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Keywords:	physical activity, sedentary lifestyle, activity breaks, glucose, cardiovascular disease, spinal cord injury

Protocol for evaluating cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) study

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Study end date: 18th January 2019

Abstract

Introduction: Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD) and could partly explain the increased prevalence of CVD in people with spinal cord injury (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute CVD risk marker response to breaking up prolonged sedentary time in people with SCI has not been investigated. **Methods and analysis:** A randomised two-condition crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-intensity arm crank activity every 20 min with 2) uninterrupted prolonged sedentary time (control) in people with SCI. Outcomes will include acute effects on postprandial glucose, insulin, lipids and blood pressure. Blood samples will be collected and blood pressure measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This study was approved by the Cambridge South NHS Research Ethics Committee. The research will help determine if breaking up prolonged sedentary time could be effective in lowering CVD risk in people with SCI. The findings of the research will be published in a peer reviewed journal and disseminated to relevant user groups. **Trial registration:** The study is registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

Strengths and limitations of this study

- This is the first study to investigate cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia.
- This study adds to the limited literature on the acute cardiovascular disease risk marker responses to intermittent physical activity in individuals with paraplegia.
- Due to the acute nature of the study, the long-term cardiovascular disease risk marker responses to a chronic intervention will remain unknown.
- The cardiovascular disease risk marker responses to breaking up prolonged sedentary time in people with tetraplegia still requires investigation.

Keywords: physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular disease; spinal cord injury

Introduction

There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading cause of death in individuals with SCI [3]. Traditional risk factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low high-density lipoprotein cholesterol (HDL), and high blood pressure. The clustering of ≥2 and ≥3 risk factors is prevalent in 87% and 72% of SCI individuals, respectively [4], which is markedly higher compared with the able-bodied population [5].

Postprandial glucose and lipid concentrations are strong independent predictors of future CVD incidence, even in those without diabetes [6]. There is a dose-response relationship between postprandial glucose area under the curve (AUC) and CVD risk, while progression of carotid atherosclerosis can be prevented by control of postprandial glucose concentrations [7, 8]. It is thus pertinent to identify interventions to reduce postprandial glucose and lipid responses in individuals with SCI to reduce their CVD risk.

Physical activity guidelines have been developed specifically for this population that recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA) three times per week for CVD health benefits [9]. Reduced levels of physical activity are proposed to largely account for the increased CVD risk in SCI [10]; it is estimated that 50% of this population engage in no leisure-time physical activity whatsoever [11]. However, sedentary behaviour (i.e. any waking behaviour in a sitting, reclining or lying posture with low energy expenditure [12]), is now recognised as being a significant CVD risk factor in the able-bodied population, independent of MVPA [13]. Experimental studies in able-bodied individuals have reported an acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity walking every 20 min [14-17]. No research has examined whether

postprandial CVD risk marker responses are attenuated in response to breaking up prolonged sedentary time in individuals with SCI.

The primary aim of this study is therefore to compare the acute CVD risk marker responses in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted sedentary time. It is hypothesised that breaking up prolonged sedentary time will result in favourable CVD risk marker responses compared with uninterrupted sedentary time in individuals with paraplegia.

Methods and analysis

Study design

A randomised two-condition crossover design will be used in accordance with the SPIRIT statement [18]. The study is registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437). The study schedule can be seen in Table 1. All research will take place at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary measures, participants will complete two experimental conditions in randomised order. The conditions will be separated by ≥6 days to eliminate any potential carryover effects. Condition order will be randomised by a researcher independent from the study using computer generated random numbers (block randomisation with balanced block sizes).

Insert Table 1 about here.

Participants

Inclusion criteria: Males and females aged 18-60 years; chronic SCI (≥1 year since injury); individuals with a traumatic SCI below Thoracic level 6 (mid to low level paraplegia); individuals with a non-traumatic SCI (as defined within the International Spinal Cord Injury Data Sets for non-traumatic SCI [19]) that present with mid to low level paraplegia. Individuals who express an interest in taking part in the study will be required to indicate their

spinal cord lesion level and completeness of injury via a questionnaire prior to preliminary measures. Participants will be encouraged to obtain relevant information from a medical professional if they are unaware of their injury level.

Exclusion criteria: individuals who regularly engage in >300 min/week of MVPA; history of severe cardiovascular complications; hypotension (resting blood pressure <90/60 mmHg); body mass index >45 kg/m^2, a history of autonomic dysreflexia; pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure, liver disease, major illness, or other health issues that may limit ability to perform the physical activity protocols.

Recruitment

Participants will be recruited through organisations and charities that promote physical activity, health and wellbeing for individuals with SCI; the National Spinal Injuries Centre, Stoke Mandeville Hospital, Buckinghamshire NHS Healthcare Trust; and local sport and activity clubs. Mail outs, social media, information on websites, posters, flyers, and visits from the research team will be used to provide information on the study to potentially eligible individuals who can then express their interest to the research team in taking part in the study. Written informed consent will be obtained by a member of the research team prior to participation in any testing protocols. As an incentive, participants will received a £25 shopping gift voucher for each main condition they complete and will have all travel expenses paid.

Preliminary measures

Participants will attend a preliminary testing session where they will have body mass measured using wheelchair double beam scales (300 series; Marsden, London, UK) and body fat% measured using dual-energy x-ray absorptiometry (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [20]. During DXA measures,

participants will be positioned as closely as possible to standard protocols and Velcro restraints will be fastened around the participant's knees and ankles to maintain correct position of the legs during scanning. Participants will be offered a wedge to be used as a pillow for comfort. Waist circumference will be measured using International Standards for Anthropometric Assessment (ISAK) guidelines [21, 22]. These measures will be taken in the standing position for participants who are able to maintain this posture and in a supine position for participants who are not able to stand [23]. Resting blood pressure will be measured on the left arm, while seated, three times after the participant has rested for 5 min with the lowest readings being recorded. Following this, participants will be familiarised with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [24]. They will then cycle using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour research [14, 25]. Participants will be asked to cycle at ~70 rpm during the test. The test will start at a low intensity (~20 Watts), which will gradually increase until an RPE of 13 has been attained. The test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of 13 during the test will be recorded for each participant and used for the physical activity breaks described in the respective main condition below. The use of the Borg 6-20 RPE scale is highly reproducible in individuals with SCI to determine physical activity intensity [26].

Experimental protocol

Error! Reference source not found. shows the experimental protocol. Participants will be instructed to refrain from caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be provided with a food diary and digital weighing scales to record volume and timings of all food and liquids consumed in the 24 h period prior to the first experimental condition. Participants will be asked to replicate their diet the day prior to the subsequent experimental condition [27]. On condition days, participants will attend in the morning following an overnight fast and avoid active travel to the laboratory. Upon arrival,

resting blood pressure will be measured after 5 min rest; two measures will be taken and the lowest of these recorded. A fasting capillary blood sample will then be collected. Participants will commence the 5.5 h condition period following consumption of a standardised breakfast. The two experimental conditions are as follows:

1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their wheelchair or a standard chair at a desk during this condition.
2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical activity.

Figure 1 about here.

