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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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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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1

1 **Abstract**

2 **Introduction:** Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD)

3 and could partly explain the increased prevalence of CVD in people with spinal cord injury

4 (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely

5 suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute

6 CVD risk marker response to breaking up prolonged sedentary time in people with SCI has

7 not been investigated. **Methods and analysis:** A randomised two-condition crossover trial

8 will compare: 1) breaking up prolonged sedentary time with 2 min moderate-intensity arm

9 crank activity every 20 min with 2) uninterrupted prolonged sedentary time (control) in people

10 with SCI. Outcomes will include acute effects on postprandial glucose, insulin, lipids and

11 blood pressure. Blood samples will be collected and blood pressure measured at regular

12 intervals during each 5.5 h condition. **Ethics and dissemination:** This study was approved

13 by the Cambridge South NHS Research Ethics Committee. The research will help determine

14 if breaking up prolonged sedentary time could be effective in lowering CVD risk in people

15 with SCI. The findings of the research will be published in a peer reviewed journal and

16 disseminated to relevant user groups. **Trial registration:** The study is registered as a clinical

17 trial on the ISRCTN register (trial ID: ISRCTN51868437).

18

19 **Strengths and limitations of this study**

20 • This is the first study to investigate cardiovascular disease risk marker responses to

21 breaking up prolonged sedentary time in individuals with paraplegia.

22 • This study adds to the limited literature on the acute cardiovascular disease risk

23 marker responses to intermittent physical activity in individuals with paraplegia.

24 • Due to the acute nature of the study, the long-term cardiovascular disease risk

25 marker responses to a chronic intervention will remain unknown.

26 • The cardiovascular disease risk marker responses to breaking up prolonged

27 sedentary time in people with tetraplegia still requires investigation.

3

30 **Introduction**

31 There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year

32 with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading

33 cause of death in individuals with SCI [3]. Traditional risk factors for CVD include impaired

34 glucose tolerance, central obesity, high triglycerides, low high-density lipoprotein cholesterol

35 (HDL), and high blood pressure. The clustering of ≥2 and ≥3 risk factors is prevalent in 87%

36 and 72% of SCI individuals, respectively [4], which is markedly higher compared with the

37 able-bodied population [5].

38

39 Postprandial glucose and lipid concentrations are strong independent predictors of future

40 CVD incidence, even in those without diabetes [6]. There is a dose-response relationship

41 between postprandial glucose area under the curve (AUC) and CVD risk, while progression

42 of carotid atherosclerosis can be prevented by control of postprandial glucose

43 concentrations [7, 8]. It is thus pertinent to identify interventions to reduce postprandial

44 glucose and lipid responses in individuals with SCI to reduce their CVD risk.

45

46 Physical activity guidelines have been developed specifically for this population that

47 recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA)

48 three times per week for CVD health benefits [9]. Reduced levels of physical activity are

49 proposed to largely account for the increased CVD risk in SCI [10]; it is estimated that 50%

50 of this population engage in no leisure-time physical activity whatsoever [11]. However,

51 sedentary behaviour (i.e. any waking behaviour in a sitting, reclining or lying posture with low

52 energy expenditure [12]), is now recognised as being a significant CVD risk factor in the

53 able-bodied population, independent of MVPA [13]. Experimental studies in able-bodied

54 individuals have reported an acute reduction in postprandial glucose, insulin, triglycerides

55 and blood pressure in response to breaking up prolonged sedentary time with 2 min bouts of

56 light or moderate-intensity walking every 20 min [14-17]. No research has examined whether

4

57 postprandial CVD risk marker responses are attenuated in response to breaking up

58 prolonged sedentary time in individuals with SCI.

59

60 The primary aim of this study is therefore to compare the acute CVD risk marker responses

61 in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted

62 sedentary time. It is hypothesised that breaking up prolonged sedentary time will result in

63 favourable CVD risk marker responses compared with uninterrupted sedentary time in

64 individuals with paraplegia.

65

66 **Methods and analysis**

67 *Study design*

68 A randomised two-condition crossover design will be used in accordance with the SPIRIT

69 statement [18]. The study is registered as a clinical trial on the ISRCTN register (trial ID:

70 ISRCTN51868437). The study schedule can be seen in Table 1. All research will take place

71 at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary

72 measures, participants will complete two experimental conditions in randomised order. The

73 conditions will be separated by ≥6 days to eliminate any potential carryover effects.

74 Condition order will be randomised by a researcher independent from the study using

75 computer generated random numbers (block randomisation with balanced block sizes).

76

77 Insert Table 1 about here.

78

79 *Participants*

80 *Inclusion criteria:* Males and females aged 18-60 years; chronic SCI (≥1 year since injury);

81 individuals with a traumatic SCI below Thoracic level 6 (mid to low level paraplegia);

82 individuals with a non-traumatic SCI (as defined within the International Spinal Cord Injury

83 Data Sets for non-traumatic SCI [19]) that present with mid to low level paraplegia.

84 Individuals who express an interest in taking part in the study will be required to indicate their

5

85 spinal cord lesion level and completeness of injury via a questionnaire prior to preliminary

86 measures. Participants will be encouraged to obtain relevant information from a medical

87 professional if they are unaware of their injury level.

88

89 *Exclusion criteria:* individuals who regularly engage in >300 min/week of MVPA; history of

90 severe cardiovascular complications; hypotension (resting blood pressure <90/60 mmHg);

91 body mass index >45 kg/m^2, a history of autonomic dysreflexia; pregnancy; taking glucose

92 lowering medication; smokers; diagnosed diabetes, renal failure, liver disease, major illness,

93 or other health issues that may limit ability to perform the physical activity protocols.

94

95 *Recruitment*

96 Participants will be recruited through organisations and charities that promote physical

97 activity, health and wellbeing for individuals with SCI; the National Spinal Injuries Centre,

98 Stoke Mandeville Hospital, Buckinghamshire NHS Healthcare Trust; and local sport and

99 activity clubs. Mail outs, social media, information on websites, posters, flyers, and visits

100 from the research team will be used to provide information on the study to potentially eligible

101 individuals who can then express their interest to the research team in taking part in the

102 study. Written informed consent will be obtained by a member of the research team prior to

103 participation in any testing protocols. As an incentive, participants will received a £25

104 shopping gift voucher for each main condition they complete and will have all travel

105 expenses paid.

106

107 *Preliminary measures*

108 Participants will attend a preliminary testing session where they will have body mass

109 measured using wheelchair double beam scales (300 series; Marsden, London, UK) and

110 body fat% measured using dual-energy x-ray absorptiometry (DXA; GE Medical Systems;

111 Chalfont St Giles, UK) in line with previous research [20]. During DXA measures,

6

112 participants will be positioned as closely as possible to standard protocols and Velcro

113 restraints will be fastened around the participant's knees and ankles to maintain correct

114 position of the legs during scanning. Participants will be offered a wedge to be used as a

115 pillow for comfort. Waist circumference will be measured using International Standards for

116 Anthropometric Assessment (ISAK) guidelines [21, 22]. These measures will be taken in the

117 standing position for participants who are able to maintain this posture and in a supine

118 position for participants who are not able to stand [23]. Resting blood pressure will be

119 measured on the left arm, while seated, three times after the participant has rested for 5 min

120 with the lowest readings being recorded. Following this, participants will be familiarised with

121 use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [24]. They will then cycle

122 using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power

123 output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour

124 research [14, 25]. Participants will be asked to cycle at ~70 rpm during the test. The test will

125 start at a low intensity (~20 Watts), which will gradually increase until an RPE of 13 has been

126 attained. The test is expected to take no longer than 15 min. The intensity that corresponds

127 to an RPE of 13 during the test will be recorded for each participant and used for the

128 physical activity breaks described in the respective main condition below. The use of the

129 Borg 6-20 RPE scale is highly reproducible in individuals with SCI to determine physical

130 activity intensity [26].

131

132 *Experimental protocol*

133 **Error! Reference source not found.** shows the experimental protocol. Participants will be

134 instructed to refrain from caffeine, alcohol and exercise for 48 h prior to each experimental

135 condition. They will also be provided with a food diary and digital weighing scales to record

136 volume and timings of all food and liquids consumed in the 24 h period prior to the first

137 experimental condition. Participants will be asked to replicate their diet the day prior to the

138 subsequent experimental condition [27]. On condition days, participants will attend in the

139 morning following an overnight fast and avoid active travel to the laboratory. Upon arrival,

7

140   resting blood pressure will be measured after 5 min rest; two measures will be taken and the

141   lowest of these recorded. A fasting capillary blood sample will then be collected. Participants

142   will commence the 5.5 h condition period following consumption of a standardised breakfast.

143   The two experimental conditions are as follows:

144

145   1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their

146   wheelchair or a standard chair at a desk during this condition.

147   2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will

148   complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using

149   the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical

150   activity.

151

152   Figure 1 about here.

153

154   An RPE of 13 for the physical activity intensity was selected in line with previous research

155   [14, 28] and the Borg 6-20 RPE scale may be used to assess and regulate upper-body

156   physical activity at moderate-to-vigorous intensity in adults with chronic SCI [26]. Moderate-

157   intensity physical activity was selected as it is well-tolerated, can be performed safely, and is

158   recommended for health risk reduction in individuals with SCI [9, 29].

159

160   Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during

161   each condition. Except during the activity bouts, participants will remain inactive and only

162   leave their desk to void and consume standardised meals in a kitchen adjacent to the test

163   laboratory; participants will be aided by a member of the research team when moving to

164   these locations so that they remain inactive. A researcher will be present to ensure

165   compliance with protocols throughout all conditions.

166

167   *Meal and water consumption*

8

168 Standardised meals will be consumed immediately prior to the start of each experimental

169 condition and at 3 h, each providing 30% of estimated daily energy requirements for each

170 participant [30]. Participants will be asked to consume each meal within a 15 min time

171 period. The time taken to consume the meals will be recorded for the first condition and

172 participants will be asked to replicate this time as closely as possible in the subsequent

173 condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice

174 (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted

175 crisps and apple (54% carbohydrate, 34% fat, 13% protein). This macronutrient composition

176 of meals was chosen as it is generally representative of UK guidelines for a balanced diet

177 [31]. The glycaemic index for these breakfast and lunch meals is 43 and 72, respectively.

178 Glycaemic index values for each food item were obtained from the International Tables of

179 Glycaemic Index and Glycaemic Load Values 2008 [32] and meal glycaemic index was

180 calculated using weighted means of the glycaemic index values for the component foods

181 [33]. Water will be available ad libitum during the first condition and this volume of intake will

182 be provided at standardised regular intervals in the subsequent condition.

183

184 *Blood collection and biochemistry*

185 Finger prick blood samples will be collected into two EDTA-containing microvettes

186 (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120,

187 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity

188 bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be

189 collected. Blood glucose concentrations will be analysed immediately using the YSI 2300

190 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of

191 blood from one microvette. Additional 30 μl volumes of whole blood will be aliquoted onto

192 two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the

193 measurement of triglyceride and HDL concentrations using the Reflotron Plus system

194 (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood ($\sim$490 μL) will be

9

195 centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK)

196 and the plasma then stored at -80°C. An enzyme-linked immunosorbent assay kit will be

197 used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

198

199 *Blood pressure*

200 Blood pressure will be measured at baseline as described above followed by single readings

201 taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly

202 activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory

203 blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

204

205 *Study outcomes*

206 *Primary outcome:* the primary outcome for the study is within-participant, between condition

207 postprandial glucose net incremental area under the curve (iAUC) [6]. *Secondary outcomes:*

208 these include within-participant, between condition mean systolic and diastolic blood

209 pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC and

210 total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit

211 comparisons across previous studies. *Feasibility measures:* to assess feasibility of the trial,

212 participant dropout, number of experimental sessions completed, fatigue at the beginning

213 and end of each day rated on an 11 point (0-10) Visual Analogue Scale (VAS), and the

214 degree of difficulty in completing the experimental conditions rated on an 11 point (0-10)

215 VAS will be recorded. Participants will also complete the Physical Activity Enjoyment Scale

216 [34] at the end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [35]

217 ("Enjoyment") 20 min after the last activity bout in the SED-ACT condition. Participants will

218 also report on the same scale how enjoyable they would find it to engage in this form of

219 physical activity most days of the week in the coming month ("Expected enjoyment").

220 *Psychological outcomes:* determinants of sedentary behaviour will be measured based on

221 the COM-B [36] and the theory of planned behaviour using standardised wording formats

222 [37] that will include overcoming barriers (self-efficacy/perceived behavioural control),

10

223 attitudes, intentions and action planning. The following questionnaires will be completed by

224 participants at baseline and at the end of each experimental condition: sedentary behaviour

225 self-efficacy using an adapted version of the Schwarzer et al. [38] Physical Exercise Self-

226 Efficacy Scale; current mood using the short Positive and Negative Affect Scale [39];

227 psychological wellbeing using the National Wellbeing Measurement [40]; and the Warwick

228 Edinburgh Mental Well-Being Scale [41].

229

230 *Sample size calculations*

231 Sample size calculations were performed using GPower [42]. Previous research reported a

232 16% reduction (effect size, F=0.61) in 5 h postprandial glucose total AUC when breaking up

233 prolonged sedentary time with 2 min light-intensity walking every 20 min versus

234 uninterrupted sitting in able-bodied participants [16]. As this study will use arm cranking

235 (localised muscular contractions) as opposed to walking where a larger muscle mass is

236 required, a smaller effect may be observed. Based on this, it was estimated that 14

237 participants would be required for this complete two-treatment crossover design to detect a

238 smaller minimum intervention effect of 10% with a within-person correlation of 0.6, 80%

239 power, and an α of 0.05. To allow for potential withdrawals, a total of 20 participants will be

240 recruited.

