

**Heterogeneity and incidence of non-response for changes in cardiorespiratory fitness
following time-efficient sprint interval exercise training**

Richard S. Metcalfe^{1*} & Niels B.J. Vollaard²

¹ Applied Sports Science Technology and Medicine Research Centre (A-STEM), Swansea
University, Swansea, SA1 8EN, UK. Email: r.s.metcalfe@swansea.ac.uk

² Faculty of Health Sciences and Sport, University of Stirling, Stirling, FK9 4LA, UK. Email:
n.vollaard@stir.ac.uk

*** Corresponding Author:**

Dr Richard S Metcalfe

Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre

College of Engineering

Swansea University

Swansea

Wales, UK

SA1 8EN

Email: r.s.metcalfe@swansea.ac.uk

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34 **Abstract**

35 Interindividual variability for training-induced changes in maximal oxygen uptake (VO_2max)
36 has been well described in response to continuous aerobic and high-intensity interval exercise.
37 However, whether similar variability is observed following time-efficient sprint interval
38 training (SIT) protocols with a minimal total training volume (i.e. reduced-exertion high-
39 intensity interval training; REHIT) is not known. We conducted a pooled analysis of $n=117$
40 (68 men) training participants (mean \pm SD: age: 30 ± 10 y; VO_2max : 34.8 ± 7.5 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$),
41 who completed a VO_2max assessment before and 3 days after 6 weeks of REHIT comprising
42 of two 10-20 second ‘all-out’ cycling sprints per session, and $n=40$ no-intervention control
43 participants (age: 30 ± 13 y; VO_2max : 31.5 ± 6.5 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) who completed repeated
44 VO_2max tests over a comparable time frame. Individual responses estimated using 50%
45 confidence intervals derived from the technical error were interpreted against a smallest
46 worthwhile change (SWC) of 1.75 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The standard deviation of individual
47 responses (SD_{IR}) was 2.39 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (Cohens $d=0.32$, i.e. ‘moderate’) demonstrating
48 clinically meaningful interindividual differences in training-induced changes in VO_2max
49 following REHIT that exceed the technical, biological and random within-subjects variability
50 of VO_2max assessment. The likely (75% probability) non-response rate was 18% (21/117), and
51 49% (57/117) of individuals demonstrated an increase in VO_2max likely higher than the SWC.
52 We conclude that the well-described increase in VO_2max observed following REHIT at the
53 group level is subject to substantial variability in magnitude at an individual level. This has
54 important implications for exercise prescription and can be harnessed by future studies aiming
55 to elucidate mechanisms of adaptation.

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57 **Keywords:** Aerobic Capacity; High-Intensity Interval Training; Sprint Interval Training;
58 Individual Responses; Individual Variability; Cardiorespiratory Fitness

59 **1. Introduction**

60 The maximal attainable rate of oxygen uptake (VO_2max) is amongst the most important
61 physiological traits that determine long term health and longevity. Indeed, a low VO_2max
62 predicts cardiovascular and all-cause mortality to a similar or greater extent compared with
63 other established risk factors, including body mass index, smoking, hypertension and type 2
64 diabetes (Ross et al., 2016). Although VO_2max is a partly heritable trait (Bouchard et al., 1998),
65 it can also be improved (on average) through regular exercise training (Bouchard et al., 1999;
66 Sisson et al., 2009), and those who are able to improve their VO_2max over several years lower
67 their risk of cardiovascular and all-cause mortality in a dose-dependent manner (Lee et al.,
68 2011).

69 Whilst VO_2max improves on average in response to both continuous endurance and high-
70 intensity interval exercise training (Bacon et al., 2013; Weston et al., 2014), it has been
71 recognised for over 3 decades that individual measured changes following standardised
72 exercise training can be highly variable and a proportion of people will demonstrate no
73 measurable change (so called, ‘non-responders’) (Bouchard et al., 1999; Lortie et al., 1984).
74 Even following several months of high-volume aerobic exercise training, measured individual
75 changes in VO_2max can range from decreases of $100 \text{ ml}\cdot\text{min}^{-1}$ to gains of more than 1100
76 $\text{ml}\cdot\text{min}^{-1}$ (Bouchard et al., 1999). This interindividual variability in response is thought to be
77 explained by a range of factors, including random or technical error, the method of
78 standardising relative exercise intensity, and genetic and epigenetic variance (Sarzynski et al.,
79 2017). Some have also argued that ‘non-responders’ to exercise training in general do not exist
80 and instead are an artefact of an insufficient training stimulus for those individuals (Bacon et
81 al., 2013; Montero and Lundby, 2017). Nonetheless, some individuals may be non-responders

82 to set training interventions (characterised by training intensity, duration, frequency, and mode)
83 that are efficacious at inducing training effects in others.

