exercise  
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56 150 guidelines for adults with SCI<sup>37</sup>, was successful in improving measures of cardiorespiratory fitness and  
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58 151 muscle strength<sup>38</sup>. Yet, Zepetnek et al.<sup>22</sup> demonstrated that this exercise paradigm (20min, twice per week)  
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60 152 did not improve markers of cardiovascular disease risk, including carotid IMT and brachial FMD. Recent  
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62 153 (2018) guidelines recommend at least 30 min of moderate-to-vigorous intensity aerobic exercise, three times  
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64 154 per week in order to improve cardiometabolic health in individuals with SCI<sup>39</sup>, suggesting that insufficient  
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66 155 exercise stimuli may explain the lack of vascular adaptations in the study by Zepetnek et al.<sup>22</sup>. Notably, to  
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68 156 date, no studies have examined the effects of the updated exercise guidelines (30 min of moderate-to-

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4 157 vigorous intensity aerobic exercise, three times per week) on vascular adaptations in manual wheelchair  
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6 158 users with SCI.  
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8 159 While isolated aerobic exercise, via arm-cranking or wheelchair ergometry, evokes positive effects on  
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10 160 cardiorespiratory fitness, these modalities/types of exercises fail to address the importance of strengthening  
11 161 the posterior shoulder musculature of the upper-extremity for individuals with SCI relying on a manual  
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13 162 wheelchair for mobility<sup>40</sup>. In addition, these modalities use repetitive contractions of the shoulder  
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15 163 musculature engaged in daily wheelchair propulsion activities, thereby increasing the risk of developing  
16 164 shoulder pain<sup>41-43</sup>. Studies have reported high prevalence of shoulder pain in long-term wheelchair users  
17  
18 165<sup>44,45</sup>, which prevents these individuals from engaging in physical activity<sup>46</sup>. As wheelchair users rely on their  
19 166 upper-extremities for most daily activities, upper-extremity pain must be prevented or limited to preserve  
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21 167 function, independence and quality of life (QOL)<sup>21,47</sup>. Indeed, health related QOL is lower in adults with SCI  
22 168 compared with the able-bodied population<sup>48,49</sup>. The development of shoulder pain has been suggested to  
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24 169 occur due to chronic overuse, shoulder strength imbalances between anterior and posterior musculature,  
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26 170 postural changes and impingement syndrome<sup>50-52</sup>. Considering the general need for strong upper extremities  
27 171 to bear weight during different transfer tasks<sup>53</sup>, to propel wheelchair<sup>54</sup>, and to reach overhead levels<sup>55</sup>, the  
28  
29 172 inclusion of resistance training in exercise training paradigms seems prudent. One modality that combines  
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31 173 aerobic and resistance components is rowing<sup>56</sup>. Specifically, it has been shown that wheelchair user-  
32 174 modified upper-body rowing ergometry challenges the cardiovascular system comparable to arm-cranking<sup>41</sup>.  
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34 175 Additionally, upper-body rowing mirrors the muscle activation observed during traditional resistance  
35 176 training for the scapular retractors<sup>57</sup>. Earlier research has demonstrated beneficial effects of resistance  
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37 177 training of the posterior shoulder and scapular retractor musculature on shoulder pain<sup>47,55,58</sup>. Thus, the use of  
38 178 upper-body rowing ergometry may evoke positive effects on both cardiometabolic health and shoulder pain  
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40 179 in manual wheelchair users, the latter through alterations in posterior vs. anterior upper-body muscle strength  
41 180 balance. However, to date, no studies have implemented upper-body rowing ergometry as exercise modality  
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43 181 in this population.

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## 46 183 **Objectives**

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48 184 The primary objective of this study is to determine the effects of 12-weeks of wheelchair user-modified  
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50 185 upper-body rowing on both traditional (insulin resistance, obesity, dyslipidemia (including low HDL-C and  
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52 186 elevated triglycerides, and blood pressure) and novel (inflammatory status, autonomic nervous system  
53 187 function, vascular structure and function, and cardiorespiratory fitness level) cardiometabolic risk factors in  
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55 188 manual wheelchair users with SCI. As secondary objectives, we will investigate the effects of the exercise  
56 189 intervention on leisure time physical activity, shoulder pain, indices of QOL, and feasibility of the  
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58 190 intervention.

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## 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<sup>59</sup>. 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 ( $\geq 1$  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

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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](http://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<sup>60</sup>. This approach increases the risk of over representing individuals who are interested in the research area<sup>60</sup>. 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<sup>20</sup>. 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<sup>39</sup>. 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<sup>61</sup>. Compared with continuous exercise, interval-based exercise have been reported to elicit higher enjoyment in individuals with SCI<sup>62</sup>, 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<sup>63</sup> 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'<sup>64,65</sup>. The validity of using RPE to control moderate and vigorous exercise intensity has been demonstrated in individuals with SCI<sup>66</sup>. During the first visit, participants will be familiarized with the RPE scale<sup>67</sup> 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<sup>66</sup>. Some

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4 258 controversy exists about the validity of using overall RPE to monitor exercise intensity<sup>67,68</sup>, as the  
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6 259 relationships between overall RPE and objective physiological markers such as oxygen consumption (VO<sub>2</sub>),  
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8 260 heart rate (HR) and ventilation (VE) in individuals with SCI have been questioned<sup>68</sup>. This have led some  
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10 261 researchers to use a differentiated RPE scale that distinguishes between central (cardiorespiratory sensations)  
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12 262 and peripheral (peripheral working limbs) sensations<sup>69</sup>. However, the current evidence does not indicate  
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14 264 greater validity for differentiated RPE compared with overall RPE<sup>67</sup>, and therefore overall RPE will be used  
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16 265 to guide exercise intensity.