241

242 *Statistical analysis*

243 Linear mixed models will be used to determine differences in the primary and secondary

244 outcome variables between the conditions. All models will adjust for potential covariates

245 explaining residual outcome variances. Statistical significance will be accepted as $p<0.05$.

246 Cohens' d effect sizes will be calculated to describe the magnitude of differences between

247 conditions [43].

248

11

249 **Ethics and dissemination**

250 This study was approved on the 19th May 2017 by the Cambridge South NHS Research

251 Ethics Committee (reference 17/EE/0076).

252

253 The findings of this research will be disseminated to lay, academic, practice, and policy-

254 based audiences via presentation at conference proceedings; publication in a peer review

255 journal; websites, newsletters, and social media; and summary reports to policy makers and

256 clinical care partners.

257

260

261 **Author contributions**

262 DB and LC conceptualised the study.

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

264 TW drafted the manuscript.

265 TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and

266 approved the final version.

267

270

271 **Conflicts of interest**

272 None of the authors have declared any conflicts of interest.

273

274

275   **References**

276   1.   Lee, BB, Cripps, RA, Fitzharris, M, et al. The global map for traumatic spinal cord
277   injury epidemiology: update 2011, global incidence rate. Spinal Cord, 2014. 52(2):
278   110-6.

279   2.   British Society of Rehabilitation Medicine. Chronic spinal cord injury: management of
280   patients in acute hospital settings: National Guidelines. Available at
281   http://www.bsrm.org.uk/downloads/sciwebversion.pdf (accessed 26 April 2016).
282   2008.

283   3.   Garshick, E, Kelley, A, Cohen, SA, et al. A prospective assessment of mortality in
284   chronic spinal cord injury. Spinal Cord, 2005. 43(7): 408-16.

285   4.   Wahman, K, Nash, MS, Westgren, N, et al. Cardiovascular disease risk factors in
286   persons with paraplegia: the Stockholm spinal cord injury study. J Rehabil Med,
287   2010. 42(3): 272-8.

288   5.   Ford, ES, Giles, WH, and Dietz, WH. Prevalence of the metabolic syndrome among
289   US adults: findings from the third National Health and Nutrition Examination Survey.
290   Jama, 2002. 287(3): 356-359.

291   6.   O'Keefe, JH and Bell, DS. Postprandial hyperglycemia/hyperlipidemia (postprandial
292   dysmetabolism) is a cardiovascular risk factor. Am J Cardiol, 2007. 100(5): 899-904.

293   7.   Esposito, K, Giugliano, D, Nappo, F, et al. Regression of carotid atherosclerosis by
294   control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation, 2004.
295   110(2): 214-9.

296   8.   Smith, NL, Barzilay, JI, Shaffer, D, et al. Fasting and 2-hour postchallenge serum
297   glucose measures and risk of incident cardiovascular events in the elderly: the
298   Cardiovascular Health Study. Archives of internal medicine, 2002. 162(2): 209-216.

299   9.   Martin Ginis, KA, van der Scheer, JW, Latimer-Cheung, AE, et al. Evidence-based
300   scientific exercise guidelines for adults with spinal cord injury: an update and a new
301   guideline. 2017.

302   10.   Ginis, KA, Hicks, AL, Latimer, AE, et al. The development of evidence-informed
303   physical activity guidelines for adults with spinal cord injury. Spinal Cord, 2011.
304   49(11): 1088-96.

305   11.   Ginis, KA, Arbour-Nicitopoulos, KP, Latimer, AE, et al. Leisure time physical activity
306   in a population-based sample of people with spinal cord injury part II: activity types,
307   intensities, and durations. Arch Phys Med Rehabil, 2010. 91(5): 729-33.

308   12.   Tremblay, MS, Aubert, S, Barnes, JD, et al. Sedentary Behavior Research Network
309   (SBRN) - Terminology Consensus Project process and outcome. Int J Behav Nutr
310   Phys Act, 2017. 14(1): 75.

13

311 13. Dunstan, DW, Thorp, AA, and Healy, GN. Prolonged sitting: is it a distinct coronary
312   heart disease risk factor? Curr Opin Cardiol, 2011. 26(5): 412-9.

313 14. Dunstan, DW, Kingwell, BA, Larsen, R, et al. Breaking up prolonged sitting reduces
314   postprandial glucose and insulin responses. Diabetes Care, 2012. 35(5): 976-83.

315 15. Miyashita, M, Edamoto, K, Kidokoro, T, et al. Interrupting Sitting Time with Regular
316   Walks Attenuates Postprandial Triglycerides. Int J Sports Med, 2016. 37(2): 97-103.

317 16. Bailey, DP and Locke, CD. Breaking up prolonged sitting with light-intensity walking
318   improves postprandial glycemia, but breaking up sitting with standing does not. J Sci
319   Med Sport, 2015. 18(3): 294-8.

320 17. Larsen, RN, Kingwell, BA, Sethi, P, et al. Breaking up prolonged sitting reduces
321   resting blood pressure in overweight/obese adults. Nutr Metab Cardiovasc Dis, 2014.
322   24(9): 976-82.

323 18. Chan, A-W, Tetzlaff, JM, Altman, DG, et al. SPIRIT 2013 statement: defining
324   standard protocol items for clinical trials. Annals of internal medicine, 2013. 158(3):
325   200-207.

326 19. New, PW and Marshall, R. International Spinal Cord Injury Data Sets for non-
327   traumatic spinal cord injury. Spinal Cord, 2014. 52(2): 123-32.

328 20. Keil, M, Totosy de Zepetnek, JO, Brooke-Wavell, K, et al. Measurement precision of
329   body composition variables in elite wheelchair athletes, using dual-energy X-ray
330   absorptiometry. European journal of sport science, 2016. 16(1): 65-71.

331 21. Marfell-Jones, MJ, Stewart, AD, and De Ridder, JH. International standards for
332   anthropometric assessment. 2012.

333 22. Willems, A, Paulson, TA, Keil, M, et al. Dual-Energy X-Ray Absorptiometry, Skinfold
334   Thickness, and Waist Circumference for Assessing Body Composition in Ambulant
335   and Non-Ambulant Wheelchair Games Players. Front Physiol, 2015. 6: 356.

336 23. Willems, A, Paulson, TAW, Keil, M, et al. Dual-energy X-ray absorptiometry, skinfold
337   thickness, and waist circumference for assessing body composition in ambulant and
338   non-ambulant wheelchair games players. Frontiers in physiology, 2015. 6.

339 24. Borg, GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc, 1982.
340   14(5): 377-81.

341 25. Bailey, DP, Maylor, BD, Orton, CJ, et al. Effects of breaking up prolonged sitting
342   following low and high glycaemic index breakfast consumption on glucose and insulin
343   concentrations. Eur J Appl Physiol, 2017.

344 26. van der Scheer, JW, Hutchinson, M, Paulson, T, et al. Reliability and validity of
345   subjective measures of aerobic intensity in adults with spinal cord injury: a systematic
346   review. PM&R, 2017.

14

347   27.   Bailey, DP, Broom, DR, Chrismas, BC, et al. Breaking up prolonged sitting time with
348   walking does not affect appetite or gut hormone concentrations but does induce an
349   energy deficit and suppresses postprandial glycaemia in sedentary adults. Appl
350   Physiol Nutr Metab, 2016. 41: 1-8.

351   28.   Bailey, DP, Broom, DR, Chrismas, BC, et al. Breaking up prolonged sitting time with
352   walking does not affect appetite or gut hormone concentrations but does induce an
353   energy deficit and suppresses postprandial glycaemia in sedentary adults. Appl
354   Physiol Nutr Metab, 2016. 41(3): 324-31.

355   29.   Burr, JF, Shephard, RJ, and Zehr, EP. Physical activity after stroke and spinal cord
356   injury: evidence-based recommendations on clearance for physical activity and
357   exercise. Can Fam Physician, 2012. 58(11): 1236-9.

358   30.   Schofield, WN. Predicting basal metabolic rate, new standards and review of
359   previous work. Hum Nutr Clin Nutr, 1985. 39 Suppl 1: 5-41.

360   31.   Food Standards Agency. FSA nutrient and food based guidelines for UK institutions.
361   Available at:
362   http://www.food.gov.uk/sites/default/files/multimedia/pdfs/nutrientinstitution.pdf
363   (accessed 18 Jan 2016). 2007.

364   32.   Atkinson, FS, Foster-Powell, K, and Brand-Miller, JC. International tables of glycemic
365   index and glycemic load values: 2008. Diabetes Care, 2008. 31(12): 2281-3.

366   33.   Wolever, TM and Jenkins, DJ. The use of the glycemic index in predicting the blood
367   glucose response to mixed meals. Am J Clin Nutr, 1986. 43(1): 167-72.

368   34.   Kendzierski, D and DeCarlo, K. Physical activity enjoyment scale: two validation
369   studies. J Sport Ex Psych, 1991. 13: 50-64.

370   35.   Svensson, E. Comparison of the Quality of Assessments Using Continuous and
371   Discrete Ordinal Rating Scales. Biom J, 2000. 42(4): 417-434.

372   36.   Michie, S, Ashford, S, Sniehotta, FF, et al. A refined taxonomy of behaviour change
373   techniques to help people change their physical activity and healthy eating
374   behaviours: the CALO-RE taxonomy. Psychol Health, 2011. 26(11): 1479-98.

375   37.   Francis, J, Eccles, MP, Johnston, M, et al. Constructing questionnaires based on the
376   theory of planned behaviour: A manual for health services researchers. Newcastle
377   upon Tyne, UK: Centre for Health Services Research, University of Newcastle upon
378   Tyne. 2004.

379   38.   Schwarzer, R and Renner, B. Social-cognitive predictors of health behavior: action
380   self-efficacy and coping self-efficacy. Health Psychol, 2000. 19(5): 487-95.

381   39.   Thompson, ER. Development and Validation of an Internationally Reliable Short-
382   Form of the Positive and Negative Affect Schedule (PANAS). Journal of Cross-
383   Cultural Psychology, 2007. 38(2): 227-242.

15

384   40.   Tinkler, L. Measuring National Well-being: Personal Well-being in the UK, 2014 to

385   2015. 2015; Available from:

386   https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/bulletins/measurin

387   gnationalwellbeing/2015-09-23.

388   41.   Tennant, R, Hiller, L, Fishwick, R, et al. The Warwick-Edinburgh Mental Well-being

389   Scale (WEMWBS): development and UK validation. Health and Quality of Life

390   Outcomes, 2007. 5(1): 63.

391   42.   Faul, F, Erdfelder, E, Lang, AG, et al. G*Power 3: a flexible statistical power analysis

392   program for the social, behavioral, and biomedical sciences. Behav Res Methods,

393   2007. 39(2): 175-91.

394   43.   Cohen, J. Statistical power analysis for the behavioral sciences. 2nd ed. 1988,

395   Hillsdale, NJ: Erlbaum.

396

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.

18

Figure 1

259x96mm (96 x 96 DPI)

SPIRIT ☑

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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_____

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Introduction

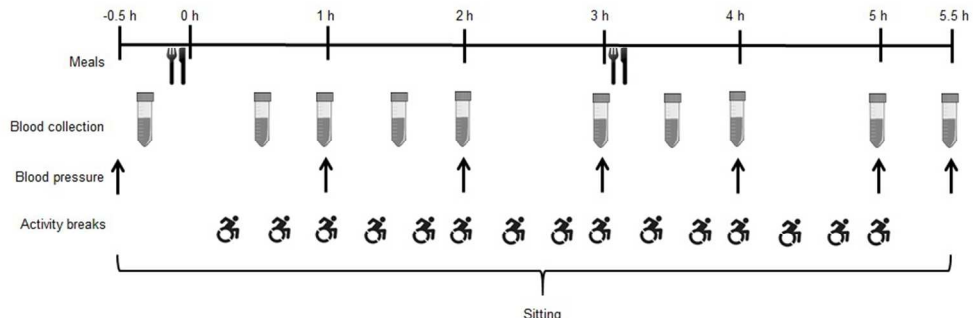|			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____4-5_____
	6b	Explanation for choice of comparators	_____NA_____
Objectives	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_____

2

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_____	

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3   Data management   19   Plans for data entry, coding, security, and storage, including any related processes to promote data quality   _____11_____
4   (eg, double data entry; range checks for data values). Reference to where details of data management
5   procedures can be found, if not in the protocol
6
7   Statistical methods   20a   Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the   _____11_____
8   statistical analysis plan can be found, if not in the protocol
9
10   20b   Methods for any additional analyses (eg, subgroup and adjusted analyses)   _____NA_____
11
12   20c   Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any
13   statistical methods to handle missing data (eg, multiple imputation)   _____NA_____
14
15   **Methods: Monitoring**
16
17   Data monitoring   21a   Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of   _____NA_____
18   whether it is independent from the sponsor and competing interests; and reference to where further details
19   about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not
20   needed
21
22
23   21b   Description of any interim analyses and stopping guidelines, including who will have access to these interim   _____NA_____
24   results and make the final decision to terminate the trial
25
26   Harms   22   Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse   _____NA_____
27   events and other unintended effects of trial interventions or trial conduct
28
29   Auditing   23   Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent   _____NA_____
30   from investigators and the sponsor
31
32   **Ethics and dissemination**
33
34   Research ethics   24   Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   _____12_____
35   approval
36
37   Protocol   25   Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes,   _____5_____
38   amendments   analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
39   regulators)
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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.