An RPE of 13 for the physical activity intensity was selected in line with previous research [14, 28] and the Borg 6-20 RPE scale may be used to assess and regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic SCI [26]. Moderate-intensity physical activity was selected as it is well-tolerated, can be performed safely, and is recommended for health risk reduction in individuals with SCI [9, 29].

Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during each condition. Except during the activity bouts, participants will remain inactive and only leave their desk to void and consume standardised meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of the research team when moving to these locations so that they remain inactive. A researcher will be present to ensure compliance with protocols throughout all conditions.

Meal and water consumption

Standardised meals will be consumed immediately prior to the start of each experimental condition and at 3 h, each providing 30% of estimated daily energy requirements for each participant [30]. Participants will be asked to consume each meal within a 15 min time period. The time taken to consume the meals will be recorded for the first condition and participants will be asked to replicate this time as closely as possible in the subsequent condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted crisps and apple (54% carbohydrate, 34% fat, 13% protein). This macronutrient composition of meals was chosen as it is generally representative of UK guidelines for a balanced diet [31]. The glycaemic index for these breakfast and lunch meals is 43 and 72, respectively. Glycaemic index values for each food item were obtained from the International Tables of Glycaemic Index and Glycaemic Load Values 2008 [32] and meal glycaemic index was calculated using weighted means of the glycaemic index values for the component foods [33]. Water will be available ad libitum during the first condition and this volume of intake will be provided at standardised regular intervals in the subsequent condition.

Blood collection and biochemistry

Finger prick blood samples will be collected into two EDTA-containing microvettes (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120, 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be collected. Blood glucose concentrations will be analysed immediately using the YSI 2300 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of blood from one microvette. Additional 30 μl volumes of whole blood will be aliquoted onto two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the measurement of triglyceride and HDL concentrations using the Reflotron Plus system (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood (~490 μL) will be

centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK) and the plasma then stored at -80°C. An enzyme-linked immunosorbent assay kit will be used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

Blood pressure

Blood pressure will be measured at baseline as described above followed by single readings taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

Study outcomes

Primary outcome: the primary outcome for the study is within-participant, between condition postprandial glucose net incremental area under the curve (iAUC) [6]. *Secondary outcomes:* these include within-participant, between condition mean systolic and diastolic blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit comparisons across previous studies. *Feasibility measures:* to assess feasibility of the trial, participant dropout, number of experimental sessions completed, fatigue at the beginning and end of each day rated on an 11 point (0-10) Visual Analogue Scale (VAS), and the degree of difficulty in completing the experimental conditions rated on an 11 point (0-10) VAS will be recorded. Participants will also complete the Physical Activity Enjoyment Scale [34] at the end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [35] ("Enjoyment") 20 min after the last activity bout in the SED-ACT condition. Participants will also report on the same scale how enjoyable they would find it to engage in this form of physical activity most days of the week in the coming month ("Expected enjoyment"). *Psychological outcomes:* determinants of sedentary behaviour will be measured based on the COM-B [36] and the theory of planned behaviour using standardised wording formats [37] that will include overcoming barriers (self-efficacy/perceived behavioural control),

attitudes, intentions and action planning. The following questionnaires will be completed by participants at baseline and at the end of each experimental condition: sedentary behaviour self-efficacy using an adapted version of the Schwarzer et al. [38] Physical Exercise Self-Efficacy Scale; current mood using the short Positive and Negative Affect Scale [39]; psychological wellbeing using the National Wellbeing Measurement [40]; and the Warwick Edinburgh Mental Well-Being Scale [41].

Sample size calculations

Sample size calculations were performed using GPower [42]. Previous research reported a 16% reduction (effect size, F=0.61) in 5 h postprandial glucose total AUC when breaking up prolonged sedentary time with 2 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied participants [16]. As this study will use arm cranking (localised muscular contractions) as opposed to walking where a larger muscle mass is required, a smaller effect may be observed. Based on this, it was estimated that 14 participants would be required for this complete two-treatment crossover design to detect a smaller minimum intervention effect of 10% with a within-person correlation of 0.6, 80% power, and an α of 0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.

Statistical analysis

Linear mixed models will be used to determine differences in the primary and secondary outcome variables between the conditions. All models will adjust for potential covariates explaining residual outcome variances. Statistical significance will be accepted as p<0.05. Cohens' d effect sizes will be calculated to describe the magnitude of differences between conditions [43].

Ethics and dissemination

This study was approved on the 19th May 2017 by the Cambridge South NHS Research Ethics Committee (reference 17/EE/0076).

The findings of this research will be disseminated to lay, academic, practice, and policy-based audiences via presentation at conference proceedings; publication in a peer review journal; websites, newsletters, and social media; and summary reports to policy makers and clinical care partners.

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Author contributions

DB and LC conceptualised the study.

TW, LC, VT, DD, CL, and DB contributed to the design of the study protocol.

TW drafted the manuscript.

TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and approved the final version.

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Conflicts of interest

None of the authors have declared any conflicts of interest.

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Table 1. Study schedule

Visit	Over phone/ email	1		2		3
Activity	Eligibility screening	Preliminary visit and randomisation to experimental condition order	≥6 day washout	Experimental condition A or B	≥6 day washout	Experimental condition A or B

Figure captions

Figure 1 Schematic of experimental protocol.

Figure 1

259x96mm (96 x 96 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	5
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol

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Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol

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Abstract

Introduction: Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD) and could partly explain the increased prevalence of CVD in people with spinal cord injury (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute CVD risk marker response to breaking up prolonged sedentary time in people with SCI has not been investigated. **Methods and analysis:** A randomised two-condition laboratory crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-intensity arm crank activity every 20 min, with 2) uninterrupted prolonged sedentary time (control) in people with SCI. Outcomes will include acute effects on postprandial glucose, insulin, lipids and blood pressure. Blood samples will be collected and blood pressure measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This study was approved by the Cambridge South NHS Research Ethics Committee. This research will help determine if breaking up prolonged sedentary time could be effective in lowering CVD risk in people with SCI. The findings of the research will be published in a peer review journal and disseminated to relevant user groups. **Trial registration:** The study is registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

Strengths and limitations of this study

- This study uses a randomised crossover design to investigate, for the first time, cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia.
- Regular collection of blood samples will permit robust time course and incremental area under the curve calculations for primary and secondary outcomes.
- Due to the acute nature of the study, the long-term cardiovascular disease risk marker responses to a chronic intervention will remain unknown.

- The cardiovascular disease risk marker responses to breaking up prolonged sedentary time in people with tetraplegia still requires investigation.

Keywords: physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular disease; spinal cord injury

Introduction

There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading cause of death in individuals with SCI [3] and this population have a significantly increased risk of heart disease and stroke compared with able-bodied individuals [4]. Traditional risk factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low high-density lipoprotein cholesterol (HDL), and high blood pressure. These risk factors often exacerbate significantly as a consequence of SCI [5] and a plethora of research has documented impaired glucose tolerance and adverse lipid profiles in individuals with SCI [5, 6]. The clustering of ≥2 and ≥3 risk factors is prevalent in 87% and 72% of SCI individuals, respectively [7], which is markedly higher compared with the able-bodied population [8]. This milieu of metabolic disturbances after SCI may be due to increases in body fat resulting from an imbalance in energy intake and expenditure [5]. Excess fat accumulation, particularly in the visceral region, is associated with inflammation that is causal in glucose intolerance and dyslipidaemia [5, 9] thus promoting atherogenesis that would increase the risk of CVD in this population [10].

