Effect of high-intensity interval training on cardiometabolic component risks in persons with paraplegia: Protocol for a randomized controlled trial

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Abstract
Individuals with a spinal cord injury (SCI) are at an increased risk of developing cardiovascular disease and present with a multitude of elevated cardiometabolic component risks. Although upper-body exercise appears an effective strategy to improve some of these outcomes, the effectiveness of high-intensity interval training (HIIT) has yet to be determined for this population. Therefore, a randomized controlled trial will be conducted to determine the effectiveness of a 6 week home-based upper-body HIIT intervention on biomarkers of cardiometabolic health in persons with spinal cord injury, in comparison to a control (CON) group. We will recruit 40 individuals with chronic (> 1 year post-injury) paraplegia (spinal cord lesion between the second thoracic and second lumbar vertebrae), aged between 18 and 65 years. After baseline testing, participants will be assigned randomly, using a 2:1 allocation, to the home-based exercise intervention (HIIT, n = 26) or control group (CON, n = 14). The HIIT intervention will consist of 30 min of arm crank-based HIIT (60 s intervals at 80–90% peak heart rate) four times per week. Participants in the CON group will be asked to maintain their habitual diet and physical activity patterns over the study period. Baseline and follow-up assessments will be made for determination of body composition, postprandial glycaemic control, fasting blood lipids and systemic inflammation, aerobic capacity, physical activity and energy intake, resting metabolic rate, resting blood pressure, and subjective measures of health and well-being. ClinicalTrials.gov, ID: NCT04397250. Registered on 21 May 2020.

KEYWORDS
cardiovascular disease, exercise, spinal cord injury

1 INTRODUCTION

Globally, it is estimated that there are ~2 million people living with a spinal cord injury (SCI) (Lee et al., 2014). In the UK, one in three deaths in persons who have sustained a traumatic SCI and survived the first year (i.e., chronic SCI) can be attributed to cardiovascular disease (CVD). When adjusted for age and sex, mortality rates associated with CVD are three times greater among people with SCI, in comparison to the general population.
to the non-injured population (Savic et al., 2017). Persons with a chronic SCI have a high prevalence of component risks associated with CVD, including impaired glucose tolerance (Cragg et al., 2013), central adiposity (Edwards et al., 2008), chronic inflammation (Wang et al., 2007) and dyslipidaemia (Gilbert et al., 2014). Therefore, therapeutic solutions are required for this population, in order to reduce their risk of developing CVD.

Despite the well-established link between physical activity and cardiovascular disease, the majority of persons with chronic SCI are habitually inactive, performing little to no moderate-to-vigorous physical activity (Buchholz et al., 2009; Nightingale et al., 2017b). The latest SCI exercise guidelines differ in the volume of exercise/physical activity recommended to reduce cardiovascular disease risk (90 min of moderate-to-vigorous exercise per week; Ginis et al., 2018) and cardiometabolic disease risk (150 min of moderate-intensity physical activity; Nash & Bilzon, 2018). However, a randomized controlled trial found that performing 4 × 45 min per week of moderate-intensity aerobic exercise was sufficient to improve cardiorespiratory fitness and fasting insulin sensitivity, although no changes were observed in lipid profile, body composition or postprandial glycaemic control, amongst physically inactive individuals with chronic SCI (Nightingale et al., 2017a). This quantity of exercise (180 min/week) is higher than the physical activity guidelines for SCI and non-injured humans (150 min/week) and suggests that a higher intensity or greater volume of exercise might be required to achieve further cardiometabolic health benefits for this population. Given the complex barriers to exercise participation faced by this population (Kehn & Kroll, 2009), promoting a higher volume of exercise seems unrealistic.

Instead, a viable solution might be to maximize the intensity of exercise performed, by prescribing high-intensity interval training (HIIT). This form of exercise can generally be characterized as involving short intervals eliciting ≥80% (but often 85–95%) of maximum heart rate (Macnnis & Gibala, 2017) and is an established training method to improve insulin sensitivity, blood pressure and body composition in individuals at risk of CVD (Campbell et al., 2019). Several meta-analyses have also reported superior effects of HIIT in comparison to moderate-intensity continuous training (MICT) for cardiorespiratory fitness (Weston et al., 2014), insulin resistance (Jolleyman et al., 2015), diastolic blood pressure (Ramos et al., 2015) and body fat mass (Viana et al., 2019), at least in non-injured humans. Meta-analyses have also reported that HIIT is equally effective as MICT at improving the lipid profile (Wood et al., 2019) and inflammatory markers (Khalafi & Symonds, 2020) in non-injured humans.