16 265 Each training session will consist of aerobic exercise performed on a wheelchair-modified upper-body  
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18 266 rowing ergometer (Concept 2, Morrisville, Vermont, USA). Due to the pulling motion of the upper-body  
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20 267 during rowing, this modality also includes a component of resistance exercise<sup>56</sup>. The modification of the  
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22 268 ergometer is made by separating it into two parts using an Adapt2row<sup>1</sup>, allowing the participants to sit in  
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24 270 their wheelchair while performing upper-body rowing. Wedges will be positioned under the rear wheels to  
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26 271 keep the wheelchair in place. Further, in case of SCI related insufficient innervation of torso musculature,  
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28 272 straps will be wrapped around the back of the wheelchair and around the trunk of the participant, thereby  
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30 273 securing the participant to the wheelchair. A pilot study<sup>41</sup> has provided promising results regarding the  
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32 274 feasibility of using adaptive upper-body rowing exercise in the SCI population. Participants will be asked to  
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34 275 empty their bladder before each training session. Average power output (W) will be recorded during each  
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36 276 exercise session to monitor training load and quantify progress in work capacity.

34 276 All exercise sessions will be supervised by the principal investigator, who is an exercise physiologist, or by  
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36 277 sport science students to ensure proper assistance and guidance of the participants. Everyone involved in  
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38 278 supervision will be thoroughly instructed in how to supervise correct exercise technique, and they will  
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40 279 receive general knowledge about SCI and wheelchair use. To allow for some flexibility regarding scheduling  
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42 280 conflicts, participants will have opportunity to exercise 2-4 days per week, with a target of 3 days per week.  
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44 281 That is, in case of a missing session one week, an additional training session can be included the following  
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46 282 week. However, to secure adequate recovery, no more than four training days per week will be allowed. The  
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48 283 intervention will be terminated after 12 weeks, irrespective of any missing training sessions. An adherence  
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50 284 rate threshold of 75% will be used ( $\geq 27$  exercise sessions out of the maximum 36)<sup>70</sup>. However, there are no  
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52 285 previous reports of adherence rates for this type of exercise intervention (12 weeks of wheelchair-modified  
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54 286 rowing) in individuals with SCI. Therefore, if some participants show low (<75%) adherence rates, we  
55  
56 287 intend to do a sensitivity analyses in order to determine how sensitive the exercise responses are to reaching  
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58 288 ( $\geq 75\%$ ) or not reaching (<75%) the *a priori* set adherence rate. If adherence rate influences the exercise  
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60 289 response, we will consider to include adherence rate as a covariate in the statistical analyses.

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<sup>1</sup> <http://www.adapt2row.com/>

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4 290 *Control group*

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6 291 The participants allocated to the control group will be asked to maintain their normal lifestyle throughout the  
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8 292 intervention period. When the 6-months follow-up testing has been terminated, the control group will receive  
9  
10 293 information about the exercise guidelines and the benefits of physical activity. Additionally, if requested, the  
11 294 principal investigator will organize contact to facilities where participants in the control group can perform  
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13 295 adapted rowing.

#### 14 15 296 **Main trial day protocol**

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17 297 The experimental procedures will be similar at baseline, halfway, post intervention, and at follow-up 6  
18  
19 298 months later. To account for within-day variation, the procedures will be performed at the same time of day  
20 299 for each participant. Participants will arrive at the exercise laboratory at Aalborg University for testing.  
21  
22 300 Participants will be asked to refrain from any strenuous exercise (>24 h), caffeine, alcohol, polyphenols,  
23 301 vitamin C, and supplements known to affect the cardiovascular system (>12 h), and attend in a fasted (>6 h)  
24  
25 302 state.<sup>71</sup> Any smokers must abstain from smoking for >6 h prior to each visit<sup>71</sup>. If participants are taking  
26 303 medication, a wash-out period of at least 4-5 times the half-life of the drug (typically 24-48 h) will be used.  
27  
28 304 If a drug cannot be withdrawn due to health issues, testing will be performed after a consistent time period  
29  
30 305 after intake, as recommended for studies examining vascular function<sup>71,72</sup>. On trial days, participants will  
31 306 receive a standardized snack (energy bar) after completion of the FMD measurement. Participants will be  
32  
33 307 asked to empty their bladder before any testing is commenced, and are allowed to drink water ad libitum  
34 308 during the test days.

35  
36 309  
37 310 INSERT FIGURE 1

#### 38 39 311 **Blood collection procedure**

40  
41 312 On a separate day, after an overnight fast (i.e.  $\geq 10$  hours of fasting), participants will have approximately 20  
42 313 mL blood drawn from a peripheral vein. Blood samples will be aliquoted and stored at  $-80^{\circ}$  at the  
43  
44 314 Department of Clinical Biochemistry, Aalborg University Hospital, until analyses. Blood samples will be  
45  
46 315 analyzed for indicators of cardiometabolic health (markers of glucose homeostasis, dyslipidemia, non-  
47 316 alcoholic fatty liver disease (NAFLD), and prothrombotic risk) as well as inflammatory markers (pro- and  
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49 317 anti-inflammatory markers). Blood sampling will be conducted within a week prior to commencing the  
50 318 intervention (baseline), between 36 and 60 hours after the last exercise session in week 6 (halfway) and week  
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52 319 12 (post) to minimize any effects from the last exercise session, and 6 months after the termination of the  
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54 320 intervention (6-months follow-up).