5

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

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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Word count: 3531

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

1

1 **Abstract**

2 **Introduction:** Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD)

3 and could partly explain the increased prevalence of CVD in people with spinal cord injury

4 (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely

5 suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute

6 CVD risk marker response to breaking up prolonged sedentary time in people with SCI has

7 not been investigated. **Methods and analysis:** A randomised two-condition laboratory

8 crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-

9 intensity arm crank activity every 20 min, with 2) uninterrupted prolonged sedentary time

10 (control) in people with SCI. Outcomes will include acute effects on postprandial glucose,

11 insulin, lipids and blood pressure. Blood samples will be collected and blood pressure

12 measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This

13 study was approved by the Cambridge South NHS Research Ethics Committee. This

14 research will help determine if breaking up prolonged sedentary time could be effective in

15 lowering CVD risk in people with SCI. The findings of the research will be published in a peer

16 review journal and disseminated to relevant user groups. **Trial registration:** The study is

17 registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

18

Strengths and limitations of this study

20 - This study uses a randomised crossover design to investigate, for the first time,

21 cardiovascular disease risk marker responses to breaking up prolonged sedentary

22 time in individuals with paraplegia.

23 - Regular collection of blood samples will permit robust time course and incremental

24 area under the curve calculations for primary and secondary outcomes.

25 - Due to the acute nature of the study, the long-term cardiovascular disease risk

26 marker responses to a chronic intervention will remain unknown.

2

27 • The cardiovascular disease risk marker responses to breaking up prolonged

28   sedentary time in people with tetraplegia still requires investigation.

29

30 **Keywords:** physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular

31 disease; spinal cord injury

Introduction

33 There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year

34 with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading

35 cause of death in individuals with SCI [3] and this population have a significantly increased

36 risk of heart disease and stroke compared with able-bodied individuals [4]. Traditional risk

37 factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low

38 high-density lipoprotein cholesterol (HDL), and high blood pressure. These risk factors often

39 exacerbate significantly as a consequence of SCI [5] and a plethora of research has

40 documented impaired glucose tolerance and adverse lipid profiles in individuals with SCI [5,

41 6]. The clustering of ≥2 and ≥3 risk factors is prevalent in 87% and 72% of SCI individuals,

42 respectively [7], which is markedly higher compared with the able-bodied population [8]. This

43 milieu of metabolic disturbances after SCI may be due to increases in body fat resulting from

44 an imbalance in energy intake and expenditure [5]. Excess fat accumulation, particularly in

45 the visceral region, is associated with inflammation that is causal in glucose intolerance and

46 dyslipidaemia [5, 9] thus promoting atherogenesis that would increase the risk of CVD in this

47 population [10].

48

49 Postprandial glucose and lipid concentrations are strong independent predictors of future

50 CVD incidence, even in those without diabetes [11]. There is a dose-response relationship

51 between postprandial glucose area under the curve (AUC) and CVD risk, while progression

52 of carotid atherosclerosis can be prevented by attenuation of postprandial glucose

53 concentrations [12, 13]. Impaired postprandial glucose metabolism was observed in 50%

54 and 62% of individuals with paraplegia and tetraplegia, respectively, compared with 18% in

55 able-bodied individuals [6]. This impaired glucose intolerance in SCI is characterised by

56 hyperinsulinaemia, which suggests that there is tissue level resistance to insulin [14]. In

57 paraplegic individuals, there appears to be no difference in postprandial glucose responses

58 between those with complete versus incomplete lesions [15, 16]. Although postprandial

59 lipaemic responses have not been compared between individuals with complete and

4

60 incomplete lesions, fasting lipid levels do not differ between these groups [17]. There does,

61 however, appear to be an exaggerated postprandial lipaemic response in individuals with

62 paraplegia compared with able-bodied individuals [18]. These observations are of potential

63 concern as the high dietary intake of carbohydrate and fat in individuals with SCI [19] may

64 lead to repeated exaggerated elevations in glucose and lipids following food intake. It is thus

65 pertinent to identify interventions to reduce postprandial glucose and lipid responses in

66 individuals with SCI to reduce their CVD risk.

67

68 Physical activity guidelines have been developed specifically for this population that

69 recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA)

70 three times per week for CVD health benefits [20]. However, it is estimated that 37 to 50% of

71 this population engage in no leisure-time physical activity whatsoever [21, 22]. Reduced

72 levels of physical activity are proposed to largely account for the increased CVD risk in SCI

73 with reduced levels of leisure-time physical activity associated with increased body fat,

74 insulin resistance, and systolic blood pressure [22, 23]. However, sedentary behaviour (i.e.

75 any waking behaviour in a sitting, reclining or lying posture with low energy expenditure

76 [24]), is now recognised as being a significant CVD risk factor in the able-bodied population,

77 independent of MVPA [25]. Experimental studies in able-bodied individuals have reported an

78 acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response

79 to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity

80 walking every 20 min [26-29]. However, no research has examined whether postprandial

81 CVD risk marker responses are attenuated in response to breaking up prolonged sedentary

82 time in individuals with SCI.

83

84 The primary aim of this study is therefore to compare the acute CVD risk marker responses

85 in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted

86 sedentary time. The CVD risk markers that will be studied include postprandial glucose

87 (primary outcome), insulin and lipids, and systolic and diastolic blood pressure (secondary

5

88   outcomes) based on evidence that these markers predict CVD outcomes and are adversely

89   affected by SCI. It is hypothesised that breaking up prolonged sedentary time will result in

90   favourable CVD risk marker responses compared with uninterrupted sedentary time in

91   individuals with paraplegia. This could identify a novel strategy for the prevention of CVD in

92   SCI that would warrant further evaluation.

93

94   **Methods and analysis**

95   *Study design*

96   A randomised two-condition crossover design will be used in accordance with the SPIRIT

97   statement [30]. The study is registered as a clinical trial on the ISRCTN register (trial ID:

98   ISRCTN51868437). The study schedule can be seen in Figure 1. All research will take place

99   at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary

100   measures, participants will complete two experimental conditions in a randomised order. The

101   conditions will be separated by ≥6 days to eliminate any potential carryover effects.

102   Condition order will be randomised by a researcher independent from the study using

103   computer generated random numbers (block randomisation with balanced block sizes).

104

105   Figure 1 about here.

106

107   *Participants*

108   *Inclusion criteria:* Males and females aged 18-60 years; chronic SCI (≥1 year since injury);

109   individuals with a traumatic SCI below T5 (mid to low level paraplegia); individuals with a

110   non-traumatic SCI (as defined by the International Spinal Cord Injury Data Sets for non-

111   traumatic SCI [31]) that present with mid to low level paraplegia. Including only individuals

112   with injuries below T5 will ensure sympathetic innervation to the major organs at the T5 level

113   so that heart rate and catecholamine responses would be unaffected by injury [32] and thus

114   minimise the potential that innervation variations could have on the study outcomes.

115   Paraplegic individuals who have complete or incomplete lesions will be included based on

6

116 evidence that these groups do not differ with respect to postprandial glucose metabolism

117 (primary outcome) [15, 16]. Individuals who express an interest in taking part in the study will

118 be required to indicate their spinal cord lesion level and completeness of injury via a

119 questionnaire and asked to provide the research team with a copy of medical records to

120 confirm injury level and ASIA impairment scale classification prior to preliminary measures.

121

122 *Exclusion criteria:* individuals who regularly engage in >300 min/week of MVPA as such high

123 levels of physical activity may offset the detrimental association of sedentary time with health

124 outcomes [33]; history of severe cardiovascular complications; hypotension (resting blood

125 pressure <90/60 mmHg); body mass index >45 kg/m^2; a history of autonomic dysreflexia;

126 pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure,

127 liver disease, major illness, or other health issues that may limit ability to perform the

128 physical activity protocols.

129

130 *Recruitment*

131 Participants will be recruited through organisations and charities relevant to individuals with

132 SCI, including the National Spinal Injuries Centre, Stoke Mandeville Hospital,

133 Buckinghamshire NHS Healthcare Trust; local sport and activity clubs; and local community

134 groups. Mail outs, social media, information on websites, posters, flyers, and visits from the

135 research team will be used to provide information on the study to potentially eligible

136 individuals who can then express their interest to the research team in taking part in the

137 study. Written informed consent will be obtained by a member of the research team prior to

138 participation in any testing protocols (see supplementary file). As an incentive, participants

139 will receive a £25 shopping gift voucher for each main condition they complete and will have

140 all travel expenses paid.

141

142 *Preliminary measures*

7

143 Participants will attend a preliminary testing session where they will have body mass

144 measured using wheelchair double beam scales (300 series; Marsden, London, UK).

145 They will also have body fat and lean tissue mass (and percent) determined for the

146 whole body and regionally via whole-body scans using dual-energy x-ray absorptiometry

147 (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [34-36].

148 During DXA measures, participants will be positioned as closely as possible to standard

149 protocols and Velcro restraints will be fastened around the participants' knees and ankles to

150 maintain correct position of the legs during scanning. Participants will be offered a wedge to

151 be used as a pillow for comfort. Waist circumference will be measured using International

152 Standards for Anthropometric Assessment (ISAK) guidelines [37, 38]. These measures will

153 be taken in the standing position for participants who are able to maintain this posture and in

154 a supine position for participants who are not able to stand [38]. Resting blood pressure will

155 be measured on the left arm, while seated, three times after the participant has rested for 5

156 min with the lowest readings being recorded. Following this, participants will be familiarised

157 with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [39]. They will then cycle

158 using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power

159 output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour

160 research [26, 40]. Participants will be asked to cycle at ~70 rpm during the test. The test will

161 start at a low intensity (~20 Watts) and the participants will then indicate their RPE at 1 min

162 intervals. The resistance will then be increased by 5-20 Watts based on the participants'

163 RPE until an RPE of 13 has been achieved, at which point the test will be terminated. The

164 test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of

165 13 during the test will be recorded for each participant and used for the physical activity

166 breaks described in the respective main condition below. The use of the Borg 6-20 RPE

167 scale has acceptable validity in individuals with SCI to determine physical activity intensity

168 [41]. This method is also suggested as a practical approach for health care professionals

8

169 and scientists as oxygen consumption testing equipment is costly and not available in many

170 rehabilitation centres and community settings [41].

171

172 *Experimental protocol*

173 Figure 2 shows the experimental protocol. Participants will be instructed to refrain from

174 caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be

175 provided with a food diary and digital weighing scales to record volume and timings of all

176 food and liquids consumed in the 24 h period prior to the first experimental condition.

177 Participants will be asked to replicate their diet the day prior to the subsequent experimental

178 condition [42]. On condition days, participants will attend in the morning following an

179 overnight fast and avoid active travel to the laboratory. Upon arrival, resting blood pressure

180 will be measured after 5 min rest; two measures will be taken and the lowest of these

181 recorded. A fasting capillary blood sample will then be collected. Participants will commence

182 the 5.5 h condition period following consumption of a standardised breakfast. The two

183 experimental conditions are as follows:

184

185 1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their

186   wheelchair or a standard chair at a desk during this condition.

187 2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will

188   complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using

189   the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical

190   activity.

191

192 Figure 2 about here.

193

194 The SED-ACT protocol was selected based on previous research that reported a significant

195 reduction in 5 h postprandial glucose in response to breaking up prolonged sitting time with 2

196 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied

9

197 participants [28]. An RPE of 13 for the physical activity intensity was selected in line with

198 previous research [26, 42] and the Borg 6-20 RPE scale may be used to assess and

199 regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic

200 SCI [41]. Moderate-intensity physical activity was selected as it is well-tolerated, can be

201 performed safely, and is recommended for health risk reduction in individuals with SCI [20,

202 43].

203

204 Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during

205 each condition. This will be standardised by asking participants to engage in the same

206 activities during each of the two experimental conditions. Except during the activity bouts,

207 participants will remain inactive and only leave their desk to void and consume standardised

208 meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of

209 the research team when moving to these locations so that they remain inactive. A researcher

210 will be present to ensure compliance with the protocols throughout all conditions.

211

212 *Meal and water consumption*

213 Standardised meals will be consumed immediately prior to the start of each experimental

214 condition and at 3 h, each providing 30% of estimated daily energy requirements for each

215 participant [44]. Participants will be asked to consume each meal within a 15 min time

216 period. The time taken to consume the meals will be recorded for the first condition and

217 participants will be asked to replicate this time as closely as possible in the subsequent

218 condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice

219 (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted

220 crisps and apple (54% carbohydrate, 34% fat, 13% protein). The macronutrient composition

221 of meals in the current study was selected as it is generally representative of UK guidelines

222 for a balanced diet [45]. The glycaemic index for these breakfast and lunch meals is 43 and

223 72, respectively. Glycaemic index values for each food item were obtained from the

224 International Tables of Glycaemic Index and Glycaemic Load Values 2008 [46] and meal

10

225 glycaemic index was calculated using weighted means of the glycaemic index values for the

226 component foods [47]. Water will be available ad libitum during the first condition and this

227 volume of intake will be provided at standardised regular intervals in the subsequent

228 condition.