There has been growing interest in prescribing HIIT for persons with SCI since Nightingale et al. (2017c) proposed a plausible biological mechanism for improving cardiometabolic health outcomes in this population. Of particular note, a randomized controlled trial determined that 5 weeks of upper-body sprint interval training (3 × 20 s ‘all-out’ sprints) was equally as effective as 25 min of MICT (45% peak power output) for improving peak power output in individuals with subacute SCI (McLeod et al., 2020). Additionally, a pilot study in persons (n = 7) with chronic SCI found that 6 weeks of upper-body HIIT was equally effective as MICT for improving insulin sensitivity and aerobic fitness, despite a reduced weekly training volume (40 vs. 90 min; Graham et al., 2019). However, to date, there are no randomized controlled trials that have assessed the effect of upper-body HIIT on a range of cardiometabolic component risks in persons with SCI.

The purpose of this randomized controlled trial is therefore to determine the effect of an upper-body HIIT intervention on cardiometabolic component risks in persons with chronic paraplegia. Participants will be assigned randomly, using a 2:1 allocation, to a 6 week home-based HIIT intervention or a control group who will maintain their normal lifestyle throughout the study period, chosen to reflect the habitually low physical activity levels in this population. The primary outcome measures will be fasting insulin, peak aerobic capacity and peak power output. We hypothesize that fasting insulin concentrations will be reduced and that both peak cardiorespiratory capacity and power output will be increased after 6 weeks of HIIT compared with the control group. Other secondary and exploratory outcome measurement categories include: (i) body composition; (ii) postprandial glycaemic control; (iii) lipid concentrations; (iv) inflammatory cytokines (including adipokines); (v) physical activity; (vi) energy intake; (vii) resting metabolic rate; and (viii) subjective perceptions of health and well-being.

2 | METHODS

2.1 | Study design

This study was approved by the South West (Bristol) National Research Ethics Committee (REC reference number 20/SW/005, Version 2, dated 9 April 2020) and registered on ClinicalTrials.gov (ID: NCT04397250) on 21 May 2020. A randomized controlled trial will be conducted, with participants assigned randomly to either a home-based upper-body HIIT intervention or a control (CON) group. Participants in the HIIT group will be asked to perform exercise (four sessions per week) for 6 weeks. Participants in the CON group will be asked to maintain their habitual diet and physical activity routine during the 6 week period. Baseline and follow-up assessments for both groups will be conducted at the DisAbility Sport & Health (DASH) laboratory at the University of Bath to determine the effectiveness of the intervention. A waiting-list control group will be used, with participants initially allocated to the CON group being offered the chance to take part in the intervention; however, no further measurements will be taken from these participants. The study will be conducted in accordance with ethical principles for studies involving human participants set out in the Declaration of Helsinki.

2.2 | Recruitment

The primary recruitment pathway will be the advertisement of the study to potentially eligible individuals on the databases of a local R&D offices (Duke of Cornwall Spinal Treatment Centre, National Spinal Injuries Centre, London Spinal Injury Centre and Welsh Centre for...
Spinal Trauma). In addition, these centres will display a recruitment poster in a publicly visible area. These offices will send out letters and participant information sheets to individuals on their database who are aged 18–65 years, with an SCI between the second thoracic (T2) and second lumbar (L2) vertebrae. For individuals from whom no communication has been received within 1 month of sending out the letter, one of the offices will contact the individuals via telephone or a follow-up letter to enquire whether they are interested in taking part. After this, there will be no further direct contact with potential participants. Participants will be invited to contact the research team at the University of Bath directly should they be interested in taking part in the study. In addition, participants will be recruited using social media advertisements through non-National Health Service charities and clinical partners. Interested potential participants will be asked to contact the principal researcher for further information via email/telephone correspondence. The principal researcher will email a participant information sheet and conduct a follow-up telephone call >48 h after the participant expresses their initial interest, in order to explain fully what the trial entails and answer any questions. Providing the potential participant indicates that they still wish to take part in the study, the principal researcher will schedule the first visit. During the first visit, participants will be asked to provide written informed consent.