84 Over the last 15 years, sprint interval training (SIT) has emerged as an efficacious exercise
85 training stimulus for improving VO₂max in previously inactive individuals (Gillen and Gibala,
86 2014; Sultana et al., 2019; Volllaard and Metcalfe, 2017; Volllaard et al., 2017). A particularly
87 interesting finding to emerge from SIT research is that the training-induced change in VO₂max
88 does not appear to increase (and possibly decreases) with an increasing number of sprint
89 repetitions (Volllaard et al., 2017). Indeed, at a group level, improvements in VO₂max have
90 been observed with as few as two or three, 20-second, all-out cycling sprints performed
91 regularly over a 6-12-week training intervention (termed ‘reduced-exertion high-intensity
92 interval training’ or REHIT) (Gillen et al., 2016; Metcalfe et al., 2016, 2012). These findings
93 have particular relevance in the search for effective, ‘real-world’, time-efficient exercise
94 strategies to overcome lack of time as a barrier to exercise initiation and adherence in low
95 active individuals (Volllaard and Metcalfe, 2017).

96 The variability in training-induced changes in VO₂max has been well described in response to
97 continuous endurance training (Bouchard et al., 1999; Sisson et al., 2009) and more recently in
98 response to high-intensity (HIIT) and sprint interval training (SIT) (Astorino and Schubert,
99 2014; Bonafiglia et al., 2016; Gurd et al., 2016; Islam et al., 2020; Phillips et al., 2017; Williams
100 et al., 2019). However, studies examining interindividual variability in response to SIT to date
101 have involved arduous SIT protocols requiring a relatively high number of sprint repetitions
102 (Astorino and Schubert, 2014; Bonafiglia et al., 2016; Gurd et al., 2016; Islam et al., 2020;
103 Williams et al., 2019), have combined HIIT and SIT protocols together (Williams et al., 2019)
104 or, in some cases, the analysis has been limited by not utilising relevant information from a
105 time-matched control condition (Astorino and Schubert, 2014). No study has characterised the

106 heterogeneity in response or the incidence of non-responders to a genuinely time-efficient SIT
107 exercise protocol such as REHIT. Given the low overall dose of exercise involved with REHIT
108 (a total of <10 minutes of sprint exercise within 3 hours of training time over a 6-week training
109 period, e.g. (Metcalf et al., 2016, 2012)), alongside suggestions that ‘non-responders’ may be
110 an artefact of an insufficient training stimulus (Bacon et al., 2013; Montero and Lundby, 2017),
111 it is reasonable to question whether the incidence of non-response would be high following this
112 training intervention, and what proportion of individuals (if any) are likely to show a change
113 that would be considered clinically meaningful. Individual variability in the training-induced
114 change in VO₂max in response to REHIT has been alluded to (Metcalf et al., 2016), but not
115 definitively demonstrated using an adequate sample size, or appropriate experimental and
116 statistical methods. The inclusion of data from no-exercise control group is particularly
117 important when assessing individual responses to exercise training in order to account for the
118 variance caused by technical error, day-to-day biological and random within subjects
119 variability (Atkinson and Batterham, 2015; Bonafiglia et al., 2019). Thus, the aim of this study
120 was firstly to establish whether true individual variability in changes in VO₂max in response
121 to REHIT exists and, if so, to characterise the heterogeneity of response and incidence of non-
122 responders to this extremely low-volume and time-efficient exercise intervention.