229

230 *Blood collection and biochemistry*

231 Finger prick blood samples will be collected into two EDTA-containing microvettes

232 (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120,

233 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity

234 bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be

235 collected. Blood glucose concentrations will be analysed immediately using the YSI 2300

236 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of

237 blood from one microvette. Additional 30 μl volumes of whole blood will be aliquoted onto

238 two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the

239 measurement of triglyceride and HDL concentrations using the Reflotron Plus system

240 (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood ($\sim$490 μL) will be

241 centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK)

242 and the plasma then stored at -80°C. An enzyme-linked immunosorbent assay kit will be

243 used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

244

245 *Blood pressure*

246 Blood pressure will be measured at baseline as described above followed by single readings

247 taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly

248 activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory

249 blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

250

251 *Study outcomes*

11

252 *Primary outcome:* the primary outcome for the study is within-participant, between condition

253 postprandial glucose net incremental area under the curve (iAUC) [11]. *Secondary*

254 *outcomes:* these include within-participant, between condition mean systolic and diastolic

255 blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC

256 and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit

257 comparisons with previous studies. *Feasibility measures:* to assess feasibility of the trial,

258 participant dropout, number of experimental sessions completed, fatigue at the beginning

259 and end of each day rated on an 11-point (0 "not fatigued at all" to 10 "extremely fatigued")

260 Visual Analogue Scale (VAS), and the degree of difficulty in completing each experimental

261 condition rated on an 11-point VAS (0 "not difficult at all" to 10 "extremely difficult") will be

262 recorded. Participants will also complete the Physical Activity Enjoyment Scale [48] at the

263 end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [49]

264 ("Enjoyment") 20 min after the last activity bout in the SED-ACT condition. Participants will

265 also report on the same scale how enjoyable they would find it to engage in this form of

266 physical activity most days of the week in the coming month ("Expected enjoyment").

267 *Psychological outcomes:* correlates of sedentary behaviour will be measured immediately

268 before and after each experimental condition to explore whether participants' mood, affect,

269 wellbeing, and social cognitions regarding their ability to overcome being sedentary may

270 differ in response to the SED-ACT condition compared with the SED condition. These

271 measures will be based on the COM-B framework [50] using standardised wording formats

272 [51] that will include overcoming barriers (self-efficacy/perceived behavioural control),

273 attitudes, intentions and action planning. The following questionnaires will be used: an

274 adapted version of the Schwarzer and Renner [52] Physical Exercise Self-Efficacy Scale to

275 measure self-efficacy to avoid long periods of sedentary time; current mood using the short

276 Positive and Negative Affect Scale [53]; psychological wellbeing using the National

277 Wellbeing Measurement [54]; and the Warwick Edinburgh Mental Well-Being Scale [55].

278 These measures will be taken within 45 min following the last bout of activity in the SED-

12

279   ACT condition, which is an appropriate time frame based on evidence that mood and affect

280   is enhanced for 3-4 hours following a single session of exercise [56].

281

282   *Sample size calculations*

283   Sample size calculations were performed using GPower [57]. Previous research reported a

284   16% reduction (effect size, F=0.61) in 5 h postprandial glucose total AUC when breaking up

285   prolonged sedentary time with 2 min light-intensity walking every 20 min versus

286   uninterrupted sitting in able-bodied participants [28]. As this study will use arm cranking

287   (localised muscular contractions) as opposed to walking where a larger muscle mass is

288   required, a smaller effect may be observed. Based on this, it was estimated that 14

289   participants would be required for this complete two-treatment crossover design to detect a

290   medium effect size (F=0.4) with a within-person correlation of 0.6, 80% power, and an α of

291   0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.

292

293   *Statistical analysis*

294   Linear mixed models will be used to determine differences in the primary and secondary

295   outcome variables between the conditions. All models will adjust for potential covariates

296   explaining residual outcome variances (age, body fat% gender, lesion level, completeness of

297   lesion and pre-prandial outcome values). Statistical significance will be accepted as p<0.05.

298   Cohens' d effect sizes will be calculated to describe the magnitude of differences between

299   conditions [58]. Individuals' responses for CVD risk marker outcomes will also be compared

300   between the conditions to determine the number of participants who respond to the

301   experimental protocols.

302

303   *Patient and Public Involvement*

304   Patients and public were not involved with the development of the research question,

305   outcome measures or study design, nor will they be involved with the conduct of the study.

13

306   The recruitment plan was informed based on feedback from patients and public. A summary

307   of the study results will be provided to each of the study participants.

14

308 **Ethics and dissemination**

309 This study was approved on the 19th May 2017 by the Cambridge South NHS Research

310 Ethics Committee (reference 17/EE/0076). Personal information about potential and enrolled

311 participants will be stored in electronic format on password protected computers or in hard

312 copy format in locked filing cabinets at the University of Bedfordshire. Only members of the

313 research team will have access to this information. All personal information will be destroyed

314 after a period of five years. Individuals will be referred to in anonymised fashion in any

315 published data.

316

317 The findings of this research will be disseminated to lay, academic, practice, and policy-

318 based audiences via presentation at conference proceedings; publication in a peer review

319 journal; websites, newsletters, and social media; and summary reports to policy makers and

320 clinical care partners. The final trial dataset will be made available as supplementary

321 material when the findings of the study are published in a peer review journal. Any protocol

322 modifications will be communicated to the Cambridge South NHS Research Ethics

323 Committee, recorded in the study's ISRCTN clinical trials registry, and detailed in a journal

324 publication of the study findings.

325

326 **Acknowledgements:** The authors would like to thank Dr Jan van der Scheer for providing

327 his advice on the design of the study protocol. We would also like to thank the patients and

328 public who helped to inform the recruitment strategy for this study.

329

330 **Author contributions**

331 DB and LC conceptualised the study.

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

333 TW drafted the manuscript.

334 TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and

335 approved the final version.

15

336

Funding statement

342

Conflicts of interest

None of the authors have declared any conflicts of interest.

345

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347 **References**

348 1. Lee, B.B., et al., *The global map for traumatic spinal cord injury epidemiology: update*
349 *2011, global incidence rate.* Spinal Cord, 2014. **52**(2): p. 110-6.

350 2. British Society of Rehabilitation Medicine, *Chronic spinal cord injury: management of*
351 *patients in acute hospital settings: National Guidelines. Available at*
352 *http://www.bsrm.org.uk/downloads/sciwebversion.pdf (accessed 26 April 2016).*
353 2008.

354 3. Garshick, E., et al., *A prospective assessment of mortality in chronic spinal cord*
355 *injury.* Spinal Cord, 2005. **43**(7): p. 408-16.

356 4. Cragg, J.J., et al., *Cardiovascular disease and spinal cord injury: results from a*
357 *national population health survey.* Neurology, 2013. **81**(8): p. 723-8.

358 5. Gorgey, A.S., et al., *Effects of spinal cord injury on body composition and metabolic*
359 *profile - part I.* J Spinal Cord Med, 2014. **37**(6): p. 693-702.

360 6. Bauman, W.A. and A.M. Spungen, *Disorders of carbohydrate and lipid metabolism in*
361 *veterans with paraplegia or quadriplegia: A model of premature aging.* Metabolism,
362 1994. **43**(6): p. 749-756.

363 7. Wahman, K., et al., *Cardiovascular disease risk factors in persons with paraplegia:*
364 *the Stockholm spinal cord injury study.* J Rehabil Med, 2010. **42**(3): p. 272-8.

365 8. Ford, E.S., W.H. Giles, and W.H. Dietz, *Prevalence of the metabolic syndrome*
366 *among US adults: findings from the third National Health and Nutrition Examination*
367 *Survey.* Jama, 2002. **287**(3): p. 356-359.

368 9. Gater, D.R., Jr., *Obesity after spinal cord injury.* Phys Med Rehabil Clin N Am, 2007.
369 **18**(2): p. 333-51, vii.

370 10. Gorgey, A.S., et al., *The effects of electrical stimulation on body composition and*
371 *metabolic profile after spinal cord injury--Part II.* J Spinal Cord Med, 2015. **38**(1): p.
372 23-37.

373 11. O'Keefe, J.H. and D.S. Bell, *Postprandial hyperglycemia/hyperlipidemia (postprandial*
374 *dysmetabolism) is a cardiovascular risk factor.* Am J Cardiol, 2007. **100**(5): p. 899-
375 904.

376 12. Esposito, K., et al., *Regression of carotid atherosclerosis by control of postprandial*
377 *hyperglycemia in type 2 diabetes mellitus.* Circulation, 2004. **110**(2): p. 214-9.

378 13. Smith, N.L., et al., *Fasting and 2-hour postchallenge serum glucose measures and*
379 *risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study.*
380 Archives of internal medicine, 2002. **162**(2): p. 209-216.

381 14. Duckworth, W.C., P. Jallepalli, and S.S. Solomon, *Glucose intolerance in spinal cord*
382 *injury.* Arch Phys Med Rehabil, 1983. **64**(3): p. 107-10.

17

383   15.   Bauman, W.A., et al., *The effect of residual neurological deficit on oral glucose*
384   *tolerance in persons with chronic spinal cord injury.* Spinal Cord, 1999. **37**(11): p.
385   765-71.
386   16.   Raymond, J., et al., *Glucose tolerance and physical activity level in people with spinal*
387   *cord injury.* Spinal Cord, 2010. **48**(8): p. 591-6.
388   17.   Bauman, W.A., et al., *The effect of residual neurological deficit on serum lipoproteins*
389   *in individuals with chronic spinal cord injury.* Spinal Cord, 1998. **36**(1): p. 13-7.
390   18.   Nash, M.S., et al., *Evidence for an exaggerated postprandial lipemia in chronic*
391   *paraplegia.* J Spinal Cord Med, 2005. **28**(4): p. 320-5.
392   19.   Groah, S.L., et al., *Nutrient intake and body habitus after spinal cord injury: an*
393   *analysis by sex and level of injury.* J Spinal Cord Med, 2009. **32**(1): p. 25-33.
394   20.   Martin Ginis, K.A., et al., *Evidence-based scientific exercise guidelines for adults with*
395   *spinal cord injury: an update and a new guideline.* 2017.
396   21.   Martin Ginis, K.A., et al., *Leisure time physical activity in a population-based sample*
397   *of people with spinal cord injury part II: activity types, intensities, and durations.* Arch
398   Phys Med Rehabil, 2010. **91**(5): p. 729-33.
399   22.   Buchholz, A.C., et al., *Greater daily leisure time physical activity is associated with*
400   *lower chronic disease risk in adults with spinal cord injury.* Appl Physiol Nutr Metab,
401   2009. **34**(4): p. 640-7.
402   23.   Martin Ginis, K.A., et al., *The development of evidence-informed physical activity*
403   *guidelines for adults with spinal cord injury.* Spinal Cord, 2011. **49**(11): p. 1088-96.
404   24.   Tremblay, M.S., et al., *Sedentary Behavior Research Network (SBRN) - Terminology*
405   *Consensus Project process and outcome.* Int J Behav Nutr Phys Act, 2017. **14**(1): p.
406   75.
407   25.   Dunstan, D.W., A.A. Thorp, and G.N. Healy, *Prolonged sitting: is it a distinct coronary*
408   *heart disease risk factor?* Curr Opin Cardiol, 2011. **26**(5): p. 412-9.
409   26.   Dunstan, D.W., et al., *Breaking up prolonged sitting reduces postprandial glucose*
410   *and insulin responses.* Diabetes Care, 2012. **35**(5): p. 976-83.
411   27.   Miyashita, M., et al., *Interrupting Sitting Time with Regular Walks Attenuates*
412   *Postprandial Triglycerides.* Int J Sports Med, 2016. **37**(2): p. 97-103.
413   28.   Bailey, D.P. and C.D. Locke, *Breaking up prolonged sitting with light-intensity walking*
414   *improves postprandial glycemia, but breaking up sitting with standing does not.* J Sci
415   Med Sport, 2015. **18**(3): p. 294-8.
416   29.   Larsen, R.N., et al., *Breaking up prolonged sitting reduces resting blood pressure in*
417   *overweight/obese adults.* Nutr Metab Cardiovasc Dis, 2014. **24**(9): p. 976-82.
418   30.   Chan, A.-W., et al., *SPIRIT 2013 statement: defining standard protocol items for*
419   *clinical trials.* Annals of internal medicine, 2013. **158**(3): p. 200-207.

18

420 31.   New, P.W. and R. Marshall, *International Spinal Cord Injury Data Sets for non-*
421   *traumatic spinal cord injury.* Spinal Cord, 2014. **52**(2): p. 123-32.

422 32.   Jacobs, P.L. and M.S. Nash, *Exercise recommendations for individuals with spinal*
423   *cord injury.* Sports Med, 2004. **34**(11): p. 727-51.