#### 55 56 321 **Outcome measures**

##### 57 58 322 *Primary outcome*

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4 323 The primary outcome is fasting insulin, since it is one of the hallmarks of the metabolic syndrome<sup>73,74</sup>, and  
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6 324 has shown to be modifiable with exercise training in individuals with SCI<sup>20</sup>.

### 8 325 ***Secondary key outcomes***

#### 10 326 *Arterial blood pressure (BP) and resting heart rate (HR)*

12  
13 327 After resting for 10 min, participants will have their resting systolic and diastolic BP and HR measured with  
14 328 an automated BP monitoring device (OMRON M3, OMRON Healthcare, Hoofddorp, Netherlands).

15  
16 329 Measurements will be performed twice, with participants in sitting position. If these measurements deviate  
17 330 >5 %, a third measurement will be performed. The lowest values will be used for further analyses.

#### 19 331 *Body composition*

21  
22 332 Participants will have their body mass measured while sitting in their wheelchair (wearing light clothing)  
23 333 using a platform wheelchair scale (Detecto® 6550 wheelchair scale, Webb City, MO, USA). Body mass will  
24 334 be derived by subtracting the weight of the wheelchair from the total mass and rounded to the nearest 0.1 kg

25 335<sup>75</sup>. Supine height (cm) will be measured in supine position using non-elastic tape. For participants with  
26 336 contractures precluding stretching of the legs, length will be measured in segments from heel to top of the  
27 337 skull<sup>76</sup>. Body mass index (BMI) will be calculated as weight (kg) divided by height squared (m<sup>2</sup>). Waist  
28 338 circumference and waist-to-hip circumference ratio will be used as a surrogate for visceral adiposity<sup>75-77</sup>.

29  
30 339 Participants will have their waist and hip circumference measured in supine position following a deep  
31 340 expiration. Waist and hip circumference will be measured immediately below the lowest rib<sup>76</sup> and widest  
32 341 part of the trochanters<sup>77</sup>, respectively. For all circumference measurements, the tape will be placed directly  
33 342 on the skin with the participants arms by the side<sup>76</sup>. Anthropometric measures will be taken in duplicate  
34 343 (height, waist and hip circumference), rounded to the nearest 0.1 cm and reported as the mean. If the  
35 344 difference between the first and second measure is >0.1 cm, a third measure will be obtained.<sup>76</sup>

#### 42 345 *Autonomic nervous system function*

43 346 Increasing evidence suggest that autonomic dysfunction accentuates the risk for adverse cardiovascular  
44 347 events<sup>78</sup>. Individuals with SCI are prone to autonomic disturbances as a consequence of disruption to the  
45 348 spinal cord<sup>7</sup>, placing them at increased risk for autonomic related cardiovascular diseases. It is generally  
46 349 accepted that the heart in individuals with SCI below T6 is innervated by both sympathetic and  
47 350 parasympathetic neurons. In contrast, due to disruption of sympathetic outflow, parasympathetic innervation  
48 351 dominates in individuals with complete cervical and upper thoracic injuries, thereby resulting in bradycardia,  
49 352 reduced cardiac output and arterial BP<sup>7</sup>. Recently, it has been shown, however, that sympathetic control can  
50 353 be partially preserved in athletes with a cervical motor complete injury, with the degree of preservation being  
51 354 an important determinant of exercise performance<sup>79</sup>. Yet, whether exercise training can alter autonomic  
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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)<sup>78,80</sup> and arterial BP changes in response to an orthostatic challenge (sit-up tilt test)<sup>79</sup> 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<sup>81,82</sup>. For the sit-up tilt test, participants will be equipped with a finger plethysmograph (Finometer, Finapres Medical Systems BV, Enschede, the Netherlands) 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°<sup>79</sup>. Changes in systolic BP and diastolic BP will be calculated as the difference between mean seated and supine BPs<sup>83</sup>. The presence of orthostatic hypotension will be defined as a  $\geq 20$  mm Hg drop in systolic BP or a  $\geq 10$  mm Hg drop in diastolic BP when moving to an upright position<sup>84</sup>.

#### *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<sup>71,85</sup> and resistance<sup>72</sup> 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<sup>29</sup>. 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<sup>71</sup>. 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<sup>86</sup>, continuous and simultaneous measurement of pulse-wave velocity (Doppler) and diameter (B-mode) using duplex ultrasound will be performed. This allows for an estimation



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4 389 of the shear stress stimuli through the calculation of shear rate, which then can be used to normalize the  
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6 390 FMD response<sup>87</sup>. Because the error of the insonation estimation increases exponentially with angles  $>60^\circ$ <sup>88</sup>,  
7  
8 391 an insonation angle of  $\leq 60^\circ$  will be used, with the sample volume adjusted to cover the total width of the  
9 392 vessel.

10  
11 393 Resistance vessel function will be determined by the magnitude of the reactive hyperemic response to cuff-  
12  
13 394 induced ischemia. Several measures obtained from the reactive hyperemic response will be reported,  
14  
15 395 including absolute blood flow (calculated based on the diameter derived cross sectional area and blood  
16 396 velocity) and velocity, peak change in blood flow, and blood flow area under the curve (AUC) across the  
17  
18 397 post-deflation time period.

19  
20 398 Although related, the measure of reactive hyperemia mirrors the magnitude of downstream resistance artery  
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22 399 dilation, whereas FMD represents conduit artery dilation<sup>72</sup>.

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24 400 To ensure that the same part of the CCA and BA will be insonated across study visits, anatomical landmarks  
25 401 will be identified and recorded together with a photo of the insonation sites. All insonation settings  
26  
27 402 (including sample volume, insonation angle, and recording time) and occlusion procedure (including cuff-  
28  
29 403 position, pressure and duration) will be held consistent within participants across study visits. For  
30 404 standardization, the same investigator will perform all measurements and all analyses (blinded to the identity  
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32 405 of the data).

