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Exercise guidelines to promote cardiometabolic health in spinal cord injured humans: time to raise the intensity?

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1 **Running head:** Exercise intensity in SCI

2

3 **Title:** Exercise guidelines to promote cardiometabolic health in spinal cord injured

4 humans: time to raise the intensity?

5

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26 **Abstract**

27 Spinal cord injury (SCI) is a life changing event that, as a result of paralysis, negatively
28 influences habitual levels of physical activity and hence cardiometabolic health.

29 Performing regular structured exercise therefore appears extremely important in persons
30 with SCI. However, exercise options are mainly limited to the upper-body, which
31 involves a smaller activated muscle mass compared to the mainly leg-based activities
32 commonly performed by non-disabled individuals. Current exercise guidelines for SCI
33 focus predominantly on relative short durations of moderate-intensity aerobic arm
34 cranking exercise, yet contemporary evidence suggests this is not sufficient to induce
35 meaningful improvements in risk factors for the prevention of cardiometabolic disease
36 in this population. As such, these guidelines and their physiological basis, require
37 reappraisal. In this special communication, we propose that high-intensity interval
38 training (HIIT) may be a viable alternative exercise strategy, to promote vigorous-
39 intensity exercise and prevent cardiometabolic disease in persons with SCI.

40 Supplementing the limited data from SCI cohorts with consistent findings from studies
41 in non-disabled populations, we present strong evidence to suggest that HIIT is superior
42 to moderate-intensity aerobic exercise for improving cardiorespiratory fitness, insulin
43 sensitivity and vascular function. The potential application and safety of HIIT in this
44 population is also discussed. We conclude that increasing exercise intensity could offer
45 a simple, readily available, time-efficient solution to improve cardiometabolic health in
46 persons with SCI. We call for high-quality randomised controlled trials to examine the
47 efficacy and safety of HIIT in this population.

48

49 **Key words:** Spinal cord injury, Cardiometabolic health, High-intensity interval
50 training, Vigorous-intensity exercise, Cardiorespiratory fitness

51 **Abbreviations:**

52 CVD- cardiovascular disease,

53 FMD- flow-mediated dilation,

54 HbA1c- glycated haemoglobin,

55 HDL-C- high-density lipoprotein cholesterol

56 HIIT- high-intensity interval training,

57 HRmax- maximum heart rate,

58 LDL-C- low-density lipoprotein cholesterol

59 MICT- moderate-intensity continuous training,

60 OGTT- oral glucose tolerance test,

61 PAG-SCI- physical activity guidelines for people with a spinal cord injury,

62 RPE- rating of perceived exertion,

63 SCI- spinal cord injury,

64 SIT- sprint interval training,

65 T2DM- type-2 diabetes mellitus,

66 $\dot{V}O_{2peak}$ - maximal oxygen uptake.

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76 **1 Introduction**

77

78 Spinal cord injury (SCI) creates a complex pathophysiology, characterised by paralysis,
79 which has wide-ranging implications for multiple body systems. For persons with SCI,
80 chronic cardiometabolic diseases occur at a heightened frequency and earlier in the
81 lifespan compared to non-disabled individuals¹⁻³. Given that more than 2 million people
82 currently live with SCI worldwide and the incidence of SCI is highest among young
83 adults⁴, it is clear that there is an increased and prolonged demand on medical and
84 support resources for persons aging with paralysis. Despite the known, undisputed
85 health benefits of physical activity in non-disabled individuals⁵⁻⁷, research suggests
86 patients with SCI perform little to no physical activity⁸⁻¹¹, and this is likely a key driver
87 of the greater prevalence of cardiometabolic disease in this population^{12,13}. Therefore,
88 it is a priority to develop evidence-based, effective physical activity recommendations
89 for the prevention of chronic disease in persons with SCI.

90

91 The recently re-published Physical Activity Guidelines for Spinal Cord Injury (PAG-
92 SCI) recommends at least 20 minutes of moderate to vigorous-intensity aerobic exercise
93 twice a week (40 min/wk)¹⁴, while a recent position statement from Exercise and Sports
94 Science Australia recommends ≥ 150 min/wk of moderate-intensity or ≥ 60 min/wk of
95 vigorous-intensity exercise¹⁵. Both of these guidelines also include strength training ≥ 2
96 day/wk^{14,15}. Regardless of the large discrepancy between these guidelines in terms of
97 the recommended volume of moderate-intensity exercise, they remain indifferent from
98 the *minimum* amount of exercise which is promoted by reputable, international health
99 authorities [Centers for Disease Control (CDC) and World Health Organisation (WHO)]
100 in order to reduce the risk of developing cardiometabolic disease in the general

101 population. However, it is noteworthy that the exercise guidelines for non-disabled
102 populations are based on lower-body or whole-body activity (e.g. walking, running,
103 cycling), whereas exercise for persons with SCI is primarily restricted to the smaller
104 upper-body skeletal muscles [e.g. arm-crank exercise or wheelchair propulsion]. As a
105 result of the smaller active muscle mass and blunted haemodynamic responses with
106 SCI, the absolute capacity for physical exercise is reduced¹⁶⁻¹⁸. Therefore, at the same
107 relative intensity, the absolute energy expenditure, cardiovascular strain, and whole-
108 body metabolic demand, will always be lower during moderate-intensity arm-crank
109 exercise or wheelchair propulsion compared with moderate-intensity walking or
110 cycling. The ability for skeletal muscle to adapt to the same stimulus will not be
111 reduced; however, the smaller active muscle mass means that modest training-induced
112 adaptations in the arm are less likely to impact biomarkers of cardiometabolic health. As
113 such, to promote a *lower* volume of exercise in this population would seem
114 physiologically counterintuitive, whilst promoting a *similar* volume of exercise would
115 likely be less effective. In accordance with this, a recent randomised controlled trial
116 demonstrated that performing PAG-SCI for 16 weeks was insufficient to promote
117 clinically meaningful changes in both novel and traditional biomarkers of
118 cardiovascular disease (CVD)¹⁹. Moreover, a systematic review requested by the
119 Consortium for Spinal Cord Medicine²⁰ concluded that the current evidence is
120 insufficient to determine whether these volumes of exercise are associated with positive
121 changes in carbohydrate and lipid metabolism (and associated disorders) amongst adults
122 with SCI. Therefore, we contend that these guidelines, and their physiological
123 justification, require reappraisal, and that there is need to develop more effective,
124 alternative approaches.