424 33.   Ekelund, U., et al., *Does physical activity attenuate, or even eliminate, the*
425   *detrimental association of sitting time with mortality? A harmonised meta-analysis of*
426   *data from more than 1 million men and women.* Lancet, 2016. **388**(10051): p. 1302-
427   10.

428 34.   Keil, M., et al., *Measurement precision of body composition variables in elite*
429   *wheelchair athletes, using dual-energy X-ray absorptiometry.* European journal of
430   sport science, 2016. **16**(1): p. 65-71.

431 35.   Spungen, A.M., et al., *Factors influencing body composition in persons with spinal*
432   *cord injury: a cross-sectional study.* J Appl Physiol (1985), 2003. **95**(6): p. 2398-407.

433 36.   Gorgey, A.S., D.R. Dolbow, and D.R. Gater, Jr., *A model of prediction and cross-*
434   *validation of fat-free mass in men with motor complete spinal cord injury.* Arch Phys
435   Med Rehabil, 2012. **93**(7): p. 1240-5.

436 37.   Marfell-Jones, M.J., A.D. Stewart, and J.H. De Ridder, *International standards for*
437   *anthropometric assessment*. 2012.

438 38.   Willems, A., et al., *Dual-Energy X-Ray Absorptiometry, Skinfold Thickness, and*
439   *Waist Circumference for Assessing Body Composition in Ambulant and Non-*
440   *Ambulant Wheelchair Games Players.* Front Physiol, 2015. **6**: p. Article 356.

441 39.   Borg, G.A., *Psychophysical bases of perceived exertion.* Med Sci Sports Exerc,
442   1982. **14**(5): p. 377-81.

443 40.   Bailey, D.P., et al., *Effects of breaking up prolonged sitting following low and high*
444   *glycaemic index breakfast consumption on glucose and insulin concentrations.* Eur J
445   Appl Physiol, 2017.

446 41.   van der Scheer, J.W., et al., *Reliability and Validity of Subjective Measures of*
447   *Aerobic Intensity in Adults With Spinal Cord Injury: A Systematic Review.* PM R,
448   2017.

449 42.   Bailey, D.P., et al., *Breaking up prolonged sitting time with walking does not affect*
450   *appetite or gut hormone concentrations but does induce an energy deficit and*
451   *suppresses postprandial glycaemia in sedentary adults.* Appl Physiol Nutr Metab,
452   2016. **41**(3): p. 324-31.

453 43.   Burr, J.F., R.J. Shephard, and E.P. Zehr, *Physical activity after stroke and spinal cord*
454   *injury: evidence-based recommendations on clearance for physical activity and*
455   *exercise.* Can Fam Physician, 2012. **58**(11): p. 1236-9.

19

456   44.   Schofield, W.N., *Predicting basal metabolic rate, new standards and review of*
457   *previous work.* Hum Nutr Clin Nutr, 1985. **39 Suppl 1**: p. 5-41.

458   45.   Food Standards Agency, *FSA nutrient and food based guidelines for UK institutions.*
459   *Available at:*
460   *http://www.food.gov.uk/sites/default/files/multimedia/pdfs/nutrientinstitution.pdf*
461   *(accessed 18 Jan 2016).* 2007.

462   46.   Atkinson, F.S., K. Foster-Powell, and J.C. Brand-Miller, *International tables of*
463   *glycemic index and glycemic load values: 2008.* Diabetes Care, 2008. **31**(12): p.
464   2281-3.

465   47.   Wolever, T.M. and D.J. Jenkins, *The use of the glycemic index in predicting the blood*
466   *glucose response to mixed meals.* Am J Clin Nutr, 1986. **43**(1): p. 167-72.

467   48.   Kendzierski, D. and K. DeCarlo, *Physical activity enjoyment scale: two validation*
468   *studies.* J Sport Ex Psych, 1991. **13**: p. 50-64.

469   49.   Svensson, E., *Comparison of the Quality of Assessments Using Continuous and*
470   *Discrete Ordinal Rating Scales.* Biom J, 2000. **42**(4): p. 417-434.

471   50.   Michie, S., et al., *A refined taxonomy of behaviour change techniques to help people*
472   *change their physical activity and healthy eating behaviours: the CALO-RE*
473   *taxonomy.* Psychol Health, 2011. **26**(11): p. 1479-98.

474   51.   Francis, J., et al., *Constructing questionnaires based on the theory of planned*
475   *behaviour: A manual for health services researchers. Newcastle upon Tyne, UK:*
476   *Centre for Health Services Research, University of Newcastle upon Tyne.* 2004.

477   52.   Schwarzer, R. and B. Renner, *Social-cognitive predictors of health behavior: action*
478   *self-efficacy and coping self-efficacy.* Health Psychol, 2000. **19**(5): p. 487-95.

479   53.   Thompson, E.R., *Development and Validation of an Internationally Reliable Short-*
480   *Form of the Positive and Negative Affect Schedule (PANAS).* Journal of Cross-
481   Cultural Psychology, 2007. **38**(2): p. 227-242.

482   54.   Tinkler, L. *Measuring National Well-being: Personal Well-being in the UK, 2014 to*
483   *2015*. 2015; Available from:
484   https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/bulletins/measurin
485   gnationalwellbeing/2015-09-23.

486   55.   Tennant, R., et al., *The Warwick-Edinburgh Mental Well-being Scale (WEMWBS):*
487   *development and UK validation.* Health and Quality of Life Outcomes, 2007. **5**(1): p.
488   63.

489   56.   Yeung, R.R., *The acute effects of exercise on mood state.* J Psychosom Res, 1996.
490   **40**(2): p. 123-41.

491   57.   Faul, F., et al., *G*Power 3: a flexible statistical power analysis program for the social,*
492   *behavioral, and biomedical sciences.* Behav Res Methods, 2007. **39**(2): p. 175-91.

20

493   58.   Cohen, J., *Statistical power analysis for the behavioral sciences*. 2nd ed. 1988,

494   Hillsdale, NJ: Erlbaum.

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Figure captions

Figure 1 Study schedule.

Figure 2 Schematic of experimental protocol.

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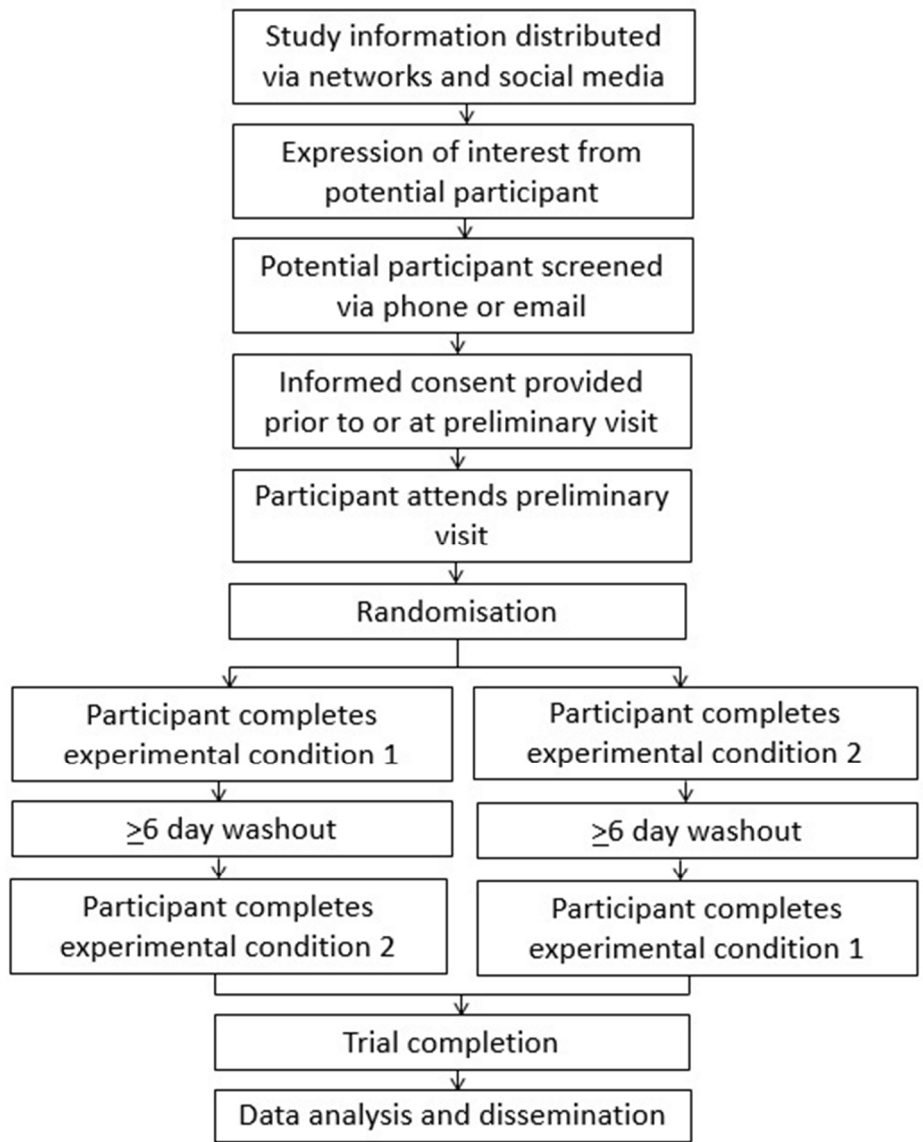50
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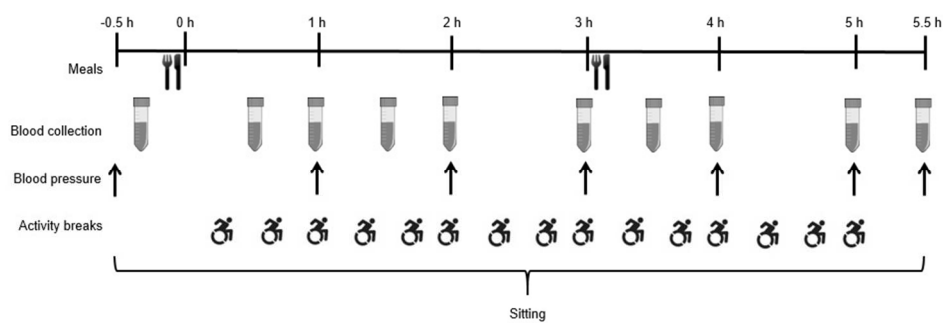60

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 ☑

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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_____

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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_____ |

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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_____

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3 Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality _____14_____
4 (eg, double data entry; range checks for data values). Reference to where details of data management
5 procedures can be found, if not in the protocol
6
7 Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the _____13_____
8 statistical analysis plan can be found, if not in the protocol
9
10 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) _____13_____
11
12 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any
13 statistical methods to handle missing data (eg, multiple imputation) _____NA_____
14
15 **Methods: Monitoring**
16
17 Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of _____NA_____
18 whether it is independent from the sponsor and competing interests; and reference to where further details
19 about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not
20 needed
21
22 21b Description of any interim analyses and stopping guidelines, including who will have access to these interim _____NA_____
23 results and make the final decision to terminate the trial
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25 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse _____NA_____
26 events and other unintended effects of trial interventions or trial conduct
27
28 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent _____NA_____
29 from investigators and the sponsor
30
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32 **Ethics and dissemination**
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34 Research ethics 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval _____14_____
35 approval
36
37 Protocol 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, _____14_____
38 amendments analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
39 regulators)
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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.

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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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1

1 **Abstract**

2 **Introduction:** Sedentary behaviour is a distinct risk factor for cardiovascular disease (CVD)

3 and could partly explain the increased prevalence of CVD in people with spinal cord injury

4 (SCI). Interrupting prolonged sitting periods with regular short bouts of walking acutely

5 suppresses postprandial glucose and lipids in able-bodied individuals. However, the acute

6 CVD risk marker response to breaking up prolonged sedentary time in people with SCI has

7 not been investigated. **Methods and analysis:** A randomised two-condition laboratory

8 crossover trial will compare: 1) breaking up prolonged sedentary time with 2 min moderate-

9 intensity arm crank activity every 20 min, with 2) uninterrupted prolonged sedentary time

10 (control) in people with SCI. Outcomes will include acute effects on postprandial glucose,

11 insulin, lipids and blood pressure. Blood samples will be collected and blood pressure

12 measured at regular intervals during each 5.5 h condition. **Ethics and dissemination:** This

13 study was approved by the Cambridge South NHS Research Ethics Committee. This

14 research will help determine if breaking up prolonged sedentary time could be effective in

15 lowering CVD risk in people with SCI. The findings of the research will be published in a peer

16 review journal and disseminated to relevant user groups. **Trial registration:** The study is

17 registered as a clinical trial on the ISRCTN register (trial ID: ISRCTN51868437).

18

Strengths and limitations of this study

20 • This study uses a randomised crossover design to investigate, for the first time,

21 cardiovascular disease risk marker responses to breaking up prolonged sedentary

22 time in individuals with paraplegia.

23 • Regular collection of blood samples will permit robust time course and incremental

24 area under the curve calculations for primary and secondary outcomes.

25 • Due to the acute nature of the study, the long-term cardiovascular disease risk

26 marker responses to a chronic intervention will remain unknown.

27 • The cardiovascular disease risk marker responses to breaking up prolonged

28 sedentary time in people with tetraplegia still requires investigation.