#### 33 34 406 *Metabolic and inflammatory profile*

35  
36 407 The metabolic and inflammatory profile will be assessed via measures of glycemic control (fasting glucose,  
37  
38 408 long-term blood glucose (HbA1c, glycosylated hemoglobin), homeostatic model assessment of insulin  
39 409 resistance (HOMA-IR)), lipid profile (HDL-c, LDL-c, total cholesterol and triglycerides (TG)), pro-  
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41 410 inflammatory (C-reactive protein (CRP), interleukin (IL) 6, tumor necrosis factor-alpha), anti-inflammatory  
42 411 (IL-10, IL1RA)), prothrombotic (PAI-1), markers of NAFLD (hepatic enzymes (alanine-aminotransferase  
43  
44 412 (ALT) and aspartate-aminotransferase (AST)), growth differentiation factor 15 (GDF15) and fibroblast  
45  
46 413 growth factor 21 (FGF21)).

#### 47 48 414 *Cardiorespiratory fitness level*

49  
50 415 Cardiorespiratory fitness level will be determined through an incremental arm-cranking test to exhaustion,  
51 416 with peak oxygen consumption ( $VO_{2peak}$ ) and ventilatory thresholds as the outcome measures. The placement  
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53 417 of the ergometer (Monark 881E, Vansbro, Sverige) will be adjusted such that the participants shoulder joint  
54 418 is aligned with the crank axis with the elbows slightly bend. Participants will be equipped with a HR  
55  
56 419 monitoring belt (Suunto Ambit3 Run; Suunto, Vantaa, Finland) and a face mask, connected to an online  
57  
58 420 open-circuit metabolic cart. The cart (JAEGGER, Vyntus CPX, Carefusion) will be calibrated to known  
59 421 volumes and gas concentrations according to manufactural guidelines. After a 1-min warm-up with zero  
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4 422 resistance, the test begins with an individualized starting load (5-90W) <sup>89</sup> with increases in work load (5 or  
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6 423 10W) every minute <sup>90</sup> until volitional fatigue, defined as an inability to maintain cadence above 55 rounds  
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8 424 per minute (rpm) <sup>89</sup>. The individual starting load and increment size will be chosen based on training history  
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9 425 and anticipated physical capacity, with the aim of reaching exhaustion within 8-12 minutes at a cadence of  
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11 426 60-70 rpm <sup>90,91</sup>. Breath-by-breath  $\text{VO}_2$  and carbon dioxide output ( $\text{VCO}_2$ ), and HR will be measured  
12  
12 427 continuously throughout the test.  $\text{VO}_{2\text{peak}}$  will be reported in both absolute ( $\text{l O}_2 \cdot \text{min}^{-1}$ ) and relative ( $\text{ml}$   
13  
14 428  $\text{O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) terms, and defined as the highest 30-s average during the test, with the corresponding HR  
15  
15 429 reported as  $\text{HR}_{\text{peak}}$ . The highest workload that is achieved for  $\geq 30$ -s will be reported as  $\text{PO}_{\text{peak}}$ . Participants  
16  
17 430 will be asked to indicate RPE (Borg 6-20 scale) during the last 15-s of each minute. On test cessation,  
18  
18 431 participants will gradually cool-down for 5-min, while their BP will be measured immediately before and  
19  
20 432 after this recovery period.

21  
22 433 As part of the cardiorespiratory fitness assessment, the first ventilatory threshold (VT1) and the second  
23  
23 434 ventilatory threshold (VT2) will be determined during the incremental arm-cranking test. V1 and V2  
24  
25 435 represents distinct physiological events, but are both related to an increase in blood lactate and a subsequent  
26  
26 436 increase in  $\text{VCO}_2$  in response to increased exercise intensity <sup>92</sup>. Each VT will be defined according to the V-  
27  
28 437 slope method or the ventilatory equivalent method, depending on which plot most clearly illustrates the  
29  
29 438 particular VT <sup>92</sup>. In addition, a plot showing the respiratory exchange ratio (RER) will be used as extra  
30  
31 439 reference in order to support the recognition of individual thresholds <sup>92</sup>. Thresholds will be determined  
32  
33 440 independently by two researchers, with the average value used for analysis <sup>93</sup>. In case of deviation of  $>5\%$   
34  
34 441 for individual thresholds, the disparity will be discussed and a mutual agreement will be found <sup>93</sup>. Although  
35  
36 442 1-min stages seems short for the attainment of steady state, the usage of 1-min stages have previously shown  
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37 443 to be efficient for the detection of VTs on a group level, especially in paraplegics <sup>92</sup>.

### 41 445 ***Other secondary outcomes***

#### 43 446 *Shoulder pain*

45  
46 447 The prevalence and severity of shoulder pain will be assessed using the Danish version <sup>94</sup> of the Wheelchair  
47  
47 448 Users Shoulder Pain Index (WUSPI) <sup>95</sup>. WUSPI is a valid and reliable measure of shoulder pain in manual  
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49 449 wheelchair users <sup>51</sup> The questionnaire utilizes a series of visual analog scales (VAS) ranging from “no pain”  
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51 450 to “worst pain ever experienced”, and it is a self-reported measure of the prevalence and severity of shoulder  
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52 451 pain during different activities such as dressing, bathing, transfer, wheeling up, sleeping etc. <sup>95</sup>. Some  
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54 452 participants may not perform all of the 15 activities. To account for that, a performance-corrected shoulder  
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55 453 pain score (PC-WUSPI) will be calculated by dividing the raw total WUSPI score by the number of  
56  
57 454 performed activities, multiplied by 15 <sup>96</sup>.