Postprandial glucose and lipid concentrations are strong independent predictors of future CVD incidence, even in those without diabetes [11]. There is a dose-response relationship between postprandial glucose area under the curve (AUC) and CVD risk, while progression of carotid atherosclerosis can be prevented by attenuation of postprandial glucose concentrations [12, 13]. Impaired postprandial glucose metabolism was observed in 50% and 62% of individuals with paraplegia and tetraplegia, respectively, compared with 18% in able-bodied individuals [6]. This impaired glucose intolerance in SCI is characterised by hyperinsulinaemia, which suggests that there is tissue level resistance to insulin [14]. In paraplegic individuals, there appears to be no difference in postprandial glucose responses between those with complete versus incomplete lesions [15, 16]. Although postprandial lipaemic responses have not been compared between individuals with complete and

incomplete lesions, fasting lipid levels do not differ between these groups [17]. There does, however, appear to be an exaggerated postprandial lipaemic response in individuals with paraplegia compared with able-bodied individuals [18]. These observations are of potential concern as the high dietary intake of carbohydrate and fat in individuals with SCI [19] may lead to repeated exaggerated elevations in glucose and lipids following food intake. It is thus pertinent to identify interventions to reduce postprandial glucose and lipid responses in individuals with SCI to reduce their CVD risk.

Physical activity guidelines have been developed specifically for this population that recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA) three times per week for CVD health benefits [20]. However, it is estimated that 37 to 50% of this population engage in no leisure-time physical activity whatsoever [21, 22]. Reduced levels of physical activity are proposed to largely account for the increased CVD risk in SCI with reduced levels of leisure-time physical activity associated with increased body fat, insulin resistance, and systolic blood pressure [22, 23]. However, sedentary behaviour (i.e. any waking behaviour in a sitting, reclining or lying posture with low energy expenditure [24]), is now recognised as being a significant CVD risk factor in the able-bodied population, independent of MVPA [25]. Experimental studies in able-bodied individuals have reported an acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity walking every 20 min [26-29]. However, no research has examined whether postprandial CVD risk marker responses are attenuated in response to breaking up prolonged sedentary time in individuals with SCI.

The primary aim of this study is therefore to compare the acute CVD risk marker responses in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted sedentary time. The CVD risk markers that will be studied include postprandial glucose (primary outcome), insulin and lipids, and systolic and diastolic blood pressure (secondary

outcomes) based on evidence that these markers predict CVD outcomes and are adversely affected by SCI. It is hypothesised that breaking up prolonged sedentary time will result in favourable CVD risk marker responses compared with uninterrupted sedentary time in individuals with paraplegia. This could identify a novel strategy for the prevention of CVD in SCI that would warrant further evaluation.

Methods and analysis

Study design

A randomised two-condition crossover design will be used in accordance with the SPIRIT statement [30]. The study is registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437). The study schedule can be seen in Figure 1. All research will take place at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary measures, participants will complete two experimental conditions in a randomised order. The conditions will be separated by ≥6 days to eliminate any potential carryover effects. Condition order will be randomised by a researcher independent from the study using computer generated random numbers (block randomisation with balanced block sizes).

Figure 1 about here.

Participants

Inclusion criteria: Males and females aged 18-60 years; chronic SCI (≥1 year since injury); individuals with a traumatic SCI below T5 (mid to low level paraplegia); individuals with a non-traumatic SCI (as defined by the International Spinal Cord Injury Data Sets for non-traumatic SCI [31]) that present with mid to low level paraplegia. Including only individuals with injuries below T5 will ensure sympathetic innervation to the major organs at the T5 level so that heart rate and catecholamine responses would be unaffected by injury [32] and thus minimise the potential that innervation variations could have on the study outcomes. Paraplegic individuals who have complete or incomplete lesions will be included based on

evidence that these groups do not differ with respect to postprandial glucose metabolism (primary outcome) [15, 16]. Individuals who express an interest in taking part in the study will be required to indicate their spinal cord lesion level and completeness of injury via a questionnaire and asked to provide the research team with a copy of medical records to confirm injury level and ASIA impairment scale classification prior to preliminary measures.

Exclusion criteria: individuals who regularly engage in >300 min/week of MVPA as such high levels of physical activity may offset the detrimental association of sedentary time with health outcomes [33]; history of severe cardiovascular complications; hypotension (resting blood pressure <90/60 mmHg); body mass index >45 kg/m^2; a history of autonomic dysreflexia; pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure, liver disease, major illness, or other health issues that may limit ability to perform the physical activity protocols.

Recruitment

Participants will be recruited through organisations and charities relevant to individuals with SCI, including the National Spinal Injuries Centre, Stoke Mandeville Hospital, Buckinghamshire NHS Healthcare Trust; local sport and activity clubs; and local community groups. Mail outs, social media, information on websites, posters, flyers, and visits from the research team will be used to provide information on the study to potentially eligible individuals who can then express their interest to the research team in taking part in the study. Written informed consent will be obtained by a member of the research team prior to participation in any testing protocols (see supplementary file). As an incentive, participants will receive a £25 shopping gift voucher for each main condition they complete and will have all travel expenses paid.

Preliminary measures

Participants will attend a preliminary testing session where they will have body mass measured using wheelchair double beam scales (300 series; Marsden, London, UK). They will also have body fat and lean tissue mass (and percent) determined for the whole body and regionally via whole-body scans using dual-energy x-ray absorptiometry (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [34-36]. During DXA measures, participants will be positioned as closely as possible to standard protocols and Velcro restraints will be fastened around the participants' knees and ankles to maintain correct position of the legs during scanning. Participants will be offered a wedge to be used as a pillow for comfort. Waist circumference will be measured using International Standards for Anthropometric Assessment (ISAK) guidelines [37, 38]. These measures will be taken in the standing position for participants who are able to maintain this posture and in a supine position for participants who are not able to stand [38]. Resting blood pressure will be measured on the left arm, while seated, three times after the participant has rested for 5 min with the lowest readings being recorded. Following this, participants will be familiarised with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [39]. They will then cycle using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour research [26, 40]. Participants will be asked to cycle at ~70 rpm during the test. The test will start at a low intensity (~20 Watts) and the participants will then indicate their RPE at 1 min intervals. The resistance will then be increased by 5-20 Watts based on the participants' RPE until an RPE of 13 has been achieved, at which point the test will be terminated. The test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of 13 during the test will be recorded for each participant and used for the physical activity breaks described in the respective main condition below. The use of the Borg 6-20 RPE scale has acceptable validity in individuals with SCI to determine physical activity intensity [41]. This method is also suggested as a practical approach for health care professionals

and scientists as oxygen consumption testing equipment is costly and not available in many rehabilitation centres and community settings [41].