125

126 There are numerous psychosocial and environmental barriers to engage in physical
127 activity for individuals that use wheelchairs²¹⁻²⁴. Moreover, compromised venous
128 return in persons with SCI blunts cardiac output²⁵, which can lead to an early onset of
129 muscle fatigue²⁶, thus reducing ones capacity for prolonged exercise. Therefore,
130 promoting a *larger* volume of moderate-intensity exercise might not be feasible in this
131 population. Functional electronic stimulation²⁷⁻³⁰ and body weight supported treadmill
132 training³¹, have received considerable research attention, but have numerous practical
133 limitations (i.e. significant cost and specialist resources required), and may have limited
134 application outside the laboratory. One potential alternative approach, which has
135 received less attention, would be to recommend high-intensity interval training (HIIT)
136 as a practical means of increasing vigorous-intensity exercise. The benefit of vigorous-
137 intensity physical activity is supported by a number of epidemiological studies, albeit in
138 non-disabled individuals, demonstrating superior reductions in the risk of
139 cardiovascular^{32, 33} and all-cause mortality³⁴⁻³⁶, in comparison to light-to-moderate
140 intensity physical activity. Moreover, accumulating evidence, from studies applying
141 HIIT in non-disabled populations, demonstrates that HIIT promotes superior peripheral
142³⁷ and whole-body adaptations³⁸⁻⁴⁰, compared with moderate-intensity continuous
143 training (MICT). HIIT may therefore offer a simple, more effective alternative to
144 current approaches for improving cardiometabolic health in persons with SCI. In the
145 following sections we put forward the case for recommending HIIT in SCI, and
146 subsequently consider its potential practical application and safety in this population.

147

148

149

150 **2 High-intensity Interval Training to Facilitate Vigorous-intensity Exercise in**
151 **Spinal Cord Injury**

152

153 HIIT encompasses exercise performed above the intensity which elicits the maximal
154 lactate steady state. Any exercise above this threshold results in the progressive
155 accumulation of intramuscular and systemic metabolites that are implicated in fatigue.
156 As such, exercise intensities above this threshold ($\sim 80\text{-}85\% \dot{V}O_{2\text{peak}}$) cannot be
157 maintained for a prolonged period of time. The exercise must therefore be performed in
158 intervals interspersed with periods of low-intensity or resting recovery. The main
159 justification for HIIT is that it allows a greater volume of vigorous-intensity exercise to
160 be accrued in a single exercise session, and accumulating evidence suggests that this can
161 be of great physiological and clinical benefit³⁸⁻⁴⁰.

162

163 A wide range of HIIT protocols have been utilised in the literature but with limited
164 standardisation of the terminology used to classify different protocols. Furthermore,
165 studies have prescribed exercise intensities as a percentage of different maximal
166 physiological responses [e.g. maximum heart rate (HR_{max} ⁴¹), heart rate reserve⁴², age-
167 predicted max heart rate⁴³ and peak oxygen uptake ($\dot{V}O_{2\text{peak}}$ ⁴⁴)] and, for these reasons,
168 may not be directly comparable, particularly in individuals with low baseline fitness⁴⁵.
169 Nevertheless, for the purposes of this review, we adopt the terminology proposed by
170 Weston *et al.*,³⁸ whereby HIIT describes protocols using intensities between 80-100%
171 of HR_{max} , whereas protocols using ‘all-out’ efforts, or efforts $\geq 100\% \dot{V}O_{2\text{peak}}$, are
172 referred to as sprint interval training (SIT) (Figure 1). There is good evidence that both
173 HIIT and SIT provide equal or even superior physiological adaptations compared with
174 MICT⁴⁶⁻⁵⁰. However, as SIT protocols may be more difficult to adapt in order to

175 provide a practical intervention for persons with SCI, in this review we draw mainly on
176 HIIT studies to support the argument for vigorous-intensity exercise. Example HIIT
177 protocols tested in both the SCI and non-disabled literature are described in Table 1.

178

179 *[INSERT FIGURE 1 ABOUT HERE]*

180

181 *[INSERT TABLE 1 ABOUT HERE]*

182

183

184 **3 Moderate vs Vigorous-intensity Exercise for Cardiometabolic Health**

185

186 **3.1 Cardiorespiratory Fitness and Skeletal Muscle Oxidative Capacity**

187

188 Poor cardiorespiratory fitness has been widely reported in individuals with SCI^{52, 53}.

189 Although just ~90 min/wk^{44, 54} of MICT is sufficient to promote modest improvements

190 (~10%) in $\dot{V}O_{2peak}$, a substantially larger volume (180 min/wk) is necessary for greater

191 improvements (~19%)⁵⁵. Vigorous-intensity exercise offers superior benefits and is

192 more time efficient. Of the two studies which have used time-matched training

193 protocols in SCI (Table 2) there are negligible (12% vs. 10%)⁴² and considerable (50%

194 vs. 17%)⁵⁶ improvements in $\dot{V}O_{2peak}$ with vigorous-intensity compared to moderate-

195 intensity exercise, respectively. The larger improvement in the De Groot *et al*,⁵⁶ study

196 could be due to participants having acute (< 225 days) injuries or the greater volume of

197 accumulated vigorous-intensity activity (additional 48 min/wk). More recently,

198 unpublished data from Sæter⁵⁷, which adopted a more robust isocaloric study design,

199 demonstrated a superior stimulus for $\dot{V}O_{2peak}$ and PPO with vigorous-intensity exercise

200 compared to MICT. Furthermore, a case-study demonstrated a 52% increase in $\dot{V}O_{2\text{peak}}$
201 in a 42 year old man with SCI following just 6 weeks of HIIT⁵⁸.