2.3 Randomization

Eligible individuals will be assigned randomly to either the HIIT or the CON group. Randomization will take place after the baseline visit and will be performed by an independent researcher according to a list generated with a Web-based platform (www.randomization.com), using a 2:1 allocation ratio, with no stratification and a fixed block size of nine (Dumville et al., 2006). An unequal allocation was chosen to allow for a greater number of participants being assigned to the HIIT group, because it is expected that there will be large inter-individual variation compared with the CON group. The research team and participants will not be blinded to group assignments after the randomized allocation.

As recommended for trials involving small sample sizes (Altman & Bland, 2005), a minimization approach will be used to balance groups for key characteristics (age, sex and time since injury) at baseline. This will be performed by an independent researcher, using a free program (https://www-users.york.ac.uk/~mb55/guide/minim.html), with factors weighted equally and no random elements.

2.4 Participants and eligibility criteria

The participants recruited will be aged between 18 and 65 years, have a chronic SCI (>1 year post-injury) between the T2 and L2, self-reporting use of a wheelchair for >75% of their waking day, and weight stable (weight not changed by ≥3%) for the last 3 months. Individuals who self-report active medical issues, such as pressure sores, urinary tract infections, cardiac disorders, cardiovascular contraindications for exercise testing (Goosey-Tolfrey, 2007) or musculoskeletal complaints of the upper extremities, will be excluded. Individuals who self-report the use of type 2 diabetes medication or drugs that affect glucose metabolism will be excluded. This will be checked on a case-by-case basis using the British National Formulary. Finally, any participants with plans to change their lifestyle (i.e., diet or physical activity level) during the study period will also be excluded.

2.5 Laboratory assessments

The same experimental procedures will be completed on both main trial days and are displayed in the Standardized Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure (Figure 1). Before each main trial day, participants will be asked to refrain from performing any moderate or strenuous exercise in the preceding 48 h and refrain from consuming alcohol and caffeine in the preceding 24 h. Participants will arrive at the laboratory at the same time for both main trial days, after an overnight fast (>10 h). Participants will also be asked to mimic their food and drink intake in the 2 days before these visits using a non-weighed food diary. Assessments will be conducted during the follicular phase of the menstrual cycle (3–10 days after the onset of menses) for all eumenorrhoeic women taking part in the study.

2.5.1 Body composition

Body mass will be measured (to the nearest 0.1 kg) using platform wheelchair scales (BRW1000; Decto, Webb City, MO, USA), with the wheelchair and participant’s shoes weighed separately and subtracted from the total mass. Participants will be asked to void before this measurement and remove all heavy clothing. For all body composition measurements, participants will be lying flat on a dual-energy X-ray absorptiometry (DEXA) scanning table (Discovery; Hologic, Bedford, UK). Supine length will be measured with participants lying flat on the bed, with their feet close together and arms at their sides. Length will be measured (to the nearest 0.5 cm) alongside the left-hand side of the body, using a non-elastic tape measure (Lufkin, Sparks, MD, USA). A wooden board will be pressed against the feet, in an attempt to achieve dorsal flexion. Waist and hip circumferences (to the nearest 0.1 cm) will be measured in duplicate, using a non-metallic tape measure. Waist circumference will be measured at the end of normal expiration, at the mid-way point between the lowest palpable rib and the iliac crest. Hip circumference will be measured at the widest portion of the buttocks. The DEXA scan will be performed with participants positioned in the middle of the scanning table, with their feet spaced evenly either side of the mid-point of the body and arms placed mid-prone with an equal gap to the trunk on both sides.