Experimental protocol

Figure 2 shows the experimental protocol. Participants will be instructed to refrain from caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be provided with a food diary and digital weighing scales to record volume and timings of all food and liquids consumed in the 24 h period prior to the first experimental condition. Participants will be asked to replicate their diet the day prior to the subsequent experimental condition [42]. On condition days, participants will attend in the morning following an overnight fast and avoid active travel to the laboratory. Upon arrival, resting blood pressure will be measured after 5 min rest; two measures will be taken and the lowest of these recorded. A fasting capillary blood sample will then be collected. Participants will commence the 5.5 h condition period following consumption of a standardised breakfast. The two experimental conditions are as follows:

1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their wheelchair or a standard chair at a desk during this condition.
2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical activity.

Figure 2 about here.

The SED-ACT protocol was selected based on previous research that reported a significant reduction in 5 h postprandial glucose in response to breaking up prolonged sitting time with 2 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied

participants [28]. An RPE of 13 for the physical activity intensity was selected in line with previous research [26, 42] and the Borg 6-20 RPE scale may be used to assess and regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic SCI [41]. Moderate-intensity physical activity was selected as it is well-tolerated, can be performed safely, and is recommended for health risk reduction in individuals with SCI [20, 43].

Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during each condition. This will be standardised by asking participants to engage in the same activities during each of the two experimental conditions. Except during the activity bouts, participants will remain inactive and only leave their desk to void and consume standardised meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of the research team when moving to these locations so that they remain inactive. A researcher will be present to ensure compliance with the protocols throughout all conditions.

Meal and water consumption

Standardised meals will be consumed immediately prior to the start of each experimental condition and at 3 h, each providing 30% of estimated daily energy requirements for each participant [44]. Participants will be asked to consume each meal within a 15 min time period. The time taken to consume the meals will be recorded for the first condition and participants will be asked to replicate this time as closely as possible in the subsequent condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted crisps and apple (54% carbohydrate, 34% fat, 13% protein). The macronutrient composition of meals in the current study was selected as it is generally representative of UK guidelines for a balanced diet [45]. The glycaemic index for these breakfast and lunch meals is 43 and 72, respectively. Glycaemic index values for each food item were obtained from the International Tables of Glycaemic Index and Glycaemic Load Values 2008 [46] and meal

glycaemic index was calculated using weighted means of the glycaemic index values for the component foods [47]. Water will be available ad libitum during the first condition and this volume of intake will be provided at standardised regular intervals in the subsequent condition.

Blood collection and biochemistry

Finger prick blood samples will be collected into two EDTA-containing microvettes (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120, 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be collected. Blood glucose concentrations will be analysed immediately using the YSI 2300 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of blood from one microvette. Additional 30 μl volumes of whole blood will be aliquoted onto two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the measurement of triglyceride and HDL concentrations using the Reflotron Plus system (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood (~490 μL) will be centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK) and the plasma then stored at -80^{o}C. An enzyme-linked immunosorbent assay kit will be used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

Blood pressure

Blood pressure will be measured at baseline as described above followed by single readings taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

Study outcomes

Primary outcome: the primary outcome for the study is within-participant, between condition postprandial glucose net incremental area under the curve (iAUC) [11]. *Secondary outcomes:* these include within-participant, between condition mean systolic and diastolic blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit comparisons with previous studies. *Feasibility measures:* to assess feasibility of the trial, participant dropout, number of experimental sessions completed, fatigue at the beginning and end of each day rated on an 11-point (0 “not fatigued at all” to 10 “extremely fatigued”) Visual Analogue Scale (VAS), and the degree of difficulty in completing each experimental condition rated on an 11-point VAS (0 “not difficult at all” to 10 “extremely difficult”) will be recorded. Participants will also complete the Physical Activity Enjoyment Scale [48] at the end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [49] (“Enjoyment”) 20 min after the last activity bout in the SED-ACT condition. Participants will also report on the same scale how enjoyable they would find it to engage in this form of physical activity most days of the week in the coming month (“Expected enjoyment”). *Psychological outcomes:* correlates of sedentary behaviour will be measured immediately before and after each experimental condition to explore whether participants’ mood, affect, wellbeing, and social cognitions regarding their ability to overcome being sedentary may differ in response to the SED-ACT condition compared with the SED condition. These measures will be based on the COM-B framework [50] using standardised wording formats [51] that will include overcoming barriers (self-efficacy/perceived behavioural control), attitudes, intentions and action planning. The following questionnaires will be used: an adapted version of the Schwarzer and Renner [52] Physical Exercise Self-Efficacy Scale to measure self-efficacy to avoid long periods of sedentary time; current mood using the short Positive and Negative Affect Scale [53]; psychological wellbeing using the National Wellbeing Measurement [54]; and the Warwick Edinburgh Mental Well-Being Scale [55]. These measures will be taken within 45 min following the last bout of activity in the SED-

ACT condition, which is an appropriate time frame based on evidence that mood and affect is enhanced for 3-4 hours following a single session of exercise [56].

Sample size calculations

Sample size calculations were performed using GPower [57]. Previous research reported a 16% reduction (effect size, F=0.61) in 5 h postprandial glucose total AUC when breaking up prolonged sedentary time with 2 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied participants [28]. As this study will use arm cranking (localised muscular contractions) as opposed to walking where a larger muscle mass is required, a smaller effect may be observed. Based on this, it was estimated that 14 participants would be required for this complete two-treatment crossover design to detect a medium effect size (F=0.4) with a within-person correlation of 0.6, 80% power, and an α of 0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.

Statistical analysis

Linear mixed models will be used to determine differences in the primary and secondary outcome variables between the conditions. All models will adjust for potential covariates explaining residual outcome variances (age, body fat% gender, lesion level, completeness of lesion and pre-prandial outcome values). Statistical significance will be accepted as p<0.05. Cohens' d effect sizes will be calculated to describe the magnitude of differences between conditions [58]. Individuals' responses for CVD risk marker outcomes will also be compared between the conditions to determine the number of participants who respond to the experimental protocols.

Patient and Public Involvement

Patients and public were not involved with the development of the research question, outcome measures or study design, nor will they be involved with the conduct of the study.

The recruitment plan was informed based on feedback from patients and public. A summary of the study results will be provided to each of the study participants.

Ethics and dissemination

This study was approved on the 19th May 2017 by the Cambridge South NHS Research Ethics Committee (reference 17/EE/0076). Personal information about potential and enrolled participants will be stored in electronic format on password protected computers or in hard copy format in locked filing cabinets at the University of Bedfordshire. Only members of the research team will have access to this information. All personal information will be destroyed after a period of five years. Individuals will be referred to in anonymised fashion in any published data.

The findings of this research will be disseminated to lay, academic, practice, and policy-based audiences via presentation at conference proceedings; publication in a peer review journal; websites, newsletters, and social media; and summary reports to policy makers and clinical care partners. The final trial dataset will be made available as supplementary material when the findings of the study are published in a peer review journal. Any protocol modifications will be communicated to the Cambridge South NHS Research Ethics Committee, recorded in the study's ISRCTN clinical trials registry, and detailed in a journal publication of the study findings.

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Author contributions

DB and LC conceptualised the study.

TW, LC, VT, DD, CL, and DB contributed to the design of the study protocol.