29

30 **Keywords:** physical activity; sedentary lifestyle; activity breaks; glucose; cardiovascular

31 disease; spinal cord injury

Introduction

33 There is a global incident rate of 180,000 traumatic spinal cord injury (SCI) cases each year

34 with a prevalence of over 40,000 in the UK [1, 2]. Cardiovascular disease (CVD) is a leading

35 cause of death in individuals with SCI [3] and this population have a significantly increased

36 risk of heart disease and stroke compared with able-bodied individuals [4]. Traditional risk

37 factors for CVD include impaired glucose tolerance, central obesity, high triglycerides, low

38 high-density lipoprotein cholesterol (HDL), and high blood pressure. These risk factors often

39 exacerbate significantly as a consequence of SCI [5] and a plethora of research has

40 documented impaired glucose tolerance and adverse lipid profiles in individuals with SCI [5,

41 6]. The clustering of ≥2 and ≥3 risk factors is prevalent in 87% and 72% of SCI individuals,

42 respectively [7], which is markedly higher compared with the able-bodied population [8]. This

43 milieu of metabolic disturbances after SCI may be due to increases in body fat resulting from

44 an imbalance in energy intake and expenditure [5]. Excess fat accumulation, particularly in

45 the visceral region, is associated with inflammation that is causal in glucose intolerance and

46 dyslipidaemia [5, 9] thus promoting atherogenesis that would increase the risk of CVD in this

47 population [10].

48

49 Postprandial glucose and lipid concentrations are strong independent predictors of future

50 CVD incidence, even in those without diabetes [11]. There is a dose-response relationship

51 between postprandial glucose area under the curve (AUC) and CVD risk, while progression

52 of carotid atherosclerosis can be prevented by attenuation of postprandial glucose

53 concentrations [12, 13]. Impaired postprandial glucose metabolism was observed in 50%

54 and 62% of individuals with paraplegia and tetraplegia, respectively, compared with 18% in

55 able-bodied individuals [6]. This impaired glucose intolerance in SCI is characterised by

56 hyperinsulinaemia, which suggests that there is tissue level resistance to insulin [14]. In

57 paraplegic individuals, there appears to be no difference in postprandial glucose responses

58 between those with complete versus incomplete lesions [15, 16]. Although postprandial

59 lipaemic responses have not been compared between individuals with complete and

4

60 incomplete lesions, fasting lipid levels do not differ between these groups [17]. There does,

61 however, appear to be an exaggerated postprandial lipaemic response in individuals with

62 paraplegia compared with able-bodied individuals [18]. These observations are of potential

63 concern as the high dietary intake of carbohydrate and fat in individuals with SCI [19] may

64 lead to repeated exaggerated elevations in glucose and lipids following food intake. It is thus

65 pertinent to identify interventions to reduce postprandial glucose and lipid responses in

66 individuals with SCI to reduce their CVD risk.

67

68 Physical activity guidelines have been developed specifically for this population that

69 recommend engaging in at least 30 min of moderate-to-vigorous physical activity (MVPA)

70 three times per week for CVD health benefits [20]. However, it is estimated that 37 to 50% of

71 this population engage in no leisure-time physical activity whatsoever [21, 22]. Reduced

72 levels of physical activity are proposed to largely account for the increased CVD risk in SCI

73 with reduced levels of leisure-time physical activity associated with increased body fat,

74 insulin resistance, and systolic blood pressure [22, 23]. However, sedentary behaviour (i.e.

75 any waking behaviour in a sitting, reclining or lying posture with low energy expenditure

76 [24]), is now recognised as being a significant CVD risk factor in the able-bodied population,

77 independent of MVPA [25]. Experimental studies in able-bodied individuals have reported an

78 acute reduction in postprandial glucose, insulin, triglycerides and blood pressure in response

79 to breaking up prolonged sedentary time with 2 min bouts of light or moderate-intensity

80 walking every 20 min [26-29]. However, no research has examined whether postprandial

81 CVD risk marker responses are attenuated in response to breaking up prolonged sedentary

82 time in individuals with SCI.

83

84 The primary aim of this study is therefore to compare the acute CVD risk marker responses

85 in individuals with SCI to 1) breaking up prolonged sedentary time, with 2) uninterrupted

86 sedentary time. The CVD risk markers that will be studied include postprandial glucose

87 (primary outcome), insulin and lipids, and systolic and diastolic blood pressure (secondary

5

88 outcomes) based on evidence that these markers predict CVD outcomes and are adversely

89 affected by SCI. It is hypothesised that breaking up prolonged sedentary time will result in

90 favourable CVD risk marker responses compared with uninterrupted sedentary time in

91 individuals with paraplegia. This could identify a novel strategy for the prevention of CVD in

92 SCI that would warrant further evaluation.

93

94 **Methods and analysis**

95 *Study design*

96 A randomised two-condition crossover design will be used in accordance with the SPIRIT

97 statement [30]. The study is registered as a clinical trial on the ISRCTN register (trial ID:

98 ISRCTN51868437). The study schedule can be seen in Figure 1. All research will take place

99 at the University of Bedfordshire Sport and Exercise Science Laboratories. After preliminary

100 measures, participants will complete two experimental conditions in a randomised order. The

101 conditions will be separated by ≥6 days to eliminate any potential carryover effects.

102 Condition order will be randomised by a researcher independent from the study using

103 computer generated random numbers (block randomisation with balanced block sizes).

104

105 Figure 1 about here.

106

107 *Participants*

108 *Inclusion criteria:* Males and females aged 18-60 years; chronic SCI (≥1 year since injury);

109 individuals with a traumatic SCI below T5 (mid to low level paraplegia); individuals with a

110 non-traumatic SCI (as defined by the International Spinal Cord Injury Data Sets for non-

111 traumatic SCI [31]) that present with mid to low level paraplegia. Including only individuals

112 with injuries below T5 will ensure sympathetic innervation to the major organs at the T5 level

113 so that heart rate and catecholamine responses would be unaffected by injury [32] and thus

114 minimise the potential that innervation variations could have on the study outcomes.

115 Paraplegic individuals who have complete or incomplete lesions will be included based on

6

116   evidence that these groups do not differ with respect to postprandial glucose metabolism

117   (primary outcome) [15, 16]. Individuals who express an interest in taking part in the study will

118   be required to indicate their spinal cord lesion level and completeness of injury via a

119   questionnaire and asked to provide the research team with a copy of medical records to

120   confirm injury level and ASIA impairment scale classification prior to preliminary measures.

121

122   *Exclusion criteria:* individuals who regularly engage in >300 min/week of MVPA as such high

123   levels of physical activity may offset the detrimental association of sedentary time with health

124   outcomes [33]; history of severe cardiovascular complications; hypotension (resting blood

125   pressure <90/60 mmHg); body mass index >45 kg/m^2; a history of autonomic dysreflexia;

126   pregnancy; taking glucose lowering medication; smokers; diagnosed diabetes, renal failure,

127   liver disease, major illness, or other health issues that may limit ability to perform the

128   physical activity protocols.

129

130   *Recruitment*

131   Participants will be recruited through organisations and charities relevant to individuals with

132   SCI, including the National Spinal Injuries Centre, Stoke Mandeville Hospital,

133   Buckinghamshire NHS Healthcare Trust; local sport and activity clubs; and local community

134   groups. Mail outs, social media, information on websites, posters, flyers, and visits from the

135   research team will be used to provide information on the study to potentially eligible

136   individuals who can then express their interest to the research team in taking part in the

137   study. Written informed consent will be obtained by a member of the research team prior to

138   participation in any testing protocols (see supplementary file). As an incentive, participants

139   will receive a £25 shopping gift voucher for each main condition they complete and will have

140   all travel expenses paid.

141

142   *Preliminary measures*

7

143 Participants will attend a preliminary testing session where they will have body mass

144 measured using wheelchair double beam scales (300 series; Marsden, London, UK).

145 They will also have body fat and lean tissue mass (and percent) determined for the

146 whole body and regionally via whole-body scans using dual-energy x-ray absorptiometry

147 (DXA; GE Medical Systems; Chalfont St Giles, UK) in line with previous research [34-36].

148 During DXA measures, participants will be positioned as closely as possible to standard

149 protocols and Velcro restraints will be fastened around the participants' knees and ankles to

150 maintain correct position of the legs during scanning. Participants will be offered a wedge to

151 be used as a pillow for comfort. Waist circumference will be measured using International

152 Standards for Anthropometric Assessment (ISAK) guidelines [37, 38]. These measures will

153 be taken in the standing position for participants who are able to maintain this posture and in

154 a supine position for participants who are not able to stand [38]. Resting blood pressure will

155 be measured on the left arm, while seated, three times after the participant has rested for 5

156 min with the lowest readings being recorded. Following this, participants will be familiarised

157 with use of the Borg 6-20 Rating of Perceived Exertion (RPE) scale [39]. They will then cycle

158 using an arm ergometer (Lode Angio; Lode, Netherlands) to determine the intensity (power

159 output) that yields an RPE of 13 (somewhat hard) in line with previous sedentary behaviour

160 research [26, 40]. Participants will be asked to cycle at ~70 rpm during the test. The test will

161 start at a low intensity (~20 Watts) and the participants will then indicate their RPE at 1 min

162 intervals. The resistance will then be increased by 5-20 Watts based on the participants'

163 RPE until an RPE of 13 has been achieved, at which point the test will be terminated. The

164 test is expected to take no longer than 15 min. The intensity that corresponds to an RPE of

165 13 during the test will be recorded for each participant and used for the physical activity

166 breaks described in the respective main condition below. The use of the Borg 6-20 RPE

167 scale has acceptable validity in individuals with SCI to determine physical activity intensity

168 [41]. This method is also suggested as a practical approach for health care professionals

169 and scientists as oxygen consumption testing equipment is costly and not available in many

170 rehabilitation centres and community settings [41].

171

172 *Experimental protocol*

173 Figure 2 shows the experimental protocol. Participants will be instructed to refrain from

174 caffeine, alcohol and exercise for 48 h prior to each experimental condition. They will also be

175 provided with a food diary and digital weighing scales to record volume and timings of all

176 food and liquids consumed in the 24 h period prior to the first experimental condition.

177 Participants will be asked to replicate their diet the day prior to the subsequent experimental

178 condition [42]. On condition days, participants will attend in the morning following an

179 overnight fast and avoid active travel to the laboratory. Upon arrival, resting blood pressure

180 will be measured after 5 min rest; two measures will be taken and the lowest of these

181 recorded. A fasting capillary blood sample will then be collected. Participants will commence

182 the 5.5 h condition period following consumption of a standardised breakfast. The two

183 experimental conditions are as follows:

184

185 1. *Uninterrupted sedentary time (SED)*: participants will remain seated and inactive in their

186 wheelchair or a standard chair at a desk during this condition.

187 2. *Sedentary time interrupted with physical activity breaks (SED-ACT)*: participants will

188 complete 2 min of moderate-intensity arm crank activity every 20 min at ~70 rpm using

189 the Lode Angio arm ergometer. These 15 breaks will equate to a total of 30 min physical

190 activity.

191

192 Figure 2 about here.

193

194 The SED-ACT protocol was selected based on previous research that reported a significant

195 reduction in 5 h postprandial glucose in response to breaking up prolonged sitting time with 2

196 min light-intensity walking every 20 min versus uninterrupted sitting in able-bodied

9

197 participants [28]. An RPE of 13 for the physical activity intensity was selected in line with

198 previous research [26, 42] and the Borg 6-20 RPE scale may be used to assess and

199 regulate upper-body physical activity at moderate-to-vigorous intensity in adults with chronic

200 SCI [41]. Moderate-intensity physical activity was selected as it is well-tolerated, can be

201 performed safely, and is recommended for health risk reduction in individuals with SCI [20,

202 43].

203

204 Participants will be permitted to work on a laptop computer, read, talk, or watch DVDs during

205 each condition. This will be standardised by asking participants to engage in the same

206 activities during each of the two experimental conditions. Except during the activity bouts,

207 participants will remain inactive and only leave their desk to void and consume standardised

208 meals in a kitchen adjacent to the test laboratory; participants will be aided by a member of

209 the research team when moving to these locations so that they remain inactive. A researcher

210 will be present to ensure compliance with the protocols throughout all conditions.

211

212 *Meal and water consumption*

213 Standardised meals will be consumed immediately prior to the start of each experimental

214 condition and at 3 h, each providing 30% of estimated daily energy requirements for each

215 participant [44]. Participants will be asked to consume each meal within a 15 min time

216 period. The time taken to consume the meals will be recorded for the first condition and

217 participants will be asked to replicate this time as closely as possible in the subsequent

218 condition. Breakfast will consist of bran flakes, whole milk, croissant, butter and orange juice

219 (55% carbohydrate, 34% fat, 12% protein) and lunch will be a chicken sandwich, salted

220 crisps and apple (54% carbohydrate, 34% fat, 13% protein). The macronutrient composition

221 of meals in the current study was selected as it is generally representative of UK guidelines

222 for a balanced diet [45]. The glycaemic index for these breakfast and lunch meals is 43 and

223 72, respectively. Glycaemic index values for each food item were obtained from the

224 International Tables of Glycaemic Index and Glycaemic Load Values 2008 [46] and meal

10

225 glycaemic index was calculated using weighted means of the glycaemic index values for the

226 component foods [47]. Water will be available ad libitum during the first condition and this

227 volume of intake will be provided at standardised regular intervals in the subsequent

228 condition.