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2. Methods

2.1. Participants / Sample

We conducted a secondary analysis of six published studies conducted in our laboratories between 2012 and 2020 (Metcalf et al., 2020, 2016, 2012; Nalçakan et al., 2018; Songsorn et al., 2016; Thomas et al., 2020). This included a sample of 117 pooled training participants (68 male, 49 female) who underwent an almost identical SIT intervention (described in full below), and 40 pooled no-intervention control participants (16 male, 24 female) from three of these studies who underwent two assessments of maximal oxygen uptake either ~4 (n=14; (Songsorn et al., 2016)) or ~6 (n=26; (Metcalf et al., 2020, 2012)) weeks apart. Training participants from two of the included studies who underwent substantially different SIT interventions, either involving single 20-s sprints (Songsorn et al., 2016) or reduced sprint duration (Nalçakan et al., 2018), were excluded because these studies demonstrated that these interventions either do not alter VO₂max (single 20-s sprints; (Songsorn et al., 2016)) or results in a significantly lower mean increase (reduced sprint duration; (Nalçakan et al., 2018)). The inclusion and exclusion criteria were similar across all six included studies. All participants were classified as either sedentary or moderately physically active on enrolment onto the study according to the criteria of the International Physical Activity Questionnaire. Participants with any contraindication to exercise based on a self-report health history questionnaire and an assessment of high resting blood pressure (>140/90 mmHg) or high resting heart rate (>100 bpm) were excluded. The pooled participant characteristics are shown in **Table 1**. Ethical approval was obtained for all included experiments (details and approval references are available in the original articles (Metcalf et al., 2020, 2016, 2012; Nalçakan et al., 2018;

156 Songsorn et al., 2016; Thomas et al., 2020)) and all participants provided their written consent
157 to take part after they received information about the study both verbally and in writing. All
158 experiments were conducted in accordance with the Declaration of Helsinki.

159 **Table 1** Baseline Participant Characteristics

	Training (n=117)	Control (n=40)	p-value
Male / Female (n)	68/49	16/24	-
Age (y)	30 ± 10	30 ± 13	0.98
Height (m)	1.72 ± 0.09	1.69 ± 0.09	0.17
Body Mass (kg)	74.7 ± 15.5	70.4 ± 16.1	0.14
BMI (kg·m ⁻²)	25.2 ± 4.2	24.4 ± 4.6	0.30
VO ₂ max (ml·kg ⁻¹ ·min ⁻¹)	34.8 ± 7.5	31.5 ± 6.5	0.01

160 *Data is presented as mean ± SD. p-values derived from independent t-test.*

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163 **2.2. Assessment of Maximal Oxygen Uptake**

164 All participants underwent an incremental cycling test to their limit of tolerance to determine
165 maximal oxygen uptake. In participants in the SIT groups, these were conducted in the week
166 prior to training and then ~3 days following the final training session. The specific protocols
167 have been described previously (Metcalf et al., 2020, 2016, 2012; Nałçakan et al., 2018;
168 Songsorn et al., 2016; Thomas et al., 2020). Although there were slight variations in the
169 protocol and equipment used across studies, the mean and standard deviation of the change in
170 VO₂max are strikingly similar (**Table 3**) suggesting these are ‘typical’ for studies of this nature
171 and hence appropriate for a pooled analysis. In the majority (n=103) of training participants
172 and all (n=40) of the control participants, breath by breath measurements of pulmonary gas
173 exchange were captured continuously during the test using a metabolic cart. Breath by breath
174 measurements of oxygen uptake (VO₂) were converted into 15-breath rolling averages and
175 VO₂max was taken as the highest value for a 15-breath rolling average achieved during the
176 test. This method was used in all but one of the included experiments which was reanalysed
177 for the present analysis (Metcalf et al., 2012). For a small sample of training participants

178 (n=14) from one study (Metcalf et al., 2016), pulmonary gas exchange was measured using
179 the Douglas Bag technique. It was considered appropriate to retain these participants in this
180 analysis because previous independent studies have reported similar test-retest reliability for
181 VO_2max measured using Douglas Bags or breath by breath methods (Katch et al., 1982;
182 Phillips et al., 2017). The following secondary criteria were used to verify a maximal effort: 1)
183 volitional exhaustion, 2) a plateau in VO_2 despite increasing workload, 3) $\text{RER} > 1.15$ and 4) a
184 maximal heart rate within 10 beats of age predicted maximum ($220 - \text{age}$). All participants
185 achieved two or more of these criteria.