TW drafted the manuscript.

TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and approved the final version.

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Conflicts of interest

None of the authors have declared any conflicts of interest.

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Figure captions

Figure 1 Study schedule.

Figure 2 Schematic of experimental protocol.

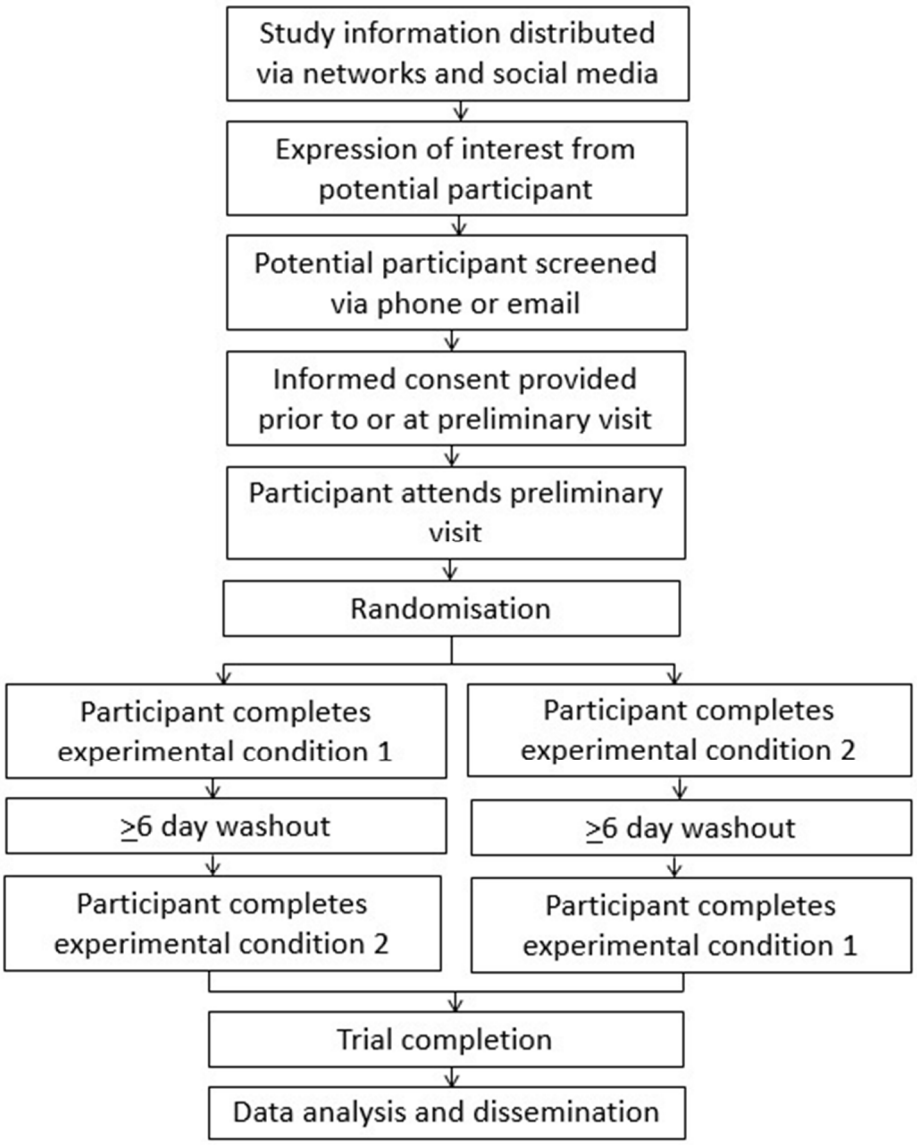

Figure 1 Study schedule.

43x56mm (300 x 300 DPI)

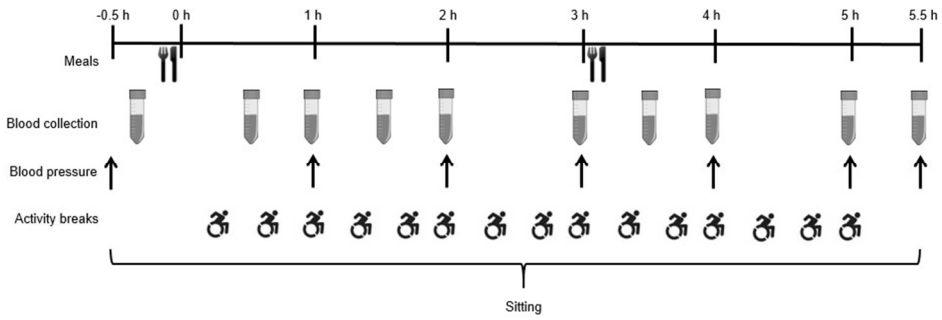

Figure 2 Schematic of experimental protocol.

85x30mm (300 x 300 DPI)

University of Bedfordshire Version 2 (14/03/2017) Participant Identification Number for this trial:___

CONSENT FORM

Title of Project: The Spinal Cord Injury Move More (SCIMM) study: The benefits of breaking up prolonged sedentary time on cardiovascular disease risk markers in people with spinal cord injury

Please initial box

1. I confirm that I have read and understand the information sheet dated [07/08/2017] (version 9) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my data collected during the study may be looked at by individuals from the University of Bedfordshire or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. In the event that the results from the DXA bone scan show that I have low bone mineral density I agree to being notified of this in a letter that will advise me to contact my GP for further investigation about the results. ☐
5. I agree to my GP being notified of my taking part in this study. ☐
6. I agree to take part in the above study. ☐

_____ _____ _____
Name of Participant Date Signature

_____ _____
Email Mobile

_____
GP Name

_____
GP Address

_____ _____ _____
Researcher Date Signature

Please return this form to: Thomas Withers, Institute for Sport and Physical Activity Research, University of Bedfordshire, Polhill Avenue, Bedford, MK41 9EA.

Email: thomas.withers@beds.ac.uk

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol

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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Public health
Keywords:	physical activity, sedentary lifestyle, activity breaks, glucose, cardiovascular disease, spinal cord injury

Cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia: the Spinal Cord Injury Move More (SCIMM) randomised crossover laboratory trial protocol

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Study start date: 19th May 2017
Study end date: 18th January 2019

Abstract

Introduction: Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD) and could partly explain the increased prevalence of CVD in people with spinal cord injury (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute CVD risk marker response to breaking up prolonged sedentary time in people with SCI has not been investigated. **Methods and analysis:** A randomised two-condition laboratory crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-intensity arm crank activity every 20 min, with 2) uninterrupted prolonged sedentary time (control) in people with SCI. Outcomes will include acute effects on postprandial glucose, insulin, lipids and blood pressure. Blood samples will be collected and blood pressure measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This study was approved by the Cambridge South NHS Research Ethics Committee. This research will help determine if breaking up prolonged sedentary time could be effective in lowering CVD risk in people with SCI. The findings of the research will be published in a peer review journal and disseminated to relevant user groups. **Trial registration:** The study is registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

Strengths and limitations of this study

- This study uses a randomised crossover design to investigate, for the first time, cardiovascular disease risk marker responses to breaking up prolonged sedentary time in individuals with paraplegia.
- Regular collection of blood samples will permit robust time course and incremental area under the curve calculations for primary and secondary outcomes.
- Due to the acute nature of the study, the long-term cardiovascular disease risk marker responses to a chronic intervention will remain unknown.