229

230 *Blood collection and biochemistry*

231 Finger prick blood samples will be collected into two EDTA-containing microvettes

232 (Microvette CB300 EDTA, Sarstedt Ltd, Leicester, UK) at baseline and at 30, 60, 90, 120,

233 180, 210, 240, 300 and 330 min. Blood samples will be collected before the hourly activity

234 bouts in SED-ACT. At each time point, approximately 600 μL of whole blood will be

235 collected. Blood glucose concentrations will be analysed immediately using the YSI 2300

236 STAT plus glucose and lactate analyzer (YSI Inc., Yellow Springs, OH, USA) from 30 μL of

237 blood from one microvette. Additional 30 μl volumes of whole blood will be aliquoted onto

238 two separate Reflotron test strips (Roche Diagnostics, Burgess Hill, UK) for the

239 measurement of triglyceride and HDL concentrations using the Reflotron Plus system

240 (Roche Diagnostics, Burgess Hill, UK). The remaining whole blood ($\sim$490 μL) will be

241 centrifuged at 2500 x g for 5 min (Heraeus Pico 17, Thermo Scientific, Loughborough, UK)

242 and the plasma then stored at -80°C. An enzyme-linked immunosorbent assay kit will be

243 used to determine plasma concentrations of insulin (Mercodia, Uppsala, Sweden).

244

245 *Blood pressure*

246 Blood pressure will be measured at baseline as described above followed by single readings

247 taken at 60, 120, 180, 240, 300, and 330 min. Readings will be taken 5 min before the hourly

248 activity bouts in SED-ACT. Blood pressure will be measured using an automated oscillatory

249 blood pressure monitor (Omron M5-I; Omron Matsusaka Co. Ltd., Matsusaka, Japan).

250

251 *Study outcomes*

11

252 *Primary outcome:* the primary outcome for the study is within-participant, between condition

253 postprandial glucose net incremental area under the curve (iAUC) [11]. *Secondary*

254 *outcomes:* these include within-participant, between condition mean systolic and diastolic

255 blood pressure, and net iAUC for postprandial triglycerides, HDL and insulin. Positive iAUC

256 and total AUC will also be calculated for postprandial triglycerides, HDL and insulin to permit

257 comparisons with previous studies. *Feasibility measures:* to assess feasibility of the trial,

258 participant dropout, number of experimental sessions completed, fatigue at the beginning

259 and end of each day rated on an 11-point (0 "not fatigued at all" to 10 "extremely fatigued")

260 Visual Analogue Scale (VAS), and the degree of difficulty in completing each experimental

261 condition rated on an 11-point VAS (0 "not difficult at all" to 10 "extremely difficult") will be

262 recorded. Participants will also complete the Physical Activity Enjoyment Scale [48] at the

263 end of the SED-ACT condition and report their enjoyment on a 200 mm VAS [49]

264 ("Enjoyment") 20 min after the last activity bout in the SED-ACT condition. Participants will

265 also report on the same scale how enjoyable they would find it to engage in this form of

266 physical activity most days of the week in the coming month ("Expected enjoyment").

267 *Psychological outcomes:* correlates of sedentary behaviour will be measured immediately

268 before and after each experimental condition to explore whether participants' mood, affect,

269 wellbeing, and social cognitions regarding their ability to overcome being sedentary may

270 differ in response to the SED-ACT condition compared with the SED condition. These

271 measures will be based on the COM-B framework [50] using standardised wording formats

272 [51] that will include overcoming barriers (self-efficacy/perceived behavioural control),

273 attitudes, intentions and action planning. The following questionnaires will be completed in

274 this order: psychological wellbeing using the National Wellbeing Measurement [52]; the

275 Warwick Edinburgh Mental Well-Being Scale [53]; current mood using the short Positive and

276 Negative Affect Scale [54]; and an adapted version of the Schwarzer and Renner [55]

277 Physical Exercise Self-Efficacy Scale to measure self-efficacy to avoid long periods of

278 sedentary time. These measures will be taken at the end of each experimental condition

279 (330 min) meaning that each questionnaire will be completed within 45 min following the last

12

280 bout of activity in the SED-ACT condition. This is an appropriate time frame based on

281 evidence that mood and affect is enhanced for 3-4 hours following a single session of

282 exercise [56]. Although between-participant variation in the time taken to complete each

283 questionnaire is anticipated, within-participant variation is expected to be limited therefore

284 permitting valid between-condition comparisons.

285

286 *Sample size calculations*

287 Sample size calculations were performed using GPower [57]. Previous research reported a

288 16% reduction (effect size, F=0.61) in 5 h postprandial glucose total AUC when breaking up

289 prolonged sedentary time with 2 min light-intensity walking every 20 min versus

290 uninterrupted sitting in able-bodied participants [28]. As this study will use arm cranking

291 (localised muscular contractions) as opposed to walking where a larger muscle mass is

292 required, a smaller effect may be observed. Based on this, it was estimated that 14

293 participants would be required for this complete two-treatment crossover design to detect a

294 medium effect size (F=0.4) with a within-person correlation of 0.6, 80% power, and an α of

295 0.05. To allow for potential withdrawals, a total of 20 participants will be recruited.

296

297 *Statistical analysis*

298 Linear mixed models will be used to determine differences in the primary and secondary

299 outcome variables between the conditions. All models will adjust for potential covariates

300 explaining residual outcome variances (age, body fat% gender, lesion level, completeness of

301 lesion and pre-prandial outcome values). Statistical significance will be accepted as p<0.05.

302 Cohens' d effect sizes will be calculated to describe the magnitude of differences between

303 conditions [58]. Individuals' responses for CVD risk marker outcomes will also be compared

304 between the conditions to determine the number of participants who respond to the

305 experimental protocols.

306

307 *Patient and Public Involvement*

13

308 Patients and public were not involved with the development of the research question,

309 outcome measures or study design, nor will they be involved with the conduct of the study.

310 The recruitment plan was informed based on feedback from patients and public. A summary

311 of the study results will be provided to each of the study participants.

14

Ethics and dissemination

312

313 This study was approved on the 19th May 2017 by the Cambridge South NHS Research

314 Ethics Committee (reference 17/EE/0076). Personal information about potential and enrolled

315 participants will be stored in electronic format on password protected computers or in hard

316 copy format in locked filing cabinets at the University of Bedfordshire. Only members of the

317 research team will have access to this information. All personal information will be destroyed

318 after a period of five years. Individuals will be referred to in anonymised fashion in any

319 published data.

320

321 The findings of this research will be disseminated to lay, academic, practice, and policy-

322 based audiences via presentation at conference proceedings; publication in a peer review

323 journal; websites, newsletters, and social media; and summary reports to policy makers and

324 clinical care partners. The final trial dataset will be made available as supplementary

325 material when the findings of the study are published in a peer review journal. Any protocol

326 modifications will be communicated to the Cambridge South NHS Research Ethics

327 Committee, recorded in the study's ISRCTN clinical trials registry, and detailed in a journal

328 publication of the study findings.

329

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332 public who helped to inform the recruitment strategy for this study.

333

334 **Author contributions**

335 DB and LC conceptualised the study.

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

337 TW drafted the manuscript.

338 TW, LC, VT, DD, CL, and DB commented and edited each section of the manuscript and

339 approved the final version.

15

340

Funding statement

346

Conflicts of interest

None of the authors have declared any conflicts of interest.

349

350

16

351 **References**

352   1.   Lee, B.B., et al., *The global map for traumatic spinal cord injury epidemiology: update*
353   *2011, global incidence rate.* Spinal Cord, 2014. **52**(2): p. 110-6.

354   2.   British Society of Rehabilitation Medicine, *Chronic spinal cord injury: management of*
355   *patients in acute hospital settings: National Guidelines. Available at*
356   *http://www.bsrm.org.uk/downloads/sciwebversion.pdf (accessed 26 April 2016).*
357   2008.

358   3.   Garshick, E., et al., *A prospective assessment of mortality in chronic spinal cord*
359   *injury.* Spinal Cord, 2005. **43**(7): p. 408-16.

360   4.   Cragg, J.J., et al., *Cardiovascular disease and spinal cord injury: results from a*
361   *national population health survey.* Neurology, 2013. **81**(8): p. 723-8.

362   5.   Gorgey, A.S., et al., *Effects of spinal cord injury on body composition and metabolic*
363   *profile - part I.* J Spinal Cord Med, 2014. **37**(6): p. 693-702.

364   6.   Bauman, W.A. and A.M. Spungen, *Disorders of carbohydrate and lipid metabolism in*
365   *veterans with paraplegia or quadriplegia: A model of premature aging.* Metabolism,
366   1994. **43**(6): p. 749-756.

367   7.   Wahman, K., et al., *Cardiovascular disease risk factors in persons with paraplegia:*
368   *the Stockholm spinal cord injury study.* J Rehabil Med, 2010. **42**(3): p. 272-8.

369   8.   Ford, E.S., W.H. Giles, and W.H. Dietz, *Prevalence of the metabolic syndrome*
370   *among US adults: findings from the third National Health and Nutrition Examination*
371   *Survey.* Jama, 2002. **287**(3): p. 356-359.

372   9.   Gater, D.R., Jr., *Obesity after spinal cord injury.* Phys Med Rehabil Clin N Am, 2007.
373   **18**(2): p. 333-51, vii.

374   10. Gorgey, A.S., et al., *The effects of electrical stimulation on body composition and*
375   *metabolic profile after spinal cord injury--Part II.* J Spinal Cord Med, 2015. **38**(1): p.
376   23-37.

377   11. O'Keefe, J.H. and D.S. Bell, *Postprandial hyperglycemia/hyperlipidemia (postprandial*
378   *dysmetabolism) is a cardiovascular risk factor.* Am J Cardiol, 2007. **100**(5): p. 899-
379   904.

380   12. Esposito, K., et al., *Regression of carotid atherosclerosis by control of postprandial*
381   *hyperglycemia in type 2 diabetes mellitus.* Circulation, 2004. **110**(2): p. 214-9.

382   13. Smith, N.L., et al., *Fasting and 2-hour postchallenge serum glucose measures and*
383   *risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study.*
384   Archives of internal medicine, 2002. **162**(2): p. 209-216.

385   14. Duckworth, W.C., P. Jallepalli, and S.S. Solomon, *Glucose intolerance in spinal cord*
386   *injury.* Arch Phys Med Rehabil, 1983. **64**(3): p. 107-10.

17

387   15.   Bauman, W.A., et al., *The effect of residual neurological deficit on oral glucose*

388   *tolerance in persons with chronic spinal cord injury.* Spinal Cord, 1999. **37**(11): p.

389   765-71.

390   16.   Raymond, J., et al., *Glucose tolerance and physical activity level in people with spinal*

391   *cord injury.* Spinal Cord, 2010. **48**(8): p. 591-6.

392   17.   Bauman, W.A., et al., *The effect of residual neurological deficit on serum lipoproteins*

393   *in individuals with chronic spinal cord injury.* Spinal Cord, 1998. **36**(1): p. 13-7.

394   18.   Nash, M.S., et al., *Evidence for an exaggerated postprandial lipemia in chronic*

395   *paraplegia.* J Spinal Cord Med, 2005. **28**(4): p. 320-5.

396   19.   Groah, S.L., et al., *Nutrient intake and body habitus after spinal cord injury: an*

397   *analysis by sex and level of injury.* J Spinal Cord Med, 2009. **32**(1): p. 25-33.

398   20.   Martin Ginis, K.A., et al., *Evidence-based scientific exercise guidelines for adults with*

399   *spinal cord injury: an update and a new guideline.* 2017.

400   21.   Martin Ginis, K.A., et al., *Leisure time physical activity in a population-based sample*

401   *of people with spinal cord injury part II: activity types, intensities, and durations.* Arch

402   Phys Med Rehabil, 2010. **91**(5): p. 729-33.

403   22.   Buchholz, A.C., et al., *Greater daily leisure time physical activity is associated with*

404   *lower chronic disease risk in adults with spinal cord injury.* Appl Physiol Nutr Metab,

405   2009. **34**(4): p. 640-7.

406   23.   Martin Ginis, K.A., et al., *The development of evidence-informed physical activity*

407   *guidelines for adults with spinal cord injury.* Spinal Cord, 2011. **49**(11): p. 1088-96.

408   24.   Tremblay, M.S., et al., *Sedentary Behavior Research Network (SBRN) - Terminology*

409   *Consensus Project process and outcome.* Int J Behav Nutr Phys Act, 2017. **14**(1): p.

410   75.

411   25.   Dunstan, D.W., A.A. Thorp, and G.N. Healy, *Prolonged sitting: is it a distinct coronary*

412   *heart disease risk factor?* Curr Opin Cardiol, 2011. **26**(5): p. 412-9.

413   26.   Dunstan, D.W., et al., *Breaking up prolonged sitting reduces postprandial glucose*

414   *and insulin responses.* Diabetes Care, 2012. **35**(5): p. 976-83.

415   27.   Miyashita, M., et al., *Interrupting Sitting Time with Regular Walks Attenuates*

416   *Postprandial Triglycerides.* Int J Sports Med, 2016. **37**(2): p. 97-103.

