1   **Heterogeneity and incidence of non-response for changes in cardiorespiratory fitness**

2   **following time-efficient sprint interval exercise training**

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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±SD: age: 30±10 y; VO_2max: 34.8±7.5 $ml \cdot kg^{-1} \cdot min^{-1}$),

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 $ml \cdot kg^{-1} \cdot min^{-1}$) 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 $ml \cdot kg^{-1} \cdot min^{-1}$. The standard deviation of individual

47   responses (SD_{IR}) was 2.39 $ml \cdot kg^{-1} \cdot min^{-1}$ (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.

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 ml·min^{-1} to gains of more than 1100

76 ml·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 VO_2max in previously inactive individuals (Gillen and Gibala,

86   2014; Sultana et al., 2019; Vollaard and Metcalfe, 2017; Vollaard et al., 2017). A particularly

87   interesting finding to emerge from SIT research is that the training-induced change in VO_2max

88   does not appear to increase (and possibly decreases) with an increasing number of sprint

89   repetitions (Vollaard et al., 2017). Indeed, at a group level, improvements in VO_2max 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 (Vollaard and Metcalfe, 2017).

96   The variability in training-induced changes in VO_2max 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. (Metcalfe 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 VO_2max in response to REHIT has been alluded to (Metcalfe 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 VO_2max 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 (Metcalfe 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; (Metcalfe 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 VO_2max (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 (Metcalfe 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 (Metcalfe et al., 2020, 2016, 2012; Nalçakan 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   VO$_2$max 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 (VO$_2$) were converted into 15-breath rolling averages and

175   VO$_2$max 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 (Metcalfe et al., 2012). For a small sample of training participants

178   (n=14) from one study (Metcalfe 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) RER >1.15 and 4) a

184   maximal heart rate within 10 beats of age predicted maximum (220-age). All participants

185   achieved two or more of these criteria.

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) (Metcalfe 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 (CAROL[TM], Integrated Health

193   Partners Ltd, London, UK) (Metcalfe 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 VO_2max 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):

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

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:

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

231   Typical error for relative VO_2max was 1.30 ml·kg^{-1}·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 ml·kg^{-1}·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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3. Results

3.1. Group Effects and SD_{IR}

For relative VO_2max, there were main effects of group ($F=13.2$, $p<0.001$) and time ($F=35.7$, $p<0.001$) as well as a group x time interaction ($F=39.8$, $p<0.001$): mean relative VO_2max increased in the SIT group compared to the control group (**Table 3 and Figure 1,** $d=0.43$). The SD_{IR} for the change in relative VO_2max following SIT compared to the control group was 2.39 $ml \cdot kg^{-1} \cdot min^{-1}$ with an effect size of 0.32 ('moderate'). The SD_{IR} was not substantially altered (2.30 $ml \cdot kg^{-1} \cdot min^{-1}$) when one potentially influential SIT participant with a -5.99 $ml \cdot kg^{-1} \cdot min^{-1}$ decrease in VO_2max was removed from the analysis ($d=0.30$, 'moderate'). Thus, there is evidence of individual differences in VO_2max trainability in response to REHIT that exceed the smallest clinically worthwhile effect of 1.75 $ml \cdot kg^{-1} \cdot min^{-1}$.

Table 3 Changes in absolute and relative VO_2max following SIT

		Absolute ($L \cdot min^{-1}$)			Relative ($ml \cdot kg^{-1} \cdot min^{-1}$)		
	Study	**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 |

Data is presented as mean ± SD

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

When considered against a threshold of zero, 5/117 (4%) of participants were classified as likely non-responders, 29/117 (25%) were classified as uncertain responders, and 83/117 (71%) of the participants showed an increase in VO_2max that was likely higher than zero (**Figure 2A**). When considered against the minimal clinically relevant threshold, 18% (21/117) of participants were likely non-responders, 39/117 (33%) were classified as uncertain responders, and 57/117 (49%) showed an increase likely higher than the minimal clinically relevant threshold of 1.75 ml·kg^{-1}·min^{-1} (**Figure 2B**). Furthermore, 33 out of those 57 (i.e. 33/117; 28%) of those participants showed an increase likely higher than 3.5 ml·kg^{-1}·min^{-1} (**Figure 2B**).

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4. Discussion

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

Several previous studies have quantified non-response rates to a high dose of aerobic exercise training and to HIIT and SIT protocols involving a greater number/duration of high-intensity or all-out sprint efforts (Astorino and Schubert, 2014; Bonafiglia et al., 2016; Gurd et al., 2016; Islam et al., 2020; Phillips et al., 2017; Sisson et al., 2009; Williams et al., 2019). Direct comparisons with these HIIT and SIT studies are somewhat challenging because different thresholds have been applied to quantify non-response, including a change <1xTE (i.e. <0.86 ml·kg^{-1}·min^{-1}; (Phillips et al., 2017)), <2xTE (i.e. <1.74 ml·kg^{-1}·min^{-1}; (Gurd et al., 2016)), <1 coefficient of variation (CV) of repeated measurement (i.e. <~1.3 ml·kg^{-1}·min^{-1}; (Astorino and Schubert, 2014)), or <SWC minus 1 x TE (i.e. <1.80 ml·kg^{-1}·min^{-1}; (Williams et al., 2019)). In the largest pooled analysis of HIIT (n=299) and SIT (n=116) to date, Williams reported a non-response rate of 35% for HIIT and 52% for SIT, using a threshold of <1.8 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_2max 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 HRmax or VO_2max, 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_2max 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_2max 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_2max 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_2max

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 $ml \cdot kg^{-1} \cdot min^{-}$

362   ^{1} but not of a magnitude which exceeded the minimal clinically important difference threshold

363   of 1.75 $ml \cdot kg^{-1} \cdot min^{-1}$. 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_2max 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 VO_2max 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 ml·kg^{-1}·min^{-1} compared

411 to 2.39 ml·kg^{-1}·min^{-1} when all control participants were included. Similarly, a comparable SDir

412 of 2.36 ml·kg^{-1}·min^{-1} was found when training participants undergoing VO_2max 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

of response / non-response. Finally, it should also be noted that other important health markers were not considered in this analysis and so at present it remains unknown whether non-responders for VO$_2$max in response to SIT would be able to improve markers of cardiometabolic health.

In conclusion, we demonstrate for the first time that the well described increase in VO$_2$max observed following REHIT at the group level, is subject to substantial variability in magnitude at an individual level. This is an important observation with potential future implications for prescribing SIT/REHIT as an intervention for improving health and can be harnessed by future studies aiming to elucidate the mechanisms by which REHIT improves VO$_2$max.

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Figure Legends:

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Figure 1 Changes in VO$_2$max following SIT (panel A) and following a no-intervention control (panel B). Data is presented as mean and SD (bars) on the primary y-axis, or as individual change scores (black dots) on the secondary y-axis.

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Figure 2 Individual changes in VO$_2$max following SIT classified against either a zero (panel A) or clinically relevant thresholds of 1.75 ml·kg^{-1}·min^{-1} (light blue dashed and dotted line) and 3.5 ml·kg^{-1}·min^{-1} (dark blue dashed line) (panel B). Dots are individual changes and error bars are 50% confidence intervals. Red square = likely non-responder, orange diamond = uncertain responder, light blue circle = likely responder (>0 ml·kg^{-1}·min^{-1} in panel A and >1.75 ml·kg^{-1}·min^{-1} in panel B). In panel B, dark blue circle = likely responder >3.5 ml·kg^{-1}·min^{-1}. Pie charts show the absolute proportion (n) of participants in each category.

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Conflict of Interest Statement:

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