- The cardiovascular disease risk marker responses to breaking up prolonged sedentary time in people with tetraplegia still requires investigation.

Keywords: physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular disease; spinal cord injury

Introduction

There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading cause of death in individuals with SCI [3] and this population have a significantly increased risk of heart disease and stroke compared with able-bodied individuals [4]. Traditional risk factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low high-density lipoprotein cholesterol (HDL), and high blood pressure. These risk factors often exacerbate significantly as a consequence of SCI [5] and a plethora of research has documented impaired glucose tolerance and adverse lipid profiles in individuals with SCI [5, 6]. The clustering of ≥2 and ≥3 risk factors is prevalent in 87% and 72% of SCI individuals, respectively [7], which is markedly higher compared with the able-bodied population [8]. This milieu of metabolic disturbances after SCI may be due to increases in body fat resulting from an imbalance in energy intake and expenditure [5]. Excess fat accumulation, particularly in the visceral region, is associated with inflammation that is causal in glucose intolerance and dyslipidaemia [5, 9] thus promoting atherogenesis that would increase the risk of CVD in this population [10].

Postprandial glucose and lipid concentrations are strong independent predictors of future CVD incidence, even in those without diabetes [11]. There is a dose-response relationship between postprandial glucose area under the curve (AUC) and CVD risk, while progression of carotid atherosclerosis can be prevented by attenuation of postprandial glucose concentrations [12, 13]. Impaired postprandial glucose metabolism was observed in 50% and 62% of individuals with paraplegia and tetraplegia, respectively, compared with 18% in able-bodied individuals [6]. This impaired glucose intolerance in SCI is characterised by hyperinsulinaemia, which suggests that there is tissue level resistance to insulin [14]. In paraplegic individuals, there appears to be no difference in postprandial glucose responses between those with complete versus incomplete lesions [15, 16]. Although postprandial lipaemic responses have not been compared between individuals with complete and

incomplete lesions, fasting lipid levels do not differ between these groups [17]. There does, however, appear to be an exaggerated postprandial lipaemic response in individuals with paraplegia compared with able-bodied individuals [18]. These observations are of potential concern as the high dietary intake of carbohydrate and fat in individuals with SCI [19] may lead to repeated exaggerated elevations in glucose and lipids following food intake. It is thus pertinent to identify interventions to reduce postprandial glucose and lipid responses in individuals with SCI to reduce their CVD risk.

Physical activity guidelines have been developed specifically for this population that recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA) three times per week for CVD health benefits [20]. However, it is estimated that 37 to 50% of this population engage in no leisure-time physical activity whatsoever [21, 22]. Reduced levels of physical activity are proposed to largely account for the increased CVD risk in SCI with reduced levels of leisure-time physical activity associated with increased body fat, insulin resistance, and systolic blood pressure [22, 23]. However, sedentary behaviour (i.e. any waking behaviour in a sitting, reclining or lying posture with low energy expenditure [24]), is now recognised as being a significant CVD risk factor in the able-bodied population, independent of MVPA [25]. Experimental studies in able-bodied individuals have reported an acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity walking every 20 min [26-29]. However, no research has examined whether postprandial CVD risk marker responses are attenuated in response to breaking up prolonged sedentary time in individuals with SCI.

The primary aim of this study is therefore to compare the acute CVD risk marker responses in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted sedentary time. The CVD risk markers that will be studied include postprandial glucose (primary outcome), insulin and lipids, and systolic and diastolic blood pressure (secondary

outcomes) based on evidence that these markers predict CVD outcomes and are adversely affected by SCI. It is hypothesised that breaking up prolonged sedentary time will result in favourable CVD risk marker responses compared with uninterrupted sedentary time in individuals with paraplegia. This could identify a novel strategy for the prevention of CVD in SCI that would warrant further evaluation.

Methods and analysis

Study design

A randomised two-condition crossover design will be used in accordance with the SPIRIT statement [30]. The study is registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437). The study schedule can be seen in Figure 1. All research will take place at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary measures, participants will complete two experimental conditions in a randomised order. The conditions will be separated by ≥6 days to eliminate any potential carryover effects. Condition order will be randomised by a researcher independent from the study using computer generated random numbers (block randomisation with balanced block sizes).

Figure 1 about here.

Participants

Inclusion criteria: Males and females aged 18-60 years; chronic SCI (≥1 year since injury); individuals with a traumatic SCI below T5 (mid to low level paraplegia); individuals with a non-traumatic SCI (as defined by the International Spinal Cord Injury Data Sets for non-traumatic SCI [31]) that present with mid to low level paraplegia. Including only individuals with injuries below T5 will ensure sympathetic innervation to the major organs at the T5 level so that heart rate and catecholamine responses would be unaffected by injury [32] and thus minimise the potential that innervation variations could have on the study outcomes. Paraplegic individuals who have complete or incomplete lesions will be included based on

evidence that these groups do not differ with respect to postprandial glucose metabolism (primary outcome) [15, 16]. Individuals who express an interest in taking part in the study will be required to indicate their spinal cord lesion level and completeness of injury via a questionnaire and asked to provide the research team with a copy of medical records to confirm injury level and ASIA impairment scale classification prior to preliminary measures.

Exclusion criteria: individuals who regularly engage in >300 min/week of MVPA as such high levels of physical activity may offset the detrimental association of sedentary time with health outcomes [33]; history of severe cardiovascular complications; hypotension (resting blood pressure <90/60 mmHg); body mass index >45 kg/m^2; a history of autonomic dysreflexia; pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure, liver disease, major illness, or other health issues that may limit ability to perform the physical activity protocols.

Recruitment

Participants will be recruited through organisations and charities relevant to individuals with SCI, including the National Spinal Injuries Centre, Stoke Mandeville Hospital, Buckinghamshire NHS Healthcare Trust; local sport and activity clubs; and local community groups. Mail outs, social media, information on websites, posters, flyers, and visits from the research team will be used to provide information on the study to potentially eligible individuals who can then express their interest to the research team in taking part in the study. Written informed consent will be obtained by a member of the research team prior to participation in any testing protocols (see supplementary file). As an incentive, participants will receive a £25 shopping gift voucher for each main condition they complete and will have all travel expenses paid.