202

203 Several studies have directly compared the effects of energy-matched HIIT and MICT
204 on $\dot{V}O_{2\text{peak}}$ in deconditioned (non-disabled) individuals with pre-existing
205 cardiometabolic disease and these have clearly demonstrated that HIIT results in
206 superior improvements. These studies were summarised in a recent meta-analysis
207 which, using data from 10 studies and 273 participants, showed that the increase in
208 $\dot{V}O_{2\text{peak}}$ following HIIT was approximately twice (~3 ml/kg/min) that observed
209 following MICT³⁸. This finding has been reproduced in various non-disabled
210 populations including healthy young and middle-aged sedentary men^{59,60}, overweight
211 and obese men and women⁶¹, and in individuals with type-2 diabetes mellitus (T2DM)
212⁶². A 3 ml/kg/min improvement in cardiorespiratory fitness is associated with a 15% and
213 19% reduction in all-cause and CVD mortality, respectively, and is on par with a 7 cm
214 reduction in waist circumference, a 5 mmHg reduction in systolic blood pressure, or a 1
215 mmol/L drop in fasting plasma glucose^{63,64}. Given that cardiorespiratory fitness
216 consistently manifests as the strongest predictor of cardiometabolic disease risk and
217 longevity in epidemiological studies⁶⁵⁻⁶⁸, these findings are an important point of
218 reference in the argument for applying HIIT, as a model to increase vigorous-intensity
219 physical activity, in individuals with SCI.

220

221 Although still a subject of debate⁶⁹⁻⁷¹, recent evidence supports, at least partially, the
222 role of peripheral muscle characteristics, in particular absolute mitochondrial capacity
223 (i.e. maximal mitochondrial oxygen utilization), in limiting $\dot{V}O_{2\text{peak}}$, and hence
224 underpinning changes in $\dot{V}O_{2\text{peak}}$ with exercise training^{72,73}. It is noteworthy then that a

225 recent study convincingly demonstrated that cycling based HIIT induced superior
226 mitochondrial adaptations compared with MICT, in muscle taken from the lower limb
227 ³⁷. Arm exercise training may not be sufficient to induce central hemodynamic
228 adaptations ⁷⁴, but can be expected to induce peripheral mitochondrial adaptations.
229 Thus, if the superior effects observed with HIIT compared with moderate-intensity
230 cycling and walking/running in non-disabled individuals are translatable to arm exercise
231 training in persons with SCI, then HIIT may provide a more effective intervention for
232 improving $\dot{V}O_{2peak}$ in persons with SCI. Moreover, the superior changes in
233 mitochondrial oxidative capacity with HIIT may have implications for other
234 cardiometabolic risk factors such as insulin sensitivity and glycaemic control ⁷⁵.

235

236 *[INSERT TABLE 2 ABOUT HERE]*

237

238

239 **3.2 Insulin Action and Glycaemic Control**

240

241 Insulin resistance is a pre-requisite to T2DM. It is characterised by the failure of insulin
242 to exert the normal cellular effects on various tissues, leading to the impairment of
243 insulin mediated glucose disposal. Fasting hyperglycaemia can persist due to the
244 insensitivity of the liver to the suppressive effects of insulin on gluconeogenesis and
245 reduced glycogenolysis ⁷⁶. Consequently fasting plasma glucose concentrations have
246 been shown to correlate with basal rates of hepatic glucose output ⁷⁷. Therefore, as
247 fasting plasma glucose concentrations tend to be only mildly elevated in individuals
248 with SCI ⁷⁸, it is most likely that peripheral insulin resistance is the major driver behind
249 impaired glycaemic control in this population. The lack of stimulation and disuse
250 because of paralysis can have a profound impact on skeletal muscle below the level of

251 injury, including i) atrophy of lean mass⁷⁹⁻⁸², which diminishes the tissue available for
252 glucose disposal (Figure 2a)^{83, 84}, and ii) accumulation of intramuscular fat^{85, 86}.

253

254 *[INSERT FIGURE 2 ABOUT HERE]*

255

256 Recent publications have demonstrated that moderate-intensity arm-crank ergometry
257 improves insulin resistance, as determined by HOMA-IR^{87, 88}. Although this is
258 promising, HOMA-IR reflects hepatic insulin sensitivity, whereas indices derived
259 during postprandial oral glucose tolerance tests (OGTT), such as the ISI_{matsuda} , represent
260 predominantly peripheral insulin sensitivity^{89, 90}. Data from the HOMEX-SCI trial,
261 including both fasting and provocative dynamic testing, would suggest arm-crank MICT
262 (60 – 65% $\dot{V}O_{2\text{peak}}$, 180 min/wk) in persons with chronic paraplegia improves hepatic
263 but not whole-body insulin sensitivity⁵⁵. Therefore, moderate-intensity arm-crank
264 exercise might not be sufficient to overcome insulin resistance in peripheral tissues.
265 There is a paucity of research comparing both fasting and dynamic glucose and insulin
266 responses to HIIT or MICT in the context of arm-crank exercise in the SCI population.
267 Insulin sensitivity data from De Groot *et al*⁵⁶ is counter-intuitive, in that it demonstrates
268 non-significant improvements in the moderate-intensity group and reduced insulin
269 sensitivity in the high-intensity group. This may be explained by a natural regression to
270 the mean effect (i.e. greater proportion of insulin resistant individuals in the low-
271 intensity group at baseline). These results should be viewed with caution due to the, (i)
272 small sample size (n=3 per group) and, (ii) the marked age and sex differences between
273 the two groups, which could impact exercise responses.