2.5.2 Resting metabolic rate and blood pressure

Resting metabolic rate (RMR) will be estimated via indirect calorimetry from 5 min expired gas samples, collected into pre-evacuated Douglas
FIGURE 1 Standardized Protocol Items: Recommendations for Interventionsal Trials (SPIRIT) figure. Abbreviations: DEXA, dual-energy X-ray absorptiometry; OGTT, oral glucose tolerance test; PA, physical activity; RMR, resting metabolic rate; $\dot{V}_{O_{2}\text{peak}}$, peak aerobic capacity

### Activity/assessment

| Activity/assessment | STUDY PERIOD |
|---------------------|--------------|
|                     | Pre-Study | Allocation | Intervention | Follow-up |
| TIMEPOINT           | T −1 | T0 | T1 | T2 | T3 | T4 | T5 | T6 | T7 |
| Eligibility screen  | X     |     |    |    |    |    |    |    |    |
| Informed consent    | X     |     |    |    |    |    |    |    |    |
| Randomization       | X     |     |    |    |    |    |    |    |    |
| INTERVENTIONS:      |         |         |         |         |         |         |         |         |         |
| HIIT                |         |         |         |         |         |         |         |         |         |
| CON                 |         |         |         |         |         |         |         |         |         |
| ASSESSMENTS:        |         |         |         |         |         |         |         |         |         |
| DEXA scan           | X     |     |    |    |    |    |    |    |    |
| RMR                | X     |     |    |    |    |    |    |    |    |
| OGTT               | X     |     |    |    |    |    |    |    |    |
| $\dot{V}_{O_{2}\text{peak}}$ | X |     |    |    |    |    |    |    |    |
| PA Monitoring       | X     |     |    |    |    |    |    |    |    |

bags (Hans Rudolph, Kansas City, MO, USA) through a mouthpiece connected to a two-way valve. Fractions of $O_2$ and $CO_2$ will be measured using a paramagnetic $O_2$ and infrared $CO_2$ analyser (miniMP 5200; Servomex, Crowborough, UK), calibrated with known concentrations of gas (100% $N_2$, 20% $O_2$ and 8% $CO_2$) on the morning of testing. During each collection, ambient $O_2$ and $CO_2$ fractions will be measured at close proximity to the participant to account for changes in an enclosed laboratory environment (Betts & Thompson, 2012). Expired fractions of $O_2$ and $CO_2$, total volume of expired gas (Harvard Apparatus, Edenbridge, UK) and expired gas temperature (model C; Edale Instruments, Cambridge, UK) will be measured for each sample. All values will be corrected to reflect atmospheric pressure and temperature during each collection. The RMR will be calculated using stoichiometric equations (Frayn, 1983) and taken as the average of three samples differing by $\leq 100$ kcal/day. During the final 5 min of RMR, resting heart rate (Polar H10; Polar Electro, Vansbro, Sweden) will be recorded every 30 s and an average taken. After the assessment of RMR, resting blood pressure will be measured in triplicate using an automated blood pressure monitor, with 1 min rest in between each measurement.

#### 2.5.3 Blood sampling

A cannula will be interested into an antecubital vein and a 20 ml blood sample taken. Whole blood [and all blood samples during the oral glucose tolerance test (OGTT)] will be dispensed into serum and plasma separation tubes. For serum, whole blood will be placed in serum separation tubes and left to stand at room temperature for 15 min before centrifugation. For plasma, whole blood will be placed in tubes coated with EDTA and centrifuged immediately. Samples will be centrifuged at 4000g for 10 min at 4°C, with 0.5 ml aliquots obtained for serum and plasma. Aliquots will be cooled immediately on dry ice before being placed in a $−80^\circ C$ freezer for long-term storage. A small aliquot of the fasting blood sample will be placed in a tube coated with EDTA to assess leucocyte differentials (SD-300; Sysmex Ltd., Milton Keynes, UK).

#### 2.5.4 Oral glucose tolerance test

Participants will consume 113 ml of PolyCal (Nutricia Advanced Medical Nutrition, Trowbridge, UK) and 87 ml of water, within 5 min.