186 ***2.3. Sprint Interval Training and No-Intervention Control***

187 All training participants underwent a 6-week cycling based REHIT intervention with only
188 small differences across studies (**Table 2**). The majority of participants (n=104) completed this
189 supervised in an exercise physiology laboratory on a mechanically braked cycle ergometer
190 (Monark, Vansbro, Sweden) (Metcalf et al., 2016, 2012; Nalçakan et al., 2018; Thomas et al.,
191 2020). Participants (n=13) in one study completed the intervention unsupervised on a
192 commercially available electronically braked cycle ergometer (CAROLTM, Integrated Health
193 Partners Ltd, London, UK) (Metcalf et al., 2020). Each SIT session lasted ~10 min and
194 consisted of low intensity cycling interspersed with two ‘all-out’ sprints against a fixed
195 resistance (between 10 and 20 s). In the 2-3 seconds prior to each ‘all-out’ sprint, participants
196 increased their pedal cadence to their maximal speed, the braking resistance was then applied
197 to the bike, and participants cycled as fast as they could for the duration of the sprint. The
198 majority of participants completed 3 sessions/week (n=76) but a subset completed either 2
199 (n=29) or 4 (n=12) sessions/week. We recently demonstrated that the mean change in VO_2max
200 with SIT was not different across training frequencies of 2, 3 or 4 sessions/week (Thomas et
201 al., 2020), so it was deemed appropriate to pool them together in this analysis. All no-

202 intervention control participants from the 3 separate studies were given the same instructions
 203 to maintain their current physical activity levels and dietary patterns for the duration of the
 204 study.

205 **Table 2** Training interventions applied in included studies

		Metcalfe 2012	Metcalfe 2016	Nalcakan 2018	Thomas 2020	Metcalfe 2020
Intervention Duration (weeks)		6	6	6	6	6
Frequency (sessions / week)		3	3	3	2, 3 or 4	2
Total Session Duration (mins)		10	10	10	10	8:20-8:40
Sprints Per Session (n)		2	2	2	2	2
Braking Mass (% BM)		7.5	5	7.5	7.5	5
Sprint Duration(s)	Week 1	10	10	10	10	10
	Week 2	15	15	15	15	15
	Week 3	15	15	20	20	20
	Week 4	20	20	20	20	20
	Week 5	20	20	20	20	20
	Week 6	20	20	20	20	20
Warm-Up Duration (s)		180	180	120	100-110	120
Recovery Duration (s)		200-220	200-220	200-220	200-220	180
Cool Down Duration (s)		180	180	240	240	180
Intensity of Warm-Up, Recovery and Cool Down		~60 W	Unloaded	Unloaded	Unloaded	~25 W

206 *Note: in the Metcalfe et al (2012 and 2016) studies, the first session only contained 1 x 10 s*
 207 *sprint. Where a range of warm-up and recovery durations are presented, this is due to the*
 208 *increase in sprint duration during initial training weeks.*

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210 **2.4. Statistical Analysis**

211 **2.4.1. Group Responses**

212 The effect of SIT on VO₂max was analysed using a two-way repeated measures analysis of
 213 variance (group x time), performed in Graphpad Prism 8 for macOS (Version 8.4.2, San Diego,
 214 CA, USA). Alpha was set at $p < 0.05$ and effect size was calculated using Cohens d (Hopkins et
 215 al., 2009).

216 **2.4.2. Individual Variability**

217 To characterise whether true individual responses to SIT were present, the standard deviation
218 (SD) of individual responses (SD_{IR}) was calculated from the square root of the difference
219 between the square of the SD of the change (post *minus* pre) in the exercise training group
220 (SD_{ex}) and the control group (SD_{con}) (Atkinson and Batterham, 2015):

$$221 \quad SD_{IR} = \sqrt{(SD_{EX})^2 - (SD_{CON})^2}$$

222 The SD_{IR} was subsequently interpreted against thresholds for standardised mean change of 0.1
223 (small effect), 0.3 (moderate effect) and 0.6 (large effect) (Hopkins, 2015) and against the
224 smallest clinically worthwhile change (see below).