274

275 The impact of HIIT on insulin action and glycaemic control in non-disabled populations
276 has recently been summarised by Jelleyman *et al*,⁴⁰ in a meta-analysis of 50 training
277 studies. Their analyses demonstrated that HIIT was associated with improved insulin
278 sensitivity (estimated via fasting or OGTT-derived indices) and reduced fasting glucose
279 when compared to both baseline and/or changes in a no-exercise control group⁴⁰. The
280 magnitude of change appeared to be greater in populations with insulin resistance (e.g.
281 T2DM or metabolic syndrome) with reductions in glycated haemoglobin (HbA1c) also
282 observed in this group⁴⁰. When compared with MICT there appeared to be greater
283 improvements in markers of insulin sensitivity with HIIT (both fasting and dynamic
284 combined), but no difference in the change in fasting glucose, insulin or HbA1c in
285 isolation⁴⁰. These differences were apparent despite the fact that the methods varied
286 considerably between studies. This included variations in the HIIT protocols utilised
287 (e.g. SIT vs HIIT, cycling vs running), the techniques used to assess insulin sensitivity
288 (e.g. fasting vs OGTT vs clamp) and the duration after the final training session in
289 which the insulin sensitivity data was captured. Moreover, studies had been performed
290 in a wide variety of populations. As such, there is sufficient evidence that in non-
291 disabled populations with insulin resistance HIIT is associated with superior changes in
292 markers of insulin sensitivity compared to MICT^{62, 91-95}.

293

294 It is also important to consider the acute effects of MICT and HIIT on glycaemic
295 control, although this has received less research attention, especially in SCI individuals.
296 Two studies have examined the acute effects of HIIT vs MICT on glycaemic control,
297 using continuous glucose monitors to capture 24-hour glucose profiles, and have shown
298 superior effects with HIIT in both obese men⁹⁶ and individuals with T2DM⁹⁷. These
299 effects are underpinned by a plausible mechanism given that high-intensity exercise is

300 associated with greater muscle glycogen utilisation⁹⁸ and muscle glycogen
301 concentrations are an important driver of acute changes in insulin sensitivity with
302 exercise⁹⁹⁻¹⁰¹. Clearly, the acute effects of exercise, as well as comparisons of HIIT and
303 MICT, on glycaemic control in SCI individuals, is an important area of future research.

304

305

306 **3.3 Vascular Function and Blood Pressure**

307

308 Arterial stiffness¹⁰² and endothelial function^{103, 104} are important predictors of future
309 cardiovascular health. Individuals with SCI are characterised by severe deterioration of
310 structure and function of vessels below the level of injury¹⁰⁵, but evidence also suggests
311 increased stiffness and impaired endothelial function within central and regional upper
312 body arteries in SCI relative to non-disabled controls¹⁰⁶. Recent evidence suggests that
313 achieving the PAG-SCI for 16-weeks is insufficient to improve the health of both lower
314 and upper-limb, as well as central blood vessels¹⁹.

315

316 A recent meta-analysis, including 182 participants from 7 studies, demonstrated that
317 HIIT was superior to MICT for improving markers of endothelial function³⁹. Within
318 the meta-analysis, studies that had utilised a work-matched HIIT protocol, consisting of
319 4 x 4 min at 85-90% HR_{max}, appeared to show the most consistent benefit of HIIT over
320 and above improvements observed with MICT^{61, 91, 107, 108}. A 1% increase in FMD
321 (flow-mediated dilation) is associated with a 13% reduction in the risk of cardiovascular
322 events¹⁰³. Therefore the 2.6% magnitude of difference in the change in FMD observed
323 between HIIT and MICT in this meta-analysis would be expected to result in clinically
324 meaningful risk reduction³⁹.

325 Individuals with lower-level spinal cord lesions experience similar hypertension issues
326 as the general population ¹⁰⁹, whereas individuals with higher-level lesions (\geq T6) often
327 suffer from hypotension ¹¹⁰. A direct comparison of moderate and high-intensity
328 exercise training on blood pressure is not available in SCI. However, in non-disabled
329 individuals, evidence suggests that several months of HIIT or MICT are able to induce
330 comparable changes in both systolic and diastolic blood pressure in a variety of
331 populations ^{60, 61, 91, 111}.

332

333

334 **3.4 Body Composition**

335

336 Individuals with SCI demonstrate a greater propensity to accumulate excess body fat
337 compared to non-disabled populations ^{112, 113}. Furthermore, due to the accelerated loss
338 of lean mass, the distribution of adipose tissue in SCI also appears to be altered ¹¹⁴,
339 which would be expected to exert detrimental metabolic effects ¹¹⁵⁻¹¹⁸. It is therefore
340 important to consider the role physical activity plays in maintaining body composition
341 and the potential contribution towards a sustained energy deficit to reduce adiposity.
342 Yet, large additions to weekly total energy expenditure (TEE) through structured
343 exercise (i.e. on top of baseline physical activity) are required to induce meaningful
344 reductions in body fat ¹¹⁹. For example, Donnelly *et al.*, ¹²⁰ suggested that a meaningful
345 body mass reduction requires an exercise energy expenditure in excess of 2000 kcal/wk.
346 If we extrapolate from exercise data for inactive SCI participants in the HOMEX-SCI
347 trial ⁵⁵, achieving this would require approximately 448 min/wk of moderate-intensity
348 arm-crank exercise. Therefore, it is perhaps not surprising that following PAG-SCI for

349 16 weeks does not induce significant reductions in total and visceral fat mass, although
350 it may be sufficient to reduce the rate of increase in adiposity¹⁹.

351

352 There is good evidence from non-disabled studies that HIIT can be an effective
353 intervention for promoting positive changes in body composition, including reductions
354 in total body mass^{59, 91, 121-123}, total fat percentage¹²²⁻¹²⁵, total abdominal fat mass<sup>91, 122-
355 124</sup> and waist circumference^{91, 122, 126}. However, perhaps as expected, studies that have
356 compared energy-matched HIIT and MICT interventions (i.e. both interventions would
357 increase TEE to a similar extent) over several months have demonstrated comparable
358 changes in body composition^{61, 91, 121}. Interestingly, it also appears that HIIT protocols
359 requiring lower exercise volumes (e.g. low-volume HIT or SIT) are associated with
360 similar increases in total 24-hour energy expenditure to 30-50 min of MICT^{127, 128} and
361 can also induce meaningful reductions in total and abdominal fat^{124, 129}, which are
362 comparable to 30-45 min of MICT in overweight/obese individuals¹²³. Increases in leg
363 lean mass have also been observed with cycling based HIIT^{122, 124}, and this has the
364 potential to also translate to the upper-body musculature in patients with SCI. While
365 HIIT does not appear to induce a greater reduction in adiposity than MICT, the
366 reviewed evidence would suggest it is equally as effective, but with a reduction in
367 exercise time commitment.