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**FIGURE 1** Standardized Protocol Items: Recommendations for Interventionsal Trials (SPIRIT) figure. Abbreviations: DEXA, dual-energy X-ray absorptiometry; OGTT, oral glucose tolerance test; PA, physical activity; RMR, resting metabolic rate; $\dot{V}_{O_{2}\text{peak}}$, peak aerobic capacity
Blood samples (5 ml) will be obtained every 15 min for the subsequent 2 h. To ensure the cannula is kept patent, 0.9% NaCl will be flushed through after obtaining each blood sample. During the last 30 min of the OGTT, the participant will complete the Wheelchair User’s Shoulder Pain Index (WUSPI; Curtis et al., 1995), the short form-36 health survey (SF-36; Ware & Sherbourne, 1992), the Fatigue Severity Scale (FSS; Anton et al., 2008), the Exercise Self-efficacy Scale (ESES; Kroll et al., 2007) and the Spinal Cord Independent Measure (SCIM; Catz et al., 1997) questionnaires.

2.5.5 I Exercise testing

A submaximal incremental exercise test will then be performed on an electronically braked arm-crank ergometer (Lode Angio, Groningen, The Netherlands) consisting of four 3 min stages, starting at 5 W and increasing by either 10 or 15 W (depending on self-reported fitness level). Participants will be instructed to maintain a cadence of ∼75 r.p.m. throughout. They will wear a rubber facemask connected to a two-way breathing valve throughout, with expired gases (Douglas bag method, as previously described) and heart rate recorded in the final minute of each stage.

Participants will then be given a small snack before performing a maximal exercise test to determine peak aerobic capacity (\(V_{\text{O2peak}}\)). The ramp-based protocol on an electronically braked arm-crank ergometer will begin with a 2 min warm-up at 10 W before increasing by 1 W every 6 s. Participants will wear a rubber facemask connected to a two-way breathing valve, which will be connected to a computerized metabolic system (TrueOne 2400; ParvoMedics, Salt Lake City, UT, USA) calibrated with a known concentration of gases (20% O2 and 8% CO2) and a 3 litre calibration syringe, on the morning of testing. Heart rate and expired gas analysis data will be recorded simultaneously on the software throughout the test. A cadence of ∼75 r.p.m. will be encouraged throughout, and the test will be terminated at volitional fatigue or when cadence falls below 50 r.p.m.

2.6 I Exercise intervention

Participants in the HIIT group will be asked to perform four sessions per week of home-based HIIT, involving 10 × 60 s intervals at 80–90% peak heart rate (HRpeak) on a mechanically braked arm-crank ergometer (Monark 881 E; Vansbro, Sweden). To account for changes in fitness and ensure progression, the intensity will be increased by 5% every 2 weeks (i.e., 80% HRpeak for weeks 1 and 2, 85% HRpeak for weeks 3 and 4, and 90% HRpeak for weeks 5 and 6). Each exercise session will include a 5 min warm-up and cool-down at a low intensity (∼5 W), with 60 s recovery intervals at ∼5 W, resulting in a total exercise time of 30 min. During each exercise training session (weeks 1–5), participants will be asked to wear a chest-worn heart rate monitor (Wahoo Tcker X; Wahoo Fitness, Atlanta, GA, USA) and view their HR response in real time using a smartphone application. In the final week of the HIIT, heart rate data from the Actiheart (Cambridge Neurotechnology Ltd, Papworth, UK) will be used to measure compliance.

Participants will be asked to avoid performing two exercise training sessions on the same day and advised that they should avoid performing the training sessions within 1 h of food consumption to avoid gastrointestinal issues. No other time or dietary restrictions will be required for the training sessions. Participants will be asked to send their heart rate data remotely to the researcher after every exercise training session (weeks 1–5) to help monitor adherence and compliance. Participants will be contacted by the researcher on a weekly basis and adjustments to the exercise intensity made, if necessary.

2.7 I Emergencies and adverse events

Participants will be monitored for the following both during and after the peak aerobic capacity test and first home-based HIIT session: chest pain, headaches, changes in vision, dizziness and light-headedness. Blood pressure will be measured immediately after the peak aerobic capacity test to identify any individuals exceeding the limits for systolic blood pressure (<85 and >200 mmHg). The laboratory has an approved procedure for emergencies, and the research team are trained in cardiopulmonary resuscitation. Participants will be required to sign a consent form stating that they must be accompanied by an adult for all exercise training sessions at home. Additionally, any individuals who self-report regular or uncontrolled episodes of autonomic dysreflexia will be asked to obtain written consent from their general practitioner to take part in the study.