#### 59 455 *Health-related quality of life (HRQOL)*

HRQOL will be monitored using the Danish translated version of the Short Form-36 (SF-36)<sup>97</sup>, which is a reliable and validated questionnaire to assess HRQOL within both a physical and mental health domain<sup>98</sup>. 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<sup>99</sup>. Construct validity stays acceptable with this modification<sup>99</sup>. Data will be scored using the RAND 36-item Health survey 1.0 method<sup>100</sup>, 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<sup>101</sup>.

#### *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)<sup>102</sup>. 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<sup>102</sup>. 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<sup>103</sup>. 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  $\geq 3.0$  will be used as a criterion to indicate that the intervention is acceptable<sup>103</sup>. 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**

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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  $\pm$  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<sup>104 105</sup>. BP instability does occur in cervical injured individuals (tetraplegics), who may suffer from pronounced autonomic disturbances<sup>104,105</sup>. During the  $VO_{2peak}$  test and exercise sessions, special attention is devoted towards potential symptoms of autonomic dysreflexia (AD)<sup>106</sup> in individuals with  $SCI \geq T6$ . 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<sup>105</sup> and orthostatic hypotension<sup>104</sup> 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  $\geq C5$  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  $SCI \geq T5-T6$  with interrupted cardiac

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4 524 sympathetic innervation, which could affect arterial BP stabilization during conditions in which peripheral  
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6 525 vascular resistance is further reduced (i.e. during exercise). Therefore, to identify any participants that may  
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8 526 be prone to experiencing post exercise hypotension, brachial artery BP will be monitored immediately after,  
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10 527 and again 5 min after the first  $VO_{2peak}$  test. In such cases, and assuming the hypotension is well tolerated, the  
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12 528 participants will be reminded to drink appropriately during and prior any future training and testing. Further,  
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14 530 these participants will have their BP measured every second interval (i.e. every 10<sup>th</sup> min) during the training  
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16 531 sessions. If hypotension develops, the training will be interrupted and hypotensive countermovements  
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18 532 (placement in a supine position, or legs up) will be applied. If the hypotension is not tolerated, such as if the  
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20 533 participants exhibit signs of nausea, light-headedness, fatigue or presyncopal symptoms in response to either  
the  $VO_{2peak}$  test or the training, they will be excluded from further participation in the study.

21 534 Another consideration is that individuals with SCI suffer from impaired thermoregulation<sup>107</sup>. Although  
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23 535 prolonged (60 min) moderate intensity exercise in warm conditions (>31°C) have been shown sustainable for  
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25 536 some paraplegic and tetraplegic individuals<sup>108</sup>, impaired thermoregulation makes individuals with SCI more  
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27 537 vulnerable to overheating compared to able-bodied<sup>107</sup>. This is especially the case during conditions of  
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29 538 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  
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31 540 higher injury (tetraplegics) exhibit higher core temperatures during exercise compared to lower injury  
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33 541 individuals (paraplegics)<sup>108</sup>. To diminish the risk for overheating during testing and training, a fan will be  
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35 542 available for cooling of the participants and the room temperature and humidity will be continuously  
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37 543 monitored to facilitate the conditions for dry and evaporative heat loss. Moreover, the participants will be  
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39 544 asked to pay attention to proper hydration before and throughout each training session. However, if the  
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41 545 participants demonstrate signs of any adverse response, the exercise session will be terminated immediately  
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43 546 and further participation in the study will be reconsidered. Any adverse responses from the intervention will  
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45 547 be reported to the regional health research committee. The trial is reported to the Danish Data Protection  
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47 548 Agency (J.nr. 2019-899/10-0406), registered at ClinicalTrials.gov on 15 May 2020, and approved by the  
48  
49 549 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  
50  
51 550 irrespective of study outcomes.

#### 50 552 **Data statement section**

51  
52 553 All participant data will be stored in a secure web-based database (Redcap) with restricted access and ID  
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54 554 code, in accordance with data protection rules. Source documents including date, visit# and participant ID  
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56 555 will be scanned and saved as electronic copies. Participant data will be transferred directly or by use of an  
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58 556 encrypted USB stick. Each participant will be assigned an unique identification number, which will be the  
59  
60 557 only identifier exported from Redcap upon data analysis. Except for the blood samples, which will be stored

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

### 561 **Acknowledgement**

562 The authors would like to thank Dr. Rachel E. Cowan for valuable discussions regarding the study protocol,  
563 Dr. Jan Christian Brønd for discussions regarding assessment of leisure time physical activity level, and  
564 Wolturnus A/S for lending of arm ergometer and wheelchair weight

### 565 **Author Contributions**

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

### 570 **Funding**

571 This work is supported by Aage and Johanne Louis-Hansens Fond, grant number 20-2B-5947. Aage and  
572 Johanne Louis-Hansens Fond will have no influence on any part of the project design, data collection, data  
573 analysis, data interpretation or the disclosure of the results. Thus, their support is solely economical.