368

369

370 **3.5 Fasting and Postprandial Dyslipidaemia**

371

372 A recent meta-analysis¹³⁰ highlighted that persons with SCI have a unique lipid profile,
373 primarily characterised by depressed high-density lipoprotein cholesterol (HDL-C).
374 Hooker & Wells⁴² showed a trend for increased (21%) HDL-C and reduced (-15%)

375 low-density lipoprotein cholesterol (LDL-C) with vigorous but not moderate-intensity
376 exercise over 8 weeks. Other trials specifically in persons with SCI demonstrated no
377 impact of exercise-intensity on lipid profiles. Greater or similar improvements in HDL-
378 C with HIIT compared to MICT have been shown in populations with cardiometabolic
379 disease³⁸ and obese young men¹³¹, respectively. Currently the non-disabled literature is
380 unclear as to whether HIIT offers superior adaptations than MICT for lipid profiles³⁹
381¹³². However, over 24 weeks O'Donovan *et al*,¹³³ demonstrated high-intensity exercise
382 was more effective in improving lipid profiles than MICT of equal energy cost. It is
383 possible interventions of longer durations are required to determine the true-impact of
384 exercise intensity on lipid profiles.

385

386 The two studies which have used time-matched training protocols in SCI demonstrated
387 a decrease in fasting triglyceride concentrations (-19%⁴² and -31%⁵⁶) pre-post with
388 vigorous-intensity exercise, but no change with moderate-intensity exercise training.
389 Elevated fasting triglyceride concentrations have long been associated with CVD^{134, 135}.
390 Despite observing unremarkable concentrations of fasting triglycerides, participants
391 with chronic paraplegia have shown exaggerated postprandial lipaemia^{136, 137}. This
392 exaggerated postprandial lipaemia is an important stimulus for the development of
393 atherosclerosis¹³⁸, and non-fasting triglyceride concentrations has revealed a stronger
394 association with CVD than fasting¹³⁹. As a result of a more sedentary lifestyle, reduced
395 lipoprotein lipase slows postprandial triglyceride extraction from the systemic
396 circulation and the atrophy of leg lean mass limits the ability to metabolise postprandial
397 triglycerides as a fuel source¹⁴⁰. To our knowledge, no studies have been conducted
398 looking at the impact of upper-body exercise on postprandial lipaemia in persons with
399 SCI. However, several studies have examined the effect of an acute bout of HIIT on the

400 postprandial triglyceride response to a high-fat mixed meal in able-bodied individuals.
401 These were summarised in a systematic review which concluded that an acute bout of
402 HIIT is similarly effective to MICT for reducing postprandial lipaemia ¹⁴¹.

403

404

405 **4 Cardiovascular Safety of HIIT**

406

407 Concerns have been raised over the safety of HIIT in populations at risk of
408 cardiometabolic disease and this should be specifically considered with reference to
409 SCI. Evidence from one recent non-disabled study, which included 5000 patients
410 undergoing supervised cardiovascular rehabilitation over a 7-year period, suggested that
411 the rate of adverse cardiovascular events was low with both HIIT and MICT, although
412 the event rate was higher with HIIT ¹²⁶. Specifically, the study reported an adverse
413 cardiovascular event rate of 1 per ~23,000 exercise hours during HIIT (2 non-fatal
414 cardiac arrests) compared with 1 per 129,000 exercise hours during MICT (1 fatal
415 cardiac arrest) ¹²⁶. However, various HIIT protocols have been used safely in patients
416 with post infarction heart failure ^{142, 143}, diastolic dysfunction ¹⁴⁴, coronary artery disease
417 ¹⁴⁵ and atrial fibrillation ¹⁴⁶, while also improving clinical symptoms. A systematic
418 review of laboratory/hospital based exercise training studies in persons with SCI found
419 that adverse events were not common and those that occurred were not serious ¹⁴⁷. It
420 should be noted that the individuals in this review and within the studies mentioned
421 above were subject to extensive screening, and the cardiovascular safety of HIIT in this
422 population therefore requires further scientific appraisal. However, when appropriate
423 pre-participation screening is adopted the risks of adverse events are relatively low and
424 as previously suggested are '*likely comparable with the variant risks observed in the*
425 *general population*' ¹⁴⁸. SCI-specific special considerations for exercise, including the

426 management of autonomic dysreflexia, have been thoroughly addressed elsewhere¹⁵,
427 ¹⁴⁹. It is noteworthy that patients with SCI are usually well-educated regarding the
428 symptoms and management of autonomic dysreflexia and there is no reason to speculate
429 that the occurrence of this will be increased with HIIT. As with any exercise
430 prescription, it would be recommended that individuals consult their clinician prior to
431 engaging in such exercise training programmes.

432

433

434 **5 Considerations for the application of HIIT to SCI populations**

435

436 Individuals with SCI \geq T6 exhibit a blunted cardiovascular response due to an absence
437 of cardiac sympathetic innervation¹⁵⁰ and a reduced catecholamine response during
438 exercise¹⁵¹. As a result of autonomic dysregulation, HR_{peak} can be as low as 120 b/min.
439 Consequently in these individuals it would be difficult to prescribe an appropriate
440 exercise intensity using heart rate data. Evidence suggests that ratings of perceived
441 exertion (RPE)¹⁵² and a talk test¹⁵³ can be effectively used to control exercise intensity
442 in persons with paraplegia. Consequently we advise an RPE \geq 16 and ‘speaking is not
443 comfortable’ as appropriate markers of ‘vigorous-intensity’ when performing upper-
444 body exercise.