Preliminary measures

Participants will attend a preliminary testing session where they will have body mass measured using wheelchair double beam scales (300 series; Marsden, London, UK). They will also have body fat and lean tissue mass (and percent) determined for the whole body and regionally via whole-body scans using dual-energy x-ray absorptiometry (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [34-36]. During DXA measures, participants will be positioned as closely as possible to standard protocols and Velcro restraints will be fastened around the participants' knees and ankles to maintain correct position of the legs during scanning. Participants will be offered a wedge to be used as a pillow for comfort. Waist circumference will be measured using International Standards for Anthropometric Assessment (ISAK) guidelines [37, 38]. These measures will be taken in the standing position for participants who are able to maintain this posture and in a supine position for participants who are not able to stand [38]. Resting blood pressure will be measured on the left arm, while seated, three times after the participant has rested for 5 min with the lowest readings being recorded. Following this, participants will be familiarised with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [39]. They will then cycle using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour research [26, 40]. Participants will be asked to cycle at ~70 rpm during the test. The test will start at a low intensity (~20 Watts) and the participants will then indicate their RPE at 1 min intervals. The resistance will then be increased by 5-20 Watts based on the participants' RPE until an RPE of 13 has been achieved, at which point the test will be terminated. The test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of 13 during the test will be recorded for each participant and used for the physical activity breaks described in the respective main condition below. The use of the Borg 6-20 RPE scale has acceptable validity in individuals with SCI to determine physical activity intensity [41]. This method is also suggested as a practical approach for health care professionals

and scientists as oxygen consumption testing equipment is costly and not available in many rehabilitation centres and community settings [41].

Experimental protocol

Figure 2 shows the experimental protocol. Participants will be instructed to refrain from caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be provided with a food diary and digital weighing scales to record volume and timings of all food and liquids consumed in the 24 h period prior to the first experimental condition. Participants will be asked to replicate their diet the day prior to the subsequent experimental condition [42]. On condition days, participants will attend in the morning following an overnight fast and avoid active travel to the laboratory. Upon arrival, resting blood pressure will be measured after 5 min rest; two measures will be taken and the lowest of these recorded. A fasting capillary blood sample will then be collected. Participants will commence the 5.5 h condition period following consumption of a standardised breakfast. The two experimental conditions are as follows:

1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their wheelchair or a standard chair at a desk during this condition.
2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical activity.

Figure 2 about here.

The SED-ACT protocol was selected based on previous research that reported a significant reduction in 5 h postprandial glucose in response to breaking up prolonged sitting time with 2 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied

participants [28]. An RPE of 13 for the physical activity intensity was selected in line with previous research [26, 42] and the Borg 6-20 RPE scale may be used to assess and regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic SCI [41]. Moderate-intensity physical activity was selected as it is well-tolerated, can be performed safely, and is recommended for health risk reduction in individuals with SCI [20, 43].

Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during each condition. This will be standardised by asking participants to engage in the same activities during each of the two experimental conditions. Except during the activity bouts, participants will remain inactive and only leave their desk to void and consume standardised meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of the research team when moving to these locations so that they remain inactive. A researcher will be present to ensure compliance with the protocols throughout all conditions.

Meal and water consumption

Standardised meals will be consumed immediately prior to the start of each experimental condition and at 3 h, each providing 30% of estimated daily energy requirements for each participant [44]. Participants will be asked to consume each meal within a 15 min time period. The time taken to consume the meals will be recorded for the first condition and participants will be asked to replicate this time as closely as possible in the subsequent condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted crisps and apple (54% carbohydrate, 34% fat, 13% protein). The macronutrient composition of meals in the current study was selected as it is generally representative of UK guidelines for a balanced diet [45]. The glycaemic index for these breakfast and lunch meals is 43 and 72, respectively. Glycaemic index values for each food item were obtained from the International Tables of Glycaemic Index and Glycaemic Load Values 2008 [46] and meal

glycaemic index was calculated using weighted means of the glycaemic index values for the component foods [47]. Water will be available ad libitum during the first condition and this volume of intake will be provided at standardised regular intervals in the subsequent condition.

Blood collection and biochemistry

Finger prick blood samples will be collected into two EDTA-containing microvettes (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120, 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be collected. Blood glucose concentrations will be analysed immediately using the YSI 2300 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of blood from one microvette. Additional 30 μl volumes of whole blood will be aliquoted onto two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the measurement of triglyceride and HDL concentrations using the Reflotron Plus system (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood (~490 μL) will be centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK) and the plasma then stored at -80^{o}C. An enzyme-linked immunosorbent assay kit will be used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

Blood pressure

Blood pressure will be measured at baseline as described above followed by single readings taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

Study outcomes

Primary outcome: the primary outcome for the study is within-participant, between condition postprandial glucose net incremental area under the curve (iAUC) [11]. *Secondary outcomes:* these include within-participant, between condition mean systolic and diastolic blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit comparisons with previous studies. *Feasibility measures:* to assess feasibility of the trial, participant dropout, number of experimental sessions completed, fatigue at the beginning and end of each day rated on an 11-point (0 “not fatigued at all” to 10 “extremely fatigued”) Visual Analogue Scale (VAS), and the degree of difficulty in completing each experimental condition rated on an 11-point VAS (0 “not difficult at all” to 10 “extremely difficult”) will be recorded. Participants will also complete the Physical Activity Enjoyment Scale [48] at the end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [49] (“Enjoyment”) 20 min after the last activity bout in the SED-ACT condition. Participants will also report on the same scale how enjoyable they would find it to engage in this form of physical activity most days of the week in the coming month (“Expected enjoyment”). *Psychological outcomes:* correlates of sedentary behaviour will be measured immediately before and after each experimental condition to explore whether participants’ mood, affect, wellbeing, and social cognitions regarding their ability to overcome being sedentary may differ in response to the SED-ACT condition compared with the SED condition. These measures will be based on the COM-B framework [50] using standardised wording formats [51] that will include overcoming barriers (self-efficacy/perceived behavioural control), attitudes, intentions and action planning. The following questionnaires will be completed in this order: psychological wellbeing using the National Wellbeing Measurement [52]; the Warwick Edinburgh Mental Well-Being Scale [53]; current mood using the short Positive and Negative Affect Scale [54]; and an adapted version of the Schwarzer and Renner [55] Physical Exercise Self-Efficacy Scale to measure self-efficacy to avoid long periods of sedentary time. These measures will be taken at the end of each experimental condition (330 min) meaning that each questionnaire will be completed within 45 min following the last

bout of activity in the SED-ACT condition. This is an appropriate time frame based on evidence that mood and affect is enhanced for 3-4 hours following a single session of exercise [56]. Although between-participant variation in the time taken to complete each questionnaire is anticipated, within-participant variation is expected to be limited therefore permitting valid between-condition comparisons.

Sample size calculations

Sample size calculations were performed using GPower [57]. Previous research reported a 16% reduction (effect size, *F*=0.61) in 5 h postprandial glucose total AUC when breaking up prolonged sedentary time with 2 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied participants [28]. As this study will use arm cranking (localised muscular contractions) as opposed to walking where a larger muscle mass is required, a smaller effect may be observed. Based on this, it was estimated that 14 participants would be required for this complete two-treatment crossover design to detect a medium effect size (*F*=0.4) with a within-person correlation of 0.6, 80% power, and an α of 0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.

Statistical analysis

Linear mixed models will be used to determine differences in the primary and secondary outcome variables between the conditions. All models will adjust for potential covariates explaining residual outcome variances (age, body fat% gender, lesion level, completeness of lesion and pre-prandial outcome values). Statistical significance will be accepted as $p<0.05$. Cohens' d effect sizes will be calculated to describe the magnitude of differences between conditions [58]. Individuals' responses for CVD risk marker outcomes will also be compared between the conditions to determine the number of participants who respond to the experimental protocols.