225 *2.4.3. Classification of Non-, Uncertain and Positive Responders to SIT*

226 The statistical procedures recommended by Swinton et al (Swinton et al., 2018) were followed
227 to classify individual changes in VO_{2max} following SIT using 50% confidence intervals (CIs)
228 that were calculated using the typical error for repeated measurements of VO_{2max} from the
229 control participants. The typical error (TE) was calculated using the formula:

$$230 \quad TE = SD_{CON} / \sqrt{2}$$

231 Typical error for relative VO_{2max} was $1.30 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. For completeness, we classified
232 individual responses against a zero and clinically relevant response thresholds as this is more
233 likely to be informative of individual responsiveness in short term (e.g. 6 weeks) exercise
234 training studies where adaptations may still be accumulating (Islam et al., 2020). However,
235 when interpreting and discussing the data we take the more conservative approach of defining
236 responses against the smallest worthwhile change, alluding to responses against the zero
237 threshold where relevant. Responses were considered against two clinically relevant thresholds
238 of change to provide additional information on the proportion of individual responses at
239 different magnitudes: thresholds of $1.75 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (equivalent to ~ 0.5 METs) and 3.5

240 ml·kg⁻¹·min⁻¹ (equivalent to ~1 MET) were applied based on the data of Lee *et al* who
241 demonstrated an ~8% and ~16% decrease in relative risk of CVD, respectively, over ~11 years
242 of follow up (Lee et al., 2011). Both of these thresholds have been applied in previous studies
243 on this topic (Bonafiglia et al., 2018). A responder was classified if the entire 50% CI lay above
244 the specified response threshold. In these instances, the use of a 50% CI means that there is a
245 75% probability of a response for this individual, i.e. 'likely' (Hopkins, 2015). If the 50% CI
246 crossed the response threshold then this was classified as an 'uncertain response', whilst a 'non-
247 responder' was defined if the entire 50% CI lay below the response threshold (Bonafiglia et
248 al., 2018). All analysis of individual responses was performed in Microsoft Excel and
249 Graphpad Prism 8 for macOS (Version 8.4.2, San Diego, CA, USA).

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262 **3. Results**263 **3.1. Group Effects and SD_{IR}**

264 For relative VO_{2max} , there were main effects of group ($F=13.2$, $p<0.001$) and time ($F=35.7$,
 265 $p<0.001$) as well as a group x time interaction ($F=39.8$, $p<0.001$): mean relative VO_{2max}
 266 increased in the SIT group compared to the control group (**Table 3 and Figure 1**, $d=0.43$). The
 267 SD_{IR} for the change in relative VO_{2max} following SIT compared to the control group was 2.39
 268 $ml \cdot kg^{-1} \cdot min^{-1}$ with an effect size of 0.32 ('moderate'). The SD_{IR} was not substantially altered
 269 ($2.30 ml \cdot kg^{-1} \cdot min^{-1}$) when one potentially influential SIT participant with a $-5.99 ml \cdot kg^{-1} \cdot min^{-1}$
 270 1 decrease in VO_{2max} was removed from the analysis ($d=0.30$, 'moderate'). Thus, there is
 271 evidence of individual differences in VO_{2max} trainability in response to REHIT that exceed
 272 the smallest clinically worthwhile effect of $1.75 ml \cdot kg^{-1} \cdot min^{-1}$.

273 **Table 3** Changes in absolute and relative VO_{2max} following SIT

	Study	Absolute ($L \cdot min^{-1}$)			Relative ($ml \cdot kg^{-1} \cdot min^{-1}$)		
		Pre	Post	Delta	Pre	Post	Delta
Training	Metcalfe 2012	2.19±0.57	2.48±0.60	0.29±0.13	33.5±4.9	38.3±4.8	4.7±2.7
	Metcalfe 2016	2.54±0.65	2.78±0.67	0.24±0.23	35.0±7.8	38.1±7.9	3.0±3.3
	Nalcakan 2018	2.77±0.75	3.04±0.75	0.27±0.28	39.0±6.9	42.3±6.5	3.3±3.3
	Thomas 2020	2.77±0.77	3.01±0.82	0.24±0.24	35.4±7.2	38.5±7.5	3.1±2.8
	Metcalfe 2020	2.25±0.75	2.42±0.82	0.17±0.21	28.0±6.7	29.8±7.6	1.8±2.5
Control	Metcalfe 2012	2.32±0.64	2.37±0.77	0.05±0.18	33.8±5.5	34.2±6.0	0.3±2.3
	Songsorn 2015	2.07±0.69	2.08±0.68	0.01±0.10	32.0±5.8	32.2±6.0	0.2±1.6
	Metcalfe 2020	2.26±0.70	2.20±0.71	-0.06±0.09	28.1±7.3	27.4±7.2	-0.7±1.4
Pooled	Training	2.59±0.73	2.83±0.77	0.24±0.23	34.8±7.5	37.9±7.9	3.1±3.0