445

446 The advantage of HIIT is that it enables deconditioned individuals to do a substantial
447 amount of work at a relatively high-intensity by incorporating rest periods, which
448 reduce local muscular fatigue. Fatigue following an acute 20 minute bout of HIIT in
449 patients with chronic fatigue syndrome was not clinically different to moderate-intensity
450 continuous exercise of a comparable workload¹⁵⁴. Sensory impairment below the level

451 of injury can increase the risk of pressure sores when performing new activities for
452 prolonged periods in the same position. Consequently as HIIT can be more time
453 efficient and incorporates rest periods (ideal for performing regular pressure release)
454 this could mitigate this risk and prevent skin breakdown.

455

456 Due to a reduced sweating capacity and inability to dilate superficial vasculature ¹⁵⁵,
457 persons with higher-level injuries have an impaired heat loss during exercise ¹⁵⁶. While
458 workload is increased with HIIT, possibly resulting in greater heat production, the total
459 exercise time is less than MICT with recovery periods interspersed throughout.

460 Therefore we have no reason to believe that HIIT would impact core body temperature
461 more than MICT. Still precautions should be taken when persons with SCI exercise in
462 hot environments, as they have impaired thermoregulatory function ¹⁵⁷. Furthermore, to
463 overcome blood pooling in lower extremities, associated with impaired venous return,
464 an adequate cool down should be performed to prevent post-exercise hypotension.

465 Shoulder overuse injuries and musculoskeletal pain are also common in persons with
466 SCI ^{158, 159}. While the higher workloads necessary to achieve vigorous-intensity might
467 further contribute to these conditions, exercise has been proposed as a feasible,
468 conservative, therapeutic treatment for shoulder pain in persons with SCI ¹⁶⁰.

469

470 Discussions regarding behaviour change and/or maintenance are outside the scope of
471 this review. However, preliminary evidence would suggest that individuals with pre-
472 diabetic conditions can adhere to HIIT over the short-term (4 weeks) and do so at a
473 greater level than MICT ^{123, 161}. Questions have been raised regarding the adherence to
474 HIIT over the long-term ^{162, 163} but we encourage researchers and practitioners to
475 develop and evaluate strategies to incorporate HIIT into the everyday lives of persons

476 with SCI. We believe this is possible considering the evidence that non-disabled
477 participants enjoyed HIIT more and were equally as confident to engage in HIIT as they
478 were MICT¹⁶⁴. Reassuringly, unpublished data has also demonstrated persons with SCI
479 experienced greater enjoyment with HIIT and SIT protocols compared to MICT¹⁶⁵.
480 However, medical over protection may limit the prescription of vigorous-intensity
481 exercise rehabilitation in this population. To help overcome this, the safety and efficacy
482 of HIIT, particularly for persons with acute (<1 year) and higher level (\geq T6) SCI would
483 need to be demonstrated by well-controlled longitudinal training studies. This is
484 imperative when vigorous-intensity exercise has the potential to offer significantly
485 greater improvements in certain cardiometabolic outcomes than MICT in a population
486 at increased risk of chronic disease.

487

488

489 **6 Conclusions**

490

491 This special communication presents a case for the utility of HIIT as a strategy to
492 promote vigorous-intensity physical activity and reduce cardiometabolic disease in
493 persons with SCI. Data from SCI cohort studies, albeit collected using suboptimal
494 research designs, seem to agree with consistent findings from studies in the general
495 population that vigorous-intensity is superior to moderate-intensity exercise in
496 improving a variety of cardiometabolic health outcomes. Importantly, these findings can
497 be explained and supported by plausible physiological mechanisms. High-intensity
498 virtual reality arm-exercise is already being investigated in persons with SCI¹⁶⁶ and the
499 National Centre on Health, Physical Activity & Disability (NCHPAD) promote a
500 selection of adapted vigorous-intensity exercise options (e.g. wheelchair burpees).

501 Increasing exercise-intensity could offer a simple, readily available, time-efficient
502 solution to improve cardiometabolic health in persons with SCI. However, until stronger
503 evidence has been collated concerning the safety and efficacy of HIIT in this population
504 this is merely a call to action for researchers in the field and not necessarily an exercise
505 guideline to be prescribed by clinicians.

ACCEPTED MANUSCRIPT

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Table 1 High-intensity interval training (HIIT) protocols used in non-disabled and SCI research studies.

Table 2: Description of exercise training studies that have compared the impact of exercise intensity on cardiometabolic health markers in persons with SCI.

Figure 1: Schematic of sprint-interval training (SIT), high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) protocols (Adapted from Gibala *et al.*,⁵¹ with permission).

Figure 2: Whole body Dual-energy X-ray absorptiometry (DEXA) scan of a female with neurological complete T7 injury sustained 6 years previously (a) and non-disabled female for comparative purposes (b). This figure visually highlights the drastic atrophy of lean mass and accumulation of intramuscular fat in the lower extremities of individuals with SCI.

Table 1

Authors	Exercise Intervals			Recovery Intervals		Total Session Time
	Number	Intensity	Duration	Intensity	Duration	
Little <i>et al.</i> , ¹⁶⁷ N-D Harnish <i>et al.</i> , ⁵⁸ SCI	10	90-110% Wmax ≥85% HRmax RPE ≥19	1-min	20-25% Wmax	1-2 min	~25 min
Tjønnna <i>et al.</i> , ⁹¹ N-D Sæter ^{57 †} SCI	4	~85% Wmax 85-95% HRmax RPE ≥17	2.5-4 min	20-25% Wmax	3-5 min	~30 min
MacInnis <i>et al.</i> , ³⁷ N-D Harnish <i>et al.</i> , ⁵⁸ SCI	3	~70% Wmax 80-85% HRmax RPE ≥ 16	4-5 min	20-25% Wmax	3-5 min	~30 min

Table 1 Legend: *HRmax* maximum heart rate, *N-D* non-disabled, *RPE* ratings of perceived exertion, *SCI* spinal cord injury, *Wmax peak power output (Watts)*, achieved during an incremental test to fatigue