### 574 **Competing interests**

575 None declared.

### 577 **Patient consent**

578 Not required.

### 579 **License statement**

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

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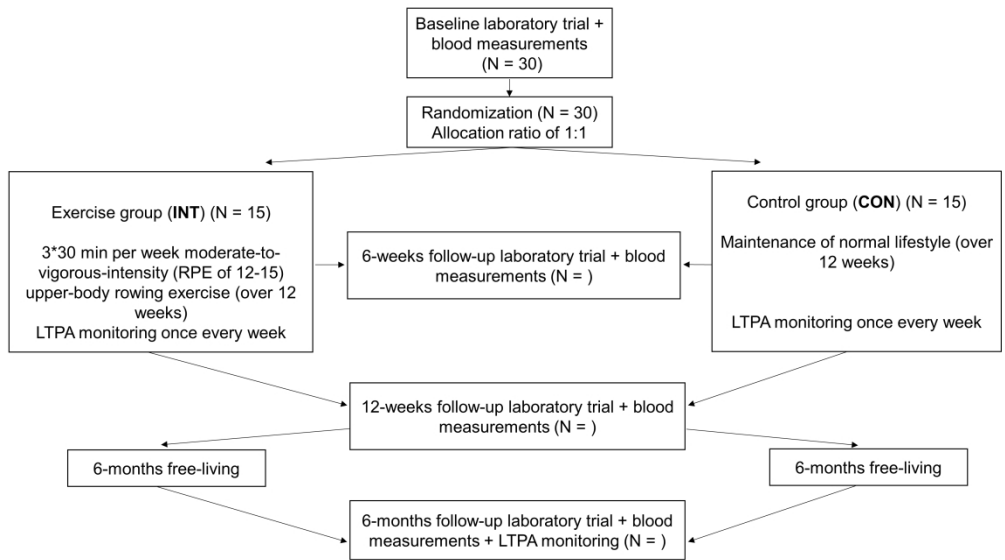


Figure 1. Study overview. INT = intervention; CON = control; RPE = rating of perceived exertion; LTPA = leisure time physical activity.

338x190mm (300 x 300 DPI)

1 Project title: Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors in spinal cord  
2 injured wheelchair users  
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7 **Informed Consent to Participation in a Health Scientific Research Project**  
8

9 Title of the research project: Effect of wheelchair-modified rowing exercise on cardiometabolic risk factors  
10 in spinal cord injured wheelchair users  
11  
12

13 **Declaration by the Volunteer**

14 I have received information about the research project both in writing and orally, and I have sufficient  
15 knowledge of the objective, method, advantages and disadvantages to confirm my participation.  
16

17  
18 I know that participation is voluntary and that I can always withdraw my consent without losing my  
19 present or future rights to treatment.  
20

21 I hereby give my consent to participation in the research project and to taking out samples of my  
22 biological material for storage in a research bio-bank. I have received a copy of this form and of all  
23 written information about the project for my own use.  
24  
25

26 Name of the Volunteer: \_\_\_\_\_  
27

28 Date: \_\_\_\_\_ Signature: \_\_\_\_\_  
29

30  
31 If new, significant health information appears during the research project, you will be informed. If you  
32 wish to **decline** receipt of this information, please tick here: \_\_\_

33  
34 Would you like to be informed of the results of the research project and of the consequences for you, if  
35 any?

36 Yes \_\_\_\_\_ No \_\_\_\_\_ (tick the appropriate field)  
37  
38

39 **Declaration by the Person giving Information**

40 I hereby declare that the Volunteer has received information both in writing and orally about the research  
41 project.  
42

43 I believe that the information given is sufficient for making a decision on participation in the research  
44 project.  
45

46 Name of the person giving the information: \_\_\_\_\_  
47

48 Date: \_\_\_\_\_ Signature: \_\_\_\_\_  
49  
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53 Project identification: N-20190053  
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56 Standard declaration of consent issued by Den Nationale Videnskabetiske Komité, December 2011.  
57 *Translation into English made by Center for Sensory-Motor Interaction, Aalborg University*  
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# 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.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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	Reporting Item	Page Number
<b>Administrative information</b>		
Title	<a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,3



1	Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not	4,9
2			yet registered, name of intended	
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7				
8				
9	Trial registration:	<a href="#">#2b</a>	All items from the World Health	n/a. The trial has been
10			Organization Trial Registration Data	registered with details
11	data set		Set	provided at Clinicaltrials.gov
12				
13				
14				
15				
16	Protocol version	<a href="#">#3</a>	Date and version identifier	1
17				
18				
19	Funding	<a href="#">#4</a>	Sources and types of financial,	20
20			material, and other support	
21				
22				
23				
24				
25	Roles and	<a href="#">#5a</a>	Names, affiliations, and roles of	1,2,20
26			protocol contributors	
27	responsibilities:			
28				
29	contributorship			
30				
31				
32	Roles and	<a href="#">#5b</a>	Name and contact information for the	20
33			trial sponsor	
34	responsibilities:			
35				
36	sponsor contact			
37				
38	information			
39				
40				
41				
42	Roles and	<a href="#">#5c</a>	Role of study sponsor and funders, if	20
43			any, in study design; collection,	
44	responsibilities:		management, analysis, and	
45			interpretation of data; writing of the	
46	sponsor and		report; and the decision to submit the	
47			report for publication, including whether	
48	funder			
49				
50				
51				
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1 they will have ultimate authority over

2  
3 any of these activities

4  
5  
6 Roles and [#5d](#) Composition, roles, and responsibilities n/a. No such committee has  
7 responsibilities: of the coordinating centre, steering been established.  
8 committees committee, endpoint adjudication  
9  
10  
11  
12  
13 committee, data management team,  
14  
15 and other individuals or groups  
16  
17 overseeing the trial, if applicable (see  
18 Item 21a for data monitoring  
19  
20  
21  
22 committee)  
23  
24

## 25 Introduction

26  
27  
28 Background and [#6a](#) Description of research question and 6-8  
29 rationale justification for undertaking the trial,  
30  
31 including summary of relevant studies  
32  
33 (published and unpublished) examining  
34  
35 benefits and harms for each  
36  
37  
38  
39 intervention  
40  
41