	Control	2.21±0.67	2.22±0.71	0.00±0.14	31.5±6.5	31.5±6.8	-0.1±1.8
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274 *Data is presented as mean ± SD*

275 **3.2. Classification of Non-, Uncertain and Positive Responders to SIT**

276 When considered against a threshold of zero, 5/117 (4%) of participants were classified as
277 likely non-responders, 29/117 (25%) were classified as uncertain responders, and 83/117
278 (71%) of the participants showed an increase in VO₂max that was likely higher than zero
279 (**Figure 2A**). When considered against the minimal clinically relevant threshold, 18% (21/117)
280 of participants were likely non-responders, 39/117 (33%) were classified as uncertain
281 responders, and 57/117 (49%) showed an increase likely higher than the minimal clinically
282 relevant threshold of 1.75 ml·kg⁻¹·min⁻¹ (**Figure 2B**). Furthermore, 33 out of those 57 (i.e.
283 33/117; 28%) of those participants showed an increase likely higher than 3.5 ml·kg⁻¹·min⁻¹
284 (**Figure 2B**).

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300 **4. Discussion**

301 Individual variability in the change in VO_2max following exercise training has important
302 implications for optimising and personalising exercise prescriptions to improve health. This is
303 the first study to report the heterogeneity of response and the incidence of non-response to a
304 genuinely time-efficient SIT protocol that has been shown to be efficacious at a group level in
305 both supervised lab (Metcalf et al., 2016, 2012; Nałçakan et al., 2018; Thomas et al., 2020)
306 and unsupervised real-world (Metcalf et al., 2020) settings. Importantly, for the first time, we
307 demonstrate statistically that inter-individual differences in training-induced changes in
308 VO_2max following REHIT exceed the technical, day-to-day biological, and random within-
309 subjects variability of VO_2max assessment over a similar time frame. Of particular note, we
310 report a non-response rate of 18% and that 49% of individuals demonstrate an increase in
311 VO_2max that is likely higher than the smallest clinically worthwhile difference.

312 Several previous studies have quantified non-response rates to a high dose of aerobic exercise
313 training and to HIIT and SIT protocols involving a greater number/duration of high-intensity
314 or all-out sprint efforts (Astorino and Schubert, 2014; Bonafiglia et al., 2016; Gurd et al., 2016;
315 Islam et al., 2020; Phillips et al., 2017; Sisson et al., 2009; Williams et al., 2019). Direct
316 comparisons with these HIIT and SIT studies are somewhat challenging because different
317 thresholds have been applied to quantify non-response, including a change $<1 \times \text{TE}$ (i.e. <0.86
318 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; (Phillips et al., 2017)), $<2 \times \text{TE}$ (i.e. $<1.74 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; (Gurd et al., 2016)), <1
319 coefficient of variation (CV) of repeated measurement (i.e. $<\sim 1.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; (Astorino and
320 Schubert, 2014)), or $<\text{SWC} \text{ minus } 1 \times \text{TE}$ (i.e. $<1.80 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; (Williams et al., 2019)). In
321 the largest pooled analysis of HIIT ($n=299$) and SIT ($n=116$) to date, Williams reported a non-
322 response rate of 35% for HIIT and 52% for SIT, using a threshold of $<1.8 \text{ ml/kg/min}$ (Williams