Suggested frequency for training interventions is 3 sessions/week. Low-intensity warm-up and extended cool-down are not included in the table, but should be incorporated into any applied protocol to optimise circulation and prevent post-exercise hypotension (Evans *et al.*,¹⁴). We have suggested appropriate RPE values so that these protocols can be followed in patients with blunted cardiovascular responses to exercise (spinal cord injury lesions ≥T6). There is scope for variation in the above HIIT protocols, as the frequency, intensity and the duration of the high-intensity intervals, as well as the characteristics and duration of the recovery periods, may all be manipulated to change the nature of the exercise stimulus and thus potentially the physiological adaptations associated with training^{168, 169}

† Unpublished data

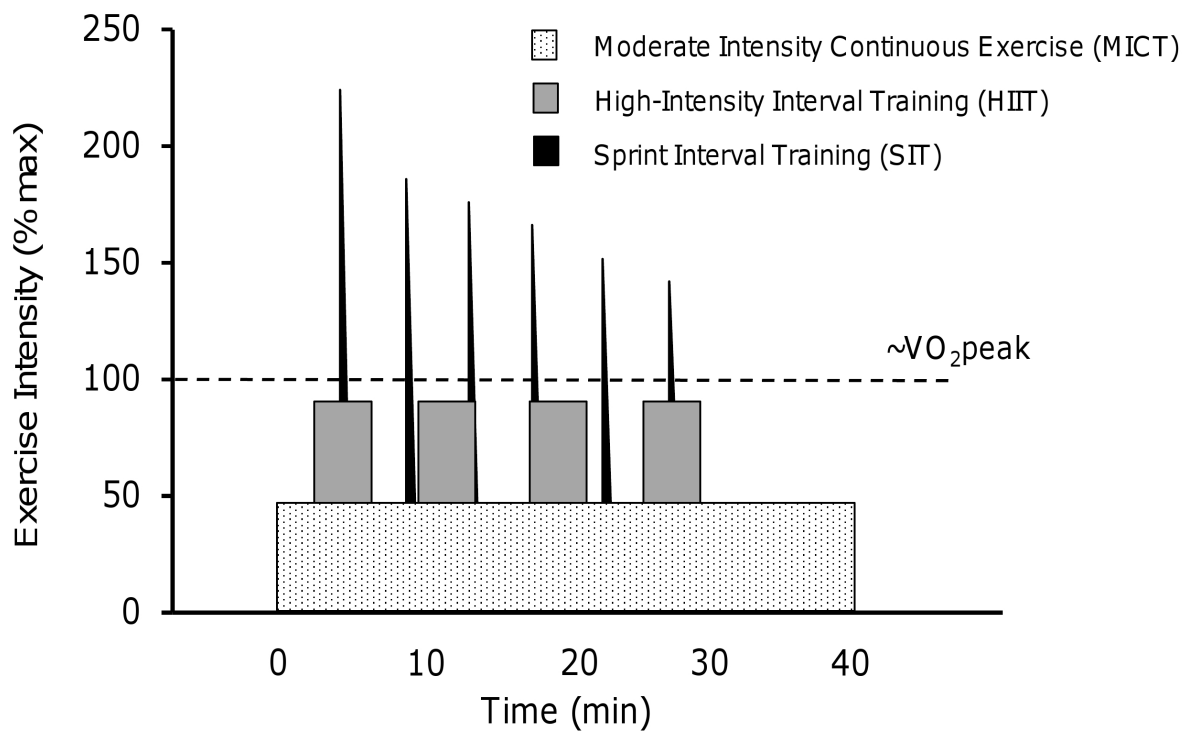
Table 2

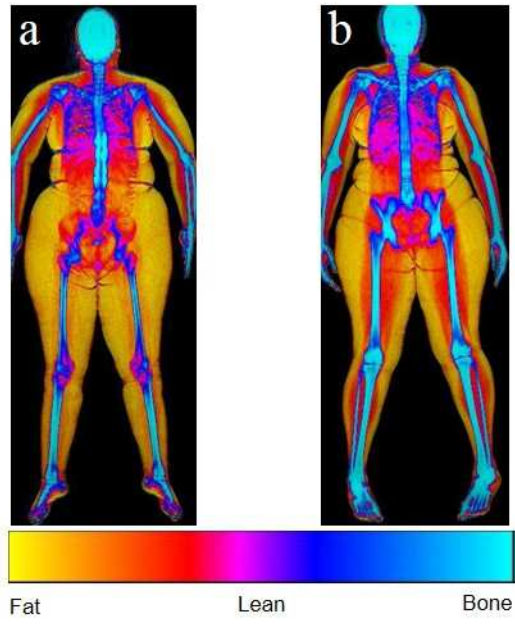
Authors	Study Design	Participant Characteristics	Intervention	Outcome Measures		
				Change	No Change	
Hooker & Wells ^{42*}	Pre-post parallel group WERG INT	6 (3F), 5 PARA, 1 TETRA, TSI; 4 mo - 19 yr Age; 26 - 36 yr	Frequency: 3 x wk Time: 20 min continuous Duration: 8 wks	Moderate-intensity (50 - 60% HRR)	↑ $\dot{V}O_2$ peak (10%), ↑ PPO (24%)	TC, TAG, LDL-C, HDL-C
		5 (2F), 3 PARA, 2 TETRA, TSI; 2 - 19 yr Age; 23 - 36 yr		High-intensity (70 - 80% HRR)	↑ $\dot{V}O_2$ peak (12%), ↑ PPO (13%) ↓ TAG (96 ± 28 to 78 ± 18 mg/dL; P ≤ 0.10), ↑ HDL-C (39 ± 11 to 47 ± 8 mg/dL; P ≤ 0.10), ↓ LDL-C (137 ± 26 to 116 ± 5 mg/dL; P ≤ 0.10)	TC
De groot <i>et al.</i> ^{56*}	Pre-post parallel group ACE INT	3 (2F), All PARA TSI; 61 - 225 days Age; 50 - 54 yr	Frequency: 3 x wk, Time: 60 min (3 & 2 minute work and rest intervals, respectively. Accumulated activity = 36 minutes) Duration: 8 wks	Moderate-intensity (40 - 50% HRR)	↑ $\dot{V}O_2$ peak (17%), ↑ PPO (24%)	TC, HDL-C, LDL-C, TAG. Non-significant improvement in IS (56%, measured via HOMA-CIGMA)
		3, 2 PARA, 1 TETRA TSI; 43 - 175 days Age; 20 - 38 yrs		High-intensity (70 - 80% HRR)	↑ $\dot{V}O_2$ peak (50%), ↑ PPO (59%) ↓ TAG (-31%), ↓ IS (-33%, measured via HOMA-CIGMA)	TC, HDL-C, LDL-C
Sæter ^{57†}	Pre-post parallel group ACE INT	5, All PARA TSI; 15 ± 11 yrs Age; 43 ± 14 yrs	Frequency: 3 x wk Time: ~ 49 min (373 kcal) Duration: 8 wks Moderate-intensity: 70% peak HR			$\dot{V}O_2$ peak, PPO, TC, HDL-C, LDL-C, TAG, glucose
		5, All PARA (1F) TSI; 15 ± 14 yrs Age; 46 ± 6 yrs	Frequency: 3 x wk Time: 28 min (including 12 min active recovery) Duration: 8 wks High-intensity: 85 - 95% peak HR (4 x 4 min intervals)		↑ $\dot{V}O_2$ peak (9%, trend for an interaction effect between groups, P = 0.051), ↑ PPO (28%)	TC, HDL-C, LDL-C, TAG, glucose