2.8 I Outcome measures

2.8.1 I Aerobic capacity

Aerobic capacity (\(V_{\text{O2peak}}\)) will be defined as the highest 15-breath rolling average for O2 uptake. Peak power output will be defined as the highest power output achieved before termination of the test. Each test must meet at least two or the following criteria to be deemed a valid \(V_{\text{O2peak}}\): peak HR ≥ 95% of age-predicted maximum for upper-body exercise (200 beats/min minus age), rating of perceived exertion ≥ 19, and a peak respiratory exchange ratio ≥ 1.10.

2.8.2 I Blood measurements

Fasting measures of insulin resistance, insulin sensitivity and pancreatic β-cell function will be calculated using the Homeostatic Model Assessment (HOMA-2) calculator (Levy et al., 1998). Insulin and glucose incremental area under the curve and Insulin Sensitivity Index (ISI-Matsuda, Matsuda & Defronzo, 1999) will be calculated to characterize responses to the OGTT. Serum and plasma samples will be analysed using enzyme-linked immunoassays and an automated analyser (Randox RX Daytona; Randox Laboratories, Antrim, UK). In addition to fasting glucose and insulin, markers of
inflammation (interleukin-6 and C-reactive protein), adipokines (leptin and adiponectin) and the lipid profile (triglycerides, total cholesterol, non-esterified fatty acids, high-density lipoprotein–cholesterol and low-density lipoprotein–cholesterol) will be determined.

2.8.3 Physical activity energy expenditure and energy intake

Participants will be asked to wear a physical activity monitor (Actiheart) for 7 days before and in the final week of the HIIT/CON period. The physical activity monitor will be calibrated individually using the heart rate and corresponding energy expenditure measured during the RMR assessment and submaximal exercise test, as previously described for manual wheelchair users (Nightingale et al., 2015). At least four valid days (>80% of data for that 24 h period), including at least one weekend day, must be recorded for the data to be included. Daily physical activity energy expenditure and time spent in different intensities of activities according to metabolic equivalents will be calculated. Participants will be asked to record their habitual food and fluid intake for the same 7 day period using a set of weighing scales. Subsequently, total energy intake and macronutrient composition will be calculated using diet analysis software (Nutritics, Dublin, Ireland).

2.9 Statistical analyses

The final analysis will be based on a modified intention-to-treat principle, whereby each participant must complete >75% (18 of 24 sessions) of planned exercise sessions to be included. Any changes in outcome measures between groups will be determined using a series of ANCOVAs, with the pre-intervention value as a covariate, and group allocation, age, sex and time since injury as fixed effects. Bonferroni comparisons will be performed to confirm the location of any differences, where significance interaction or main effects are observed. Any non-normally distributed variables will be log10-transformed, checked again for normality and used as continuous log10-transformed variables. Effect sizes (Cohen’s d) will be calculated for all variables and interpreted as follows: small effect = 0.20–0.40, medium effect = 0.50–0.79, and large effect ≥0.80. Statistical significance will be accepted at P ≤ 0.05.

2.10 Sample size

A pilot study in individuals with SCI reported that HIIT reduced fasting insulin by 9.7 ± 7.0 ml/dl in 6 weeks (d = 1.10, n = 3) (Graham et al., 2019). To adjust for the 2:1 allocation adopted, an unequal size sample size calculation was performed (www.statstodo.com/UnequalSSize_Pgm.php). Based on an expected drop-out of ~15%, and α = 0.05 and β = 0.80, we will aim to recruit a total of 40 participants (26 HIIT and 14 CON).

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The trial sponsor can be contacted at: Jonathan Knight, pro-vc-research@bath.ac.uk, 01225 386141.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of this study. MF led in writing this protocol paper and all authors contributed to the review and approval of the final manuscript.

DATA AVAILABILITY STATEMENT

All electronic files will be stored the University of Bath’s shared drive, in a folder accessible only by the research team. All confidential physical data records will be stored in a locked file cabinet, in a locked room (1 West 4.114, University of Bath, Bath BA2 7AY, UK), accessible only by the principal investigator (J.B.). All serum and plasma samples will be stored in a locked laboratory (6 West South, University of Bath, Bath BA2 7AY, UK).

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