323 et al., 2019). Applying the same criteria to the current study would yield a non-response rate
324 of 38%. Thus, it is possible to conclude that the proportion of likely non-responders observed
325 with REHIT is similar to or less than with other SIT and HIIT protocols involving a greater
326 number/duration of high-intensity or all-out sprint efforts (Williams et al., 2019). The fact that
327 similar rates of non-response are observed when applying HIIT and SIT protocols with varying
328 numbers and durations of sprints strongly suggests that non-response for $VO_2\text{max}$ is not an
329 artefact caused by an insufficient dose of exercise training. If this were the case, then the non-
330 response rate would be expected to decrease with an increased number/duration of sprints and
331 hence a greater training 'stimulus'. The application of sprints of an 'all-out' intensity adds
332 further weight to this argument because this likely overcomes any issues regarding the
333 standardisation of exercise intensity (or more specifically the homeostatic disruption) across
334 individuals during each acute training session. Whilst individual differences in the homeostatic
335 disturbance can be expected with MICT standardised using a % of $HR\text{max}$ or $VO_2\text{max}$, and
336 this may have subsequent implications for the adaptive response (Jamnick et al., 2020; Montero
337 and Lundby, 2017; Preobrazenski et al., 2018), the disruption in homeostasis with SIT / REHIT
338 is always likely to be severe and hence sufficient to switch on signalling pathways that underpin
339 adaptation (if possible for that individual). Indeed, the fact that group level increases in
340 $VO_2\text{max}$ are similar between SIT protocols applying 2-3 sprints compared with protocols
341 applying 6-8 sprints (Vollaard et al., 2017) implies that the adaptive signalling pathways
342 responsible for increasing $VO_2\text{max}$ in response to SIT become 'saturated' with only a small
343 number of acute 'all-out' sprint efforts (Vollaard and Metcalfe, 2017). Taken together, we
344 contend that non responders for $VO_2\text{max}$ in response to exercise training are a real
345 physiological phenomenon and our data show they are observed in response to REHIT/SIT.
346 That said, it remains unknown whether non-responders to REHIT/SIT for changes in $VO_2\text{max}$
347 are also non-responders for other health markers (i.e. universal non responders), but previous

348 work looking at interindividual differences in response to aerobic exercise training suggests
349 that this may not be the case (Vollaard et al., 2009). Future studies need to clearly establish
350 whether non-responders to REHIT/SIT would demonstrate adaptations to different types of
351 exercise, such as MICT. Although previous studies have attempted to examine this (Bonafiglia
352 et al., 2016), the small sample size limits the conclusions that can be made at this stage.

353 Our data show that ~half of individuals are likely to show an increase in VO_2max that is greater
354 than the smallest worthwhile change after only 6 weeks of training. This is a striking
355 observation given that REHIT involves less than 10 min of sprint exercise and a total exercise
356 time of 3 hours over that 6-week period. Nevertheless, it is worth noting that this represents a
357 relatively short-term training intervention. At a group level, the magnitude of increase in
358 VO_2max following SIT that occurs from 6 to 12 weeks is similar to that observed from 0 to 6
359 weeks of the intervention (Gillen et al., 2016) and this raises important questions about
360 individual differences in the rate at which adaptations are accrued. Indeed, in our analysis, a
361 proportion of individuals (26/117; 22%) demonstrated a change that was likely $>0 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
362 ¹ but not of a magnitude which exceeded the minimal clinically important difference threshold
363 of $1.75 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Whilst it would be expected that non-responders would continue to show
364 limited adaptation to a longer intervention, it will be important to determine whether
365 individuals showing a slower rate of adaptation at 6 weeks would continue to accrue
366 adaptations (at this lower rate) and would demonstrate a clinically meaningful magnitude of
367 response at a later time point.

368 The mechanisms that explain the individual variation in response to REHIT are unclear and
369 cannot be determined from the present study. As the training interventions applied were unable
370 (due to logistical reasons) to control the majority of environmental factors outside of the
371 training intervention (e.g. each participants pattern of nutrition, sleep, stress etc.), it can be

372 expected that some of the variability in adaptation between individuals is explained by
373 (unquantified) environment-training interactions. As an example, the dose, type and timing of
374 nutrition can have a powerful impact on the skeletal muscle signalling response to acute
375 exercise (Cluberton et al., 2005; Guerra et al., 2010; Stocks et al., 2018) and, hence, can modify
376 adaptation to exercise training. If such variables are not controlled across individuals, then it
377 can be expected that this will introduce a level of individual variability in adaptation. This may
378 also explain, at least in part, the poor reproducibility of individual responses to repeated
379 (identical) exercise training interventions in the same sample of participants (Del Giudice et
380 al., 2020).