42 Background and [#6b](#) Explanation for choice of comparators 6-8  
43 rationale: choice  
44  
45 of comparators  
46  
47  
48  
49

50 Objectives [#7](#) Specific objectives or hypotheses 8  
51  
52

53 Trial design [#8](#) Description of trial design including type 9  
54  
55 of trial (eg, parallel group, crossover,  
56  
57 factorial, single group), allocation ratio,  
58  
59

and framework (eg, superiority,  
equivalence, non-inferiority,  
exploratory)

## Methods:

### Participants, interventions, and outcomes

18	Study setting	<a href="#">#9</a>	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
30	Eligibility criteria	<a href="#">#10</a>	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
42	Interventions: description	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
52	Interventions: modifications	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in	10-11, 18-19

1		response to harms, participant request,	
2			
3		or improving / worsening disease)	
4			
5			
6	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to	10
7			
8	adherence	intervention protocols, and any	
9			
10		procedures for monitoring adherence	
11			
12		(eg, drug tablet return; laboratory tests)	
13			
14			
15			
16	Interventions:	<a href="#">#11d</a> Relevant concomitant care and	10-12
17			
18	concomitant care	interventions that are permitted or	
19			
20		prohibited during the trial	
21			
22			
23	Outcomes	<a href="#">#12</a> Primary, secondary, and other	12-17
24			
25		outcomes, including the specific	
26			
27		measurement variable (eg, systolic	
28			
29		blood pressure), analysis metric (eg,	
30			
31		change from baseline, final value, time	
32			
33		to event), method of aggregation (eg,	
34			
35		median, proportion), and time point for	
36			
37		each outcome. Explanation of the	
38			
39		clinical relevance of chosen efficacy	
40			
41		and harm outcomes is strongly	
42			
43		recommended	
44			
45			
46			
47			
48			
49	Participant	<a href="#">#13</a> Time schedule of enrolment,	12
50			
51	timeline	interventions (including any run-ins and	
52			
53		washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is	
56			
57		highly recommended (see Figure)	
58			
59			
60			

1 Sample size [#14](#) Estimated number of participants 10  
 2  
 3  
 4 needed to achieve study objectives and  
 5  
 6 how it was determined, including  
 7  
 8 clinical and statistical assumptions  
 9  
 10 supporting any sample size calculations  
 11  
 12

13 Recruitment [#15](#) Strategies for achieving adequate 10  
 14  
 15 participant enrolment to reach target  
 16  
 17 sample size  
 18  
 19  
 20

## 21 Methods:

### 22 Assignment of 23 interventions (for 24 controlled trials)

25 Allocation: [#16a](#) Method of generating the allocation 9  
 26  
 27 sequence sequence (eg, computer-generated  
 28  
 29 generation random numbers), and list of any  
 30  
 31 factors for stratification. To reduce  
 32  
 33 predictability of a random sequence,  
 34  
 35 details of any planned restriction (eg,  
 36  
 37 blocking) should be provided in a  
 38  
 39 separate document that is unavailable  
 40  
 41 to those who enrol participants or  
 42  
 43 assign interventions  
 44  
 45  
 46  
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1	Allocation	<a href="#">#16b</a>	Mechanism of implementing the	9
2				
3	concealment		allocation sequence (eg, central	
4				
5	mechanism		telephone; sequentially numbered,	
6				
7				
8			opaque, sealed envelopes), describing	
9				
10			any steps to conceal the sequence until	
11				
12			interventions are assigned	
13				
14				
15	Allocation:	<a href="#">#16c</a>	Who will generate the allocation	9-10
16				
17	implementation		sequence, who will enrol participants,	
18				
19			and who will assign participants to	
20				
21			interventions	
22				
23				
24				
25	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to	15
26				
27			interventions (eg, trial participants, care	
28				
29			providers, outcome assessors, data	
30				
31			analysts), and how	
32				
33				
34				
35	Blinding	<a href="#">#17b</a>	If blinded, circumstances under which	n/a. Participants allocated to
36				
37	(masking):		unblinding is permissible, and	the exercise and control
38				
39	emergency		procedure for revealing a participant's	group cannot be blinded to
40				
41	unblinding		allocated intervention during the trial	the PI, because PI is
42				
43				
44				
45				responsible for conducting
46				
47				the study. Parts of data
48				
49				analysis will be blinded to the
50				
51				PI.
52				
53				
54	<b>Methods: Data</b>			
55				
56	<b>collection,</b>			
57				
58				
59				
60				