Patient and Public Involvement

Patients and public were not involved with the development of the research question, outcome measures or study design, nor will they be involved with the conduct of the study. The recruitment plan was informed based on feedback from patients and public. A summary of the study results will be provided to each of the study participants.

Ethics and dissemination

This study was approved on the 19th May 2017 by the Cambridge South NHS Research Ethics Committee (reference 17/EE/0076). Personal information about potential and enrolled participants will be stored in electronic format on password protected computers or in hard copy format in locked filing cabinets at the University of Bedfordshire. Only members of the research team will have access to this information. All personal information will be destroyed after a period of five years. Individuals will be referred to in anonymised fashion in any published data.

The findings of this research will be disseminated to lay, academic, practice, and policy-based audiences via presentation at conference proceedings; publication in a peer review journal; websites, newsletters, and social media; and summary reports to policy makers and clinical care partners. The final trial dataset will be made available as supplementary material when the findings of the study are published in a peer review journal. Any protocol modifications will be communicated to the Cambridge South NHS Research Ethics Committee, recorded in the study's ISRCTN clinical trials registry, and detailed in a journal publication of the study findings.

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Author contributions

DB and LC conceptualised the study.

TW, LC, VT, DD, CL, and DB contributed to the design of the study protocol.

TW drafted the manuscript.

TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and approved the final version.

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Conflicts of interest

None of the authors have declared any conflicts of interest.

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Figure captions

Figure 1 Study schedule.

Figure 2 Schematic of experimental protocol.

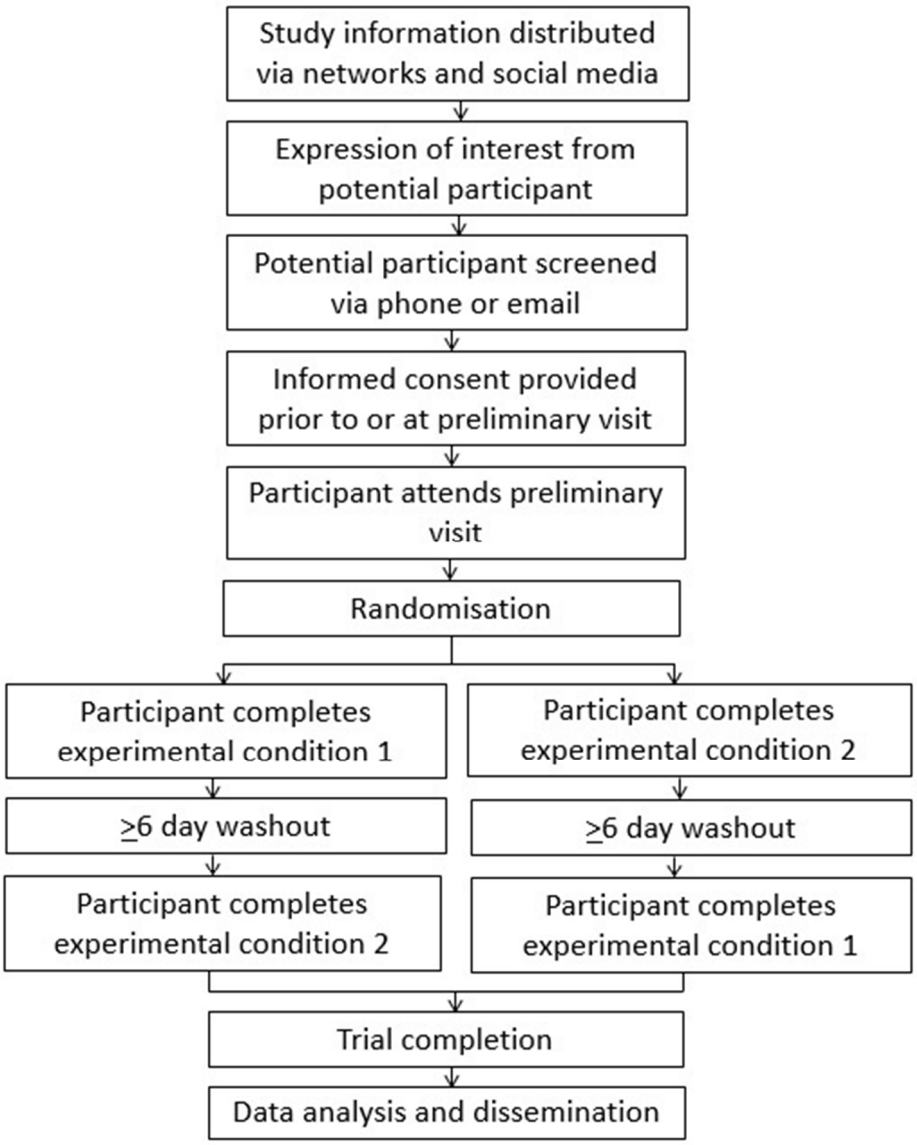

Figure 1 Study schedule.

43x56mm (300 x 300 DPI)

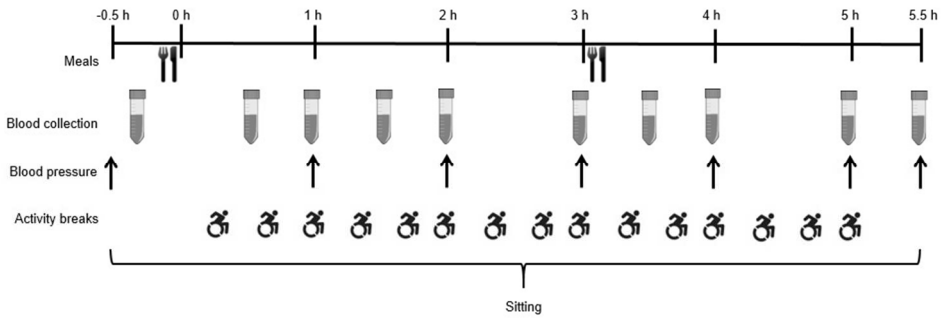

Figure 2 Schematic of experimental protocol.

85x30mm (300 x 300 DPI)

University of Bedfordshire Version 2 (14/03/2017) Participant Identification Number for this trial:___

CONSENT FORM

Title of Project: The Spinal Cord Injury Move More (SCIMM) study: The benefits of breaking up prolonged sedentary time on cardiovascular disease risk markers in people with spinal cord injury

Please initial box

1. I confirm that I have read and understand the information sheet dated [07/08/2017] (version 9) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my data collected during the study may be looked at by individuals from the University of Bedfordshire or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. In the event that the results from the DXA bone scan show that I have low bone mineral density I agree to being notified of this in a letter that will advise me to contact my GP for further investigation about the results. ☐
5. I agree to my GP being notified of my taking part in this study. ☐
6. I agree to take part in the above study. ☐

_____ _____ _____
Name of Participant Date Signature

_____ _____
Email Mobile

_____
GP Name

_____
GP Address

_____ _____ _____
Researcher Date Signature

Please return this form to: Thomas Withers, Institute for Sport and Physical Activity Research, University of Bedfordshire, Polhill Avenue, Bedford, MK41 9EA.

Email: thomas.withers@beds.ac.uk

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.