381 On the other hand, it is also clear that there is a heritable component to exercise trainability
382 (Bouchard, 2019; Bouchard et al., 1999; Sarzynski et al., 2017; Timmons et al., 2010). The
383 majority of this evidence comes from studies of the training response to aerobic and resistance
384 exercise and the relevance of this information to SIT remains unknown. Indeed, we still do not
385 know whether REHIT/SIT enhances VO_2 max through mechanisms that are similar to or
386 distinct from MICT (Gibala and Little, 2019; Vollaard and Metcalfe, 2017). However, the
387 inter-individual variability observed in the present study can be used by future investigations
388 interested in identifying (molecular) predictors of response. If responders vs. non-responders
389 to a specific intervention (e.g. SIT/REHIT) can be identified, then contrasting traits / molecular
390 signatures in groups of responders vs. non-responders provides a strong approach to identify
391 potential physiological / genetic / epigenetic factors that determine the interindividual
392 variability in training response (Keller et al., 2007). Such studies are needed to enable
393 personalised medicine, for example, to enable personalised advice on effective interventions
394 (Keller et al., 2007; Timmons et al., 2010) and can be a powerful way to elucidate molecular
395 mechanisms of training adaptations (Keller et al., 2011, 2007). An improved understanding of
396 the molecular mechanisms of adaptation to SIT would be invaluable in the effort to optimise

397 SIT protocols to enable the greatest adaptations with minimal required effort and time-
398 commitment.

399 There are a number of limitations to the current analysis that should be considered. Firstly, and
400 most importantly, whilst the large sample size is a strength of this study, this is a pooled dataset
401 from five independent studies and there were minor differences in training protocols, testing
402 procedures, and the duration of the control intervention (4-weeks for n=14 and 6-weeks for
403 n=26) between some of the studies (described in full in the methods). It is possible that these
404 differences may affect the validity of the SDir estimate, which assumes that all sources of
405 variability are equal between the exercise and control groups except that the exercise group
406 underwent exercise training (Atkinson and Batterham, 2015; Bonafiglia et al., 2019). However,
407 two pieces of information can help to mitigate these concerns. Firstly, the SD of the training-
408 induced change in $\text{VO}_{2\text{max}}$ was comparable between studies (**Table 3**). Secondly, we
409 performed a sensitivity analysis to examine how excluding the 4-week control participants
410 impacts the SDir calculation. We found a similar SDir estimate of $2.30 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ compared
411 to $2.39 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ when all control participants were included. Similarly, a comparable SDir
412 of $2.36 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was found when training participants undergoing $\text{VO}_{2\text{max}}$ assessment
413 with Douglas Bags (n=14) were excluded from the analysis. Thus, these differences in
414 methodology across the pooled independent studies to do not appear to greatly impact the
415 validity of our findings.

416 Another limitation is that most of the studies involved supervised, lab-based exercise, so it
417 remains unclear whether the results would be the same in real-world settings and this will be
418 important to address in future studies. Furthermore, this analysis is also largely limited to young
419 sedentary but healthy men and women and it is not possible to determine whether different
420 populations (e.g. lean vs overweight, young vs old, men vs women) may show different levels

421 of response / non-response. Finally, it should also be noted that other important health markers
422 were not considered in this analysis and so at present it remains unknown whether non-
423 responders for $VO_2\text{max}$ in response to SIT would be able to improve markers of
424 cardiometabolic health.

425 In conclusion, we demonstrate for the first time that the well described increase in $VO_2\text{max}$
426 observed following REHIT at the group level, is subject to substantial variability in magnitude
427 at an individual level. This is an important observation with potential future implications for
428 prescribing SIT/REHIT as an intervention for improving health and can be harnessed by future
429 studies aiming to elucidate the mechanisms by which REHIT improves $VO_2\text{max}$.

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647 **Figure Legends:**

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649 **Figure 1** Changes in VO₂max following SIT (panel A) and following a no-intervention control
650 (panel B). Data is presented as mean and SD (bars) on the primary y-axis, or as individual
651 change scores (black dots) on the secondary y-axis.

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653 **Figure 2** Individual changes in VO₂max following SIT classified against either a zero (panel
654 A) or clinically relevant thresholds of 1.75 ml·kg⁻¹·min⁻¹ (light blue dashed and dotted line)
655 and 3.5 ml·kg⁻¹·min⁻¹ (dark blue dashed line) (panel B). Dots are individual changes and error
656 bars are 50% confidence intervals. Red square = likely non-responder, orange diamond =
657 uncertain responder, light blue circle = likely responder (>0 ml·kg⁻¹·min⁻¹ in panel A and >1.75
658 ml·kg⁻¹·min⁻¹ in panel B). In panel B, dark blue circle = likely responder >3.5 ml·kg⁻¹·min⁻¹.
659 Pie charts show the absolute proportion (n) of participants in each category.

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662 **Conflict of Interest Statement:**

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664 All authors confirm they have no conflict of interest to declare.