1 **management, and**

2  
3 **analysis**

4			
5			
6	Data collection	<a href="#">#18a</a>	Plans for assessment and collection of 12-17
7			
8	plan		outcome, baseline, and other trial data,
9			
10			including any related processes to
11			
12			promote data quality (eg, duplicate
13			
14			measurements, training of assessors)
15			
16			and a description of study instruments
17			
18			(eg, questionnaires, laboratory tests)
19			
20			along with their reliability and validity, if
21			
22			known. Reference to where data
23			
24			collection forms can be found, if not in
25			
26			the protocol
27			
28			
29			
30			
31	Data collection	<a href="#">#18b</a>	Plans to promote participant retention 18
32			
33	plan: retention		and complete follow-up, including list of
34			
35			any outcome data to be collected for
36			
37			participants who discontinue or deviate
38			
39			from intervention protocols
40			
41			
42			
43	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, 19-20
44			
45			and storage, including any related
46			
47			processes to promote data quality (eg,
48			
49			double data entry; range checks for
50			
51			data values). Reference to where
52			
53			details of data management procedures
54			
55			can be found, if not in the protocol
56			
57			
58			
59			
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1	Statistics:	<a href="#">#20a</a>	Statistical methods for analysing	18
2				
3	outcomes		primary and secondary outcomes.	
4				
5			Reference to where other details of the	
6			statistical analysis plan can be found, if	
7				
8			not in the protocol	
9				
10				
11				
12				
13	Statistics:	<a href="#">#20b</a>	Methods for any additional analyses	18
14				
15	additional		(eg, subgroup and adjusted analyses)	
16				
17	analyses			
18				
19				
20				
21	Statistics: analysis	<a href="#">#20c</a>	Definition of analysis population relating	18
22				
23	population and		to protocol non-adherence (eg, as	
24				
25	missing data		randomised analysis), and any	
26				
27			statistical methods to handle missing	
28				
29			data (eg, multiple imputation)	
30				
31				
32				
33	<b>Methods:</b>			
34				
35	<b>Monitoring</b>			
36				
37				
38	Data monitoring:	<a href="#">#21a</a>	Composition of data monitoring	n/a
39				
40	formal committee		committee (DMC); summary of its role	
41				
42			and reporting structure; statement of	
43				
44			whether it is independent from the	
45				
46			sponsor and competing interests; and	
47				
48			reference to where further details about	
49				
50			its charter can be found, if not in the	
51				
52			protocol. Alternatively, an explanation	
53				
54			of why a DMC is not needed	
55				
56				
57				
58				
59				
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1	Data monitoring:	<a href="#">#21b</a>	Description of any interim analyses and	n/a
2				
3	interim analysis		stopping guidelines, including who will	
4			have access to these interim results	
5			and make the final decision to	
6			terminate the trial	
7				
8				
9				
10				
11				
12				
13	Harms	<a href="#">#22</a>	Plans for collecting, assessing,	18-19
14			reporting, and managing solicited and	
15			spontaneously reported adverse events	
16			and other unintended effects of trial	
17			interventions or trial conduct	
18				
19				
20				
21				
22				
23				
24				
25	Auditing	<a href="#">#23</a>	Frequency and procedures for auditing	19
26			trial conduct, if any, and whether the	
27			process will be independent from	
28			investigators and the sponsor	
29				
30				
31				
32				
33				
34				
35	<b>Ethics and</b>			
36	<b>dissemination</b>			
37				
38				
39				
40				
41	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics	19
42	approval		committee / institutional review board	
43			(REC / IRB) approval	
44				
45				
46				
47				
48	Protocol	<a href="#">#25</a>	Plans for communicating important	19
49	amendments		protocol modifications (eg, changes to	
50			eligibility criteria, outcomes, analyses)	
51			to relevant parties (eg, investigators,	
52				
53				
54				
55				
56				
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58				
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1		REC / IRBs, trial participants, trial	
2			
3		registries, journals, regulators)	
4			
5			
6	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or	9
7			
8		assent from potential trial participants	
9			
10		or authorised surrogates, and how (see	
11			
12		Item 32)	
13			
14			
15	Consent or	<a href="#">#26b</a> Additional consent provisions for	n/a
16			
17	assent: ancillary	collection and use of participant data	
18			
19		and biological specimens in ancillary	
20	studies	studies, if applicable	
21			
22			
23			
24			
25	Confidentiality	<a href="#">#27</a> How personal information about	19-20
26			
27		potential and enrolled participants will	
28			
29		be collected, shared, and maintained in	
30			
31		order to protect confidentiality before,	
32			
33		during, and after the trial	
34			
35			
36			
37	Declaration of	<a href="#">#28</a> Financial and other competing interests	20
38			
39	interests	for principal investigators for the overall	
40			
41		trial and each study site	
42			
43			
44			
45	Data access	<a href="#">#29</a> Statement of who will have access to	19-20
46			
47		the final trial dataset, and disclosure of	
48			
49		contractual agreements that limit such	
50			
51		access for investigators	
52			
53			
54			
55	Ancillary and post	<a href="#">#30</a> Provisions, if any, for ancillary and	n/a
56			
57	trial care	post-trial care, and for compensation to	
58			
59			
60			

1		those who suffer harm from trial	
2			
3		participation	
4			
5			
6	Dissemination	<a href="#">#31a</a> Plans for investigators and sponsor to	18-19
7			
8	policy: trial results	communicate trial results to	
9			
10		participants, healthcare professionals,	
11			
12		the public, and other relevant groups	
13			
14		(eg, via publication, reporting in results	
15		databases, or other data sharing	
16		arrangements), including any	
17			
18		publication restrictions	
19			
20			
21			
22			
23			
24	Dissemination	<a href="#">#31b</a> Authorship eligibility guidelines and any	20
25			
26	policy: authorship	intended use of professional writers	
27			
28			
29			
30	Dissemination	<a href="#">#31c</a> Plans, if any, for granting public access	n/a
31			
32	policy:	to the full protocol, participant-level	
33			
34	reproducible	dataset, and statistical code	
35			
36			
37	research		
38			
39			
40	<b>Appendices</b>		
41			
42			
43	Informed consent	<a href="#">#32</a> Model consent form and other related	9
44			
45	materials	documentation given to participants	
46			
47		and authorised surrogates	
48			
49			
50			
51	Biological	<a href="#">#33</a> Plans for collection, laboratory	12
52			
53	specimens	evaluation, and storage of biological	
54			
55		specimens for genetic or molecular	
56			
57		analysis in the current trial and for	
58			
59			
60			

1 future use in ancillary studies, if

2  
3 applicable

4  
5  
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