417   28.   Bailey, D.P. and C.D. Locke, *Breaking up prolonged sitting with light-intensity walking*

418   *improves postprandial glycemia, but breaking up sitting with standing does not.* J Sci

419   Med Sport, 2015. **18**(3): p. 294-8.

420   29.   Larsen, R.N., et al., *Breaking up prolonged sitting reduces resting blood pressure in*

421   *overweight/obese adults.* Nutr Metab Cardiovasc Dis, 2014. **24**(9): p. 976-82.

422   30.   Chan, A.-W., et al., *SPIRIT 2013 statement: defining standard protocol items for*

423   *clinical trials.* Annals of internal medicine, 2013. **158**(3): p. 200-207.

18

424 31. New, P.W. and R. Marshall, *International Spinal Cord Injury Data Sets for non-*
425   *traumatic spinal cord injury.* Spinal Cord, 2014. **52**(2): p. 123-32.
426 32. Jacobs, P.L. and M.S. Nash, *Exercise recommendations for individuals with spinal*
427   *cord injury.* Sports Med, 2004. **34**(11): p. 727-51.
428 33. Ekelund, U., et al., *Does physical activity attenuate, or even eliminate, the*
429   *detrimental association of sitting time with mortality? A harmonised meta-analysis of*
430   *data from more than 1 million men and women.* Lancet, 2016. **388**(10051): p. 1302-
431   10.
432 34. Keil, M., et al., *Measurement precision of body composition variables in elite*
433   *wheelchair athletes, using dual-energy X-ray absorptiometry.* European journal of
434   sport science, 2016. **16**(1): p. 65-71.
435 35. Spungen, A.M., et al., *Factors influencing body composition in persons with spinal*
436   *cord injury: a cross-sectional study.* J Appl Physiol (1985), 2003. **95**(6): p. 2398-407.
437 36. Gorgey, A.S., D.R. Dolbow, and D.R. Gater, Jr., *A model of prediction and cross-*
438   *validation of fat-free mass in men with motor complete spinal cord injury.* Arch Phys
439   Med Rehabil, 2012. **93**(7): p. 1240-5.
440 37. Marfell-Jones, M.J., A.D. Stewart, and J.H. De Ridder, *International standards for*
441   *anthropometric assessment.* 2012.
442 38. Willems, A., et al., *Dual-Energy X-Ray Absorptiometry, Skinfold Thickness, and*
443   *Waist Circumference for Assessing Body Composition in Ambulant and Non-*
444   *Ambulant Wheelchair Games Players.* Front Physiol, 2015. **6**: p. Article 356.
445 39. Borg, G.A., *Psychophysical bases of perceived exertion.* Med Sci Sports Exerc,
446   1982. **14**(5): p. 377-81.
447 40. Bailey, D.P., et al., *Effects of breaking up prolonged sitting following low and high*
448   *glycaemic index breakfast consumption on glucose and insulin concentrations.* Eur J
449   Appl Physiol, 2017.
450 41. van der Scheer, J.W., et al., *Reliability and Validity of Subjective Measures of*
451   *Aerobic Intensity in Adults With Spinal Cord Injury: A Systematic Review.* PM R,
452   2017.
453 42. Bailey, D.P., et al., *Breaking up prolonged sitting time with walking does not affect*
454   *appetite or gut hormone concentrations but does induce an energy deficit and*
455   *suppresses postprandial glycaemia in sedentary adults.* Appl Physiol Nutr Metab,
456   2016. **41**(3): p. 324-31.
457 43. Burr, J.F., R.J. Shephard, and E.P. Zehr, *Physical activity after stroke and spinal cord*
458   *injury: evidence-based recommendations on clearance for physical activity and*
459   *exercise.* Can Fam Physician, 2012. **58**(11): p. 1236-9.

19

460 44. Schofield, W.N., *Predicting basal metabolic rate, new standards and review of*
461   *previous work.* Hum Nutr Clin Nutr, 1985. **39 Suppl 1**: p. 5-41.
462 45. Food Standards Agency, *FSA nutrient and food based guidelines for UK institutions.*
463   *Available at:*
464   *http://www.food.gov.uk/sites/default/files/multimedia/pdfs/nutrientinstitution.pdf*
465   *(accessed 18 Jan 2016).* 2007.
466 46. Atkinson, F.S., K. Foster-Powell, and J.C. Brand-Miller, *International tables of*
467   *glycemic index and glycemic load values: 2008.* Diabetes Care, 2008. **31**(12): p.
468   2281-3.
469 47. Wolever, T.M. and D.J. Jenkins, *The use of the glycemic index in predicting the blood*
470   *glucose response to mixed meals.* Am J Clin Nutr, 1986. **43**(1): p. 167-72.
471 48. Kendzierski, D. and K. DeCarlo, *Physical activity enjoyment scale: two validation*
472   *studies.* J Sport Ex Psych, 1991. **13**: p. 50-64.
473 49. Svensson, E., *Comparison of the Quality of Assessments Using Continuous and*
474   *Discrete Ordinal Rating Scales.* Biom J, 2000. **42**(4): p. 417-434.
475 50. Michie, S., et al., *A refined taxonomy of behaviour change techniques to help people*
476   *change their physical activity and healthy eating behaviours: the CALO-RE*
477   *taxonomy.* Psychol Health, 2011. **26**(11): p. 1479-98.
478 51. Francis, J., et al., *Constructing questionnaires based on the theory of planned*
479   *behaviour: A manual for health services researchers. Newcastle upon Tyne, UK:*
480   *Centre for Health Services Research, University of Newcastle upon Tyne.* 2004.
481 52. Tinkler, L. *Measuring National Well-being: Personal Well-being in the UK, 2014 to*
482   *2015.* 2015; Available from:
483   https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/bulletins/measurin
484   gnationalwellbeing/2015-09-23.
485 53. Tennant, R., et al., *The Warwick-Edinburgh Mental Well-being Scale (WEMWBS):*
486   *development and UK validation.* Health and Quality of Life Outcomes, 2007. **5**(1): p.
487   63.
488 54. Thompson, E.R., *Development and Validation of an Internationally Reliable Short-*
489   *Form of the Positive and Negative Affect Schedule (PANAS).* Journal of Cross-
490   Cultural Psychology, 2007. **38**(2): p. 227-242.
491 55. Schwarzer, R. and B. Renner, *Social-cognitive predictors of health behavior: action*
492   *self-efficacy and coping self-efficacy.* Health Psychol, 2000. **19**(5): p. 487-95.
493 56. Yeung, R.R., *The acute effects of exercise on mood state.* J Psychosom Res, 1996.
494   **40**(2): p. 123-41.
495 57. Faul, F., et al., *G*Power 3: a flexible statistical power analysis program for the social,*
496   *behavioral, and biomedical sciences.* Behav Res Methods, 2007. **39**(2): p. 175-91.

20

497   58.   Cohen, J., *Statistical power analysis for the behavioral sciences*. 2nd ed. 1988,
498   Hillsdale, NJ: Erlbaum.
499

21

Figure captions

Figure 1 Study schedule.

Figure 2 Schematic of experimental protocol.

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          ┌─────────────────────────────┐
          │ Study information distributed│
          │  via networks and social media│
          └─────────────────────────────┘
                        ↓
          ┌─────────────────────────────┐
          │   Expression of interest from│
          │     potential participant    │
          └─────────────────────────────┘
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          │ Potential participant screened│
          │     via phone or email       │
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          │  Informed consent provided   │
          │ prior to or at preliminary visit│
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          │ Participant attends preliminary│
          │            visit             │
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          │        Randomisation         │
          └─────────────────────────────┘
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Participant completes experimental condition 1	Participant completes experimental condition 2
≥6 day washout	≥6 day washout
Participant completes experimental condition 2	Participant completes experimental condition 1

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          ┌─────────────────────────────┐
          │      Trial completion        │
          └─────────────────────────────┘
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          ┌─────────────────────────────┐
          │ Data analysis and dissemination│
          └─────────────────────────────┘
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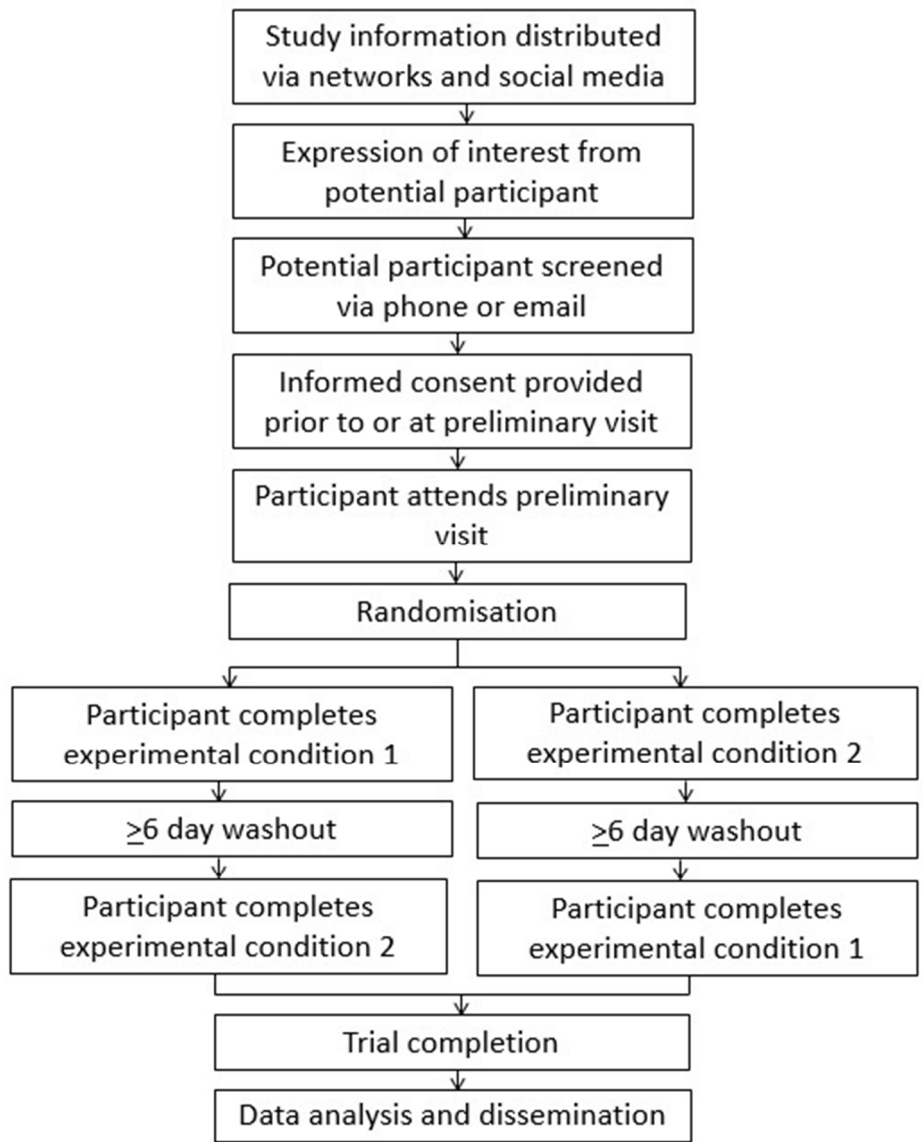
Figure 1 Study schedule.

43x56mm (300 x 300 DPI)
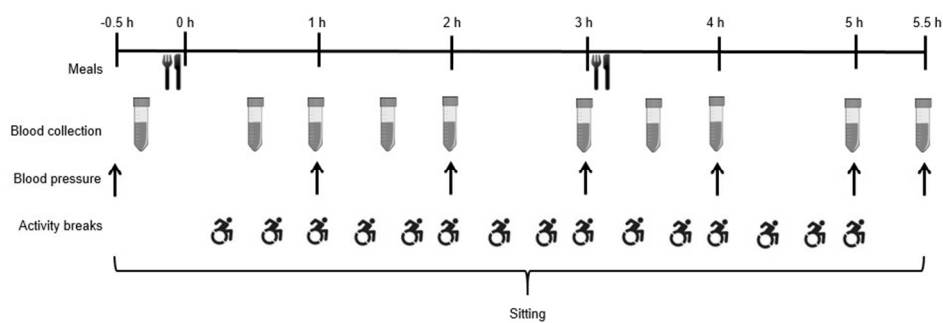
Figure 2 Schematic of experimental protocol.

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

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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_____

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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_____ |

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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_____

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3 Data management   19   Plans for data entry, coding, security, and storage, including any related processes to promote data quality   _____14_____
4   (eg, double data entry; range checks for data values). Reference to where details of data management
5   procedures can be found, if not in the protocol
6
7 Statistical methods   20a   Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the   _____13_____
8   statistical analysis plan can be found, if not in the protocol
9
10   20b   Methods for any additional analyses (eg, subgroup and adjusted analyses)   _____13_____
11
12   20c   Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any
13   statistical methods to handle missing data (eg, multiple imputation)   _____NA_____
14

Methods: Monitoring

Data monitoring   21a   Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of   _____NA_____
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

   21b   Description of any interim analyses and stopping guidelines, including who will have access to these interim   _____NA_____
results and make the final decision to terminate the trial

Harms   22   Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse   _____NA_____
events and other unintended effects of trial interventions or trial conduct

Auditing   23   Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent   _____NA_____
from investigators and the sponsor

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,   _____14_____
analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
regulators)

4

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_____ |

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