Table 1 Legend: *ACE* arm crank exercise, *HDL-C* high density lipoprotein cholesterol, *HR* heart rate, *HRR* heart rate reserve, *INT* intervention, *IS* insulin sensitivity, *LDL-C* low-density lipoprotein cholesterol, *PARA* paraplegic, *PPO* peak power output, *TAG* triglyceride, *TC* total cholesterol, *TETRA* tetraplegic, *TSI* time since injury, $\dot{V}O_2$ *peak* peak oxygen uptake, *WC* waist circumference, *WERG* wheelchair ergometry.

* Note, authors refer to 70-80% HRR between studies as moderate⁴² and high-intensity⁵⁶, respectively. The terminology to describe exercise-intensity has been reclassified into moderate (40-60% HRR) and high-intensity (70-80% HRR).

† Unpublished data





ACCEPTED MANUSCRIPT

Warm Up (10 minutes)

ACCEPTED MANUSCRIPT

Cardiovascular exercises (moving around independently in multi-directions)

- Marching with arm swings
- Walking backwards with knees straight
- Walking with leg curls
- Jogging
- Skipping
- Walking in slow motion (stepping with a one second pause before heel strike)
- Walking with longer strides
- Walking on heels
- Walking on toes

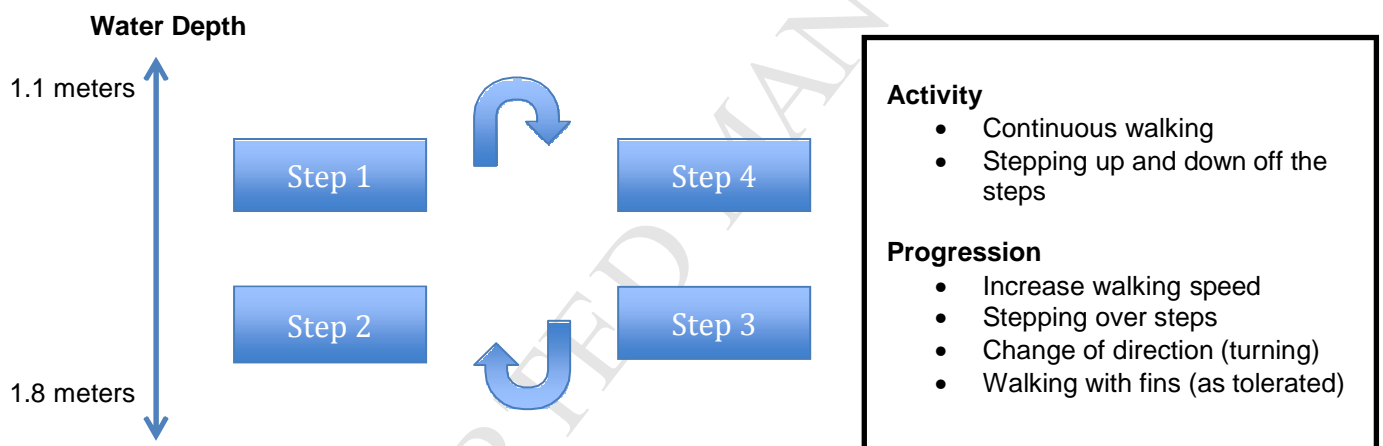
Upper body stretches

- Cervical rotation and side flexion (2 reps x 10 second hold bilaterally)
- Shoulder raises (2 reps x 5 second hold)
- Shoulder rolls (10 reps bilaterally)

Trunk stretches (with aqua noodle)

- Trunk rotation with arms abducted and externally rotated holding the aqua noodle (5 reps bilaterally)
- Arm raises reaching both arms overhead holding the noodle (5 reps bilaterally)
- Side bends pressing the aqua noodle into the water (5 reps x 5 second hold bilaterally)

Gait re-education (20 minutes)



Strength exercises (10 minutes)

(2 minutes per exercise; 3 exercises selected per class with as many repetitions carried out as possible within the time)

Circuits

- Sit to stand (using pool chair)
- Step ups (progression: raising arms up and down holding the aqua noodle)
- Side step ups
- Trunk rotation (performed standing back to back with a partner, passing ball x 10 reps bilaterally)
- Squats with aqua noodle
- Lunges

Group

- Single leg stand (light finger hold at baseline progressed to 10 seconds with no hand support by session 12)
- Calf raises (10 reps at baseline progressed to 2 sets x 15 reps by session 12)
- Single leg calf raises (5 reps at baseline progressed to 15 reps by session 12)
- Push downs with aqua noodle (15 reps at baseline progressed to 30 reps by session 12)

Cool Down (5 minutes)

(Performed standing by pool wall at water depth level T8 (8th thoracic vertebrae), 30 second hold x 3 reps)

- Quadriceps, hamstring and calf stretches performed using aqua noodle