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1 **Variability in exercise physiology: Can capturing *intra*-individual**  
2 **variation help better understand true *inter*-individual responses?**

3  
4 RUNNING TITLE: *Intra*-individual variation and *Inter*-individual responses

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20 Variability, Exercise, Training

21 **Abstract**

22

23 Exploring individual responses to exercise training is a growing area of interest. Understanding  
24 reasons behind true observed *inter*-individual responses may help personalise exercise training  
25 to maximise the benefits received. While numerous factors have been explored, an often  
26 underappreciated consideration in the sport and exercise science field is the influence *intra*-  
27 individual variation, both in a single measurement and in response to an intervention, may have  
28 on training outcomes. Several study designs and statistical approaches are available to  
29 incorporate *intra*-individual variation into interventions and accordingly provide information  
30 on whether ‘true’ *inter*-individual responses are present or if they are an artefact of *intra*-  
31 individual variation. However, such approaches are sparingly applied. Moreover, *intra*-  
32 individual variation may also be important when true *inter*-individual response differences are  
33 present. In this perspective piece, the concept of *intra*-individual variation is described before  
34 briefly summarising study designs and statistical practices to account for *intra*-individual  
35 variation. We then outline two examples of physiological practices (stratified randomisation  
36 and prescribing exercise programmes upon training parameters) to demonstrate why sport and  
37 exercise scientists should acknowledge *intra*-individual variation prior to the implementation  
38 of an intervention, which potentially offers an additional explanation behind observed true  
39 *inter*-individual responses to training. Repeated testing pre-implementation of exercise training  
40 would conceptually provide more confident estimates of training parameters, which if utilised  
41 in a study design will help attenuate biases that may dictate *inter*-individual differences.  
42 Moreover, the incorporation of *intra*-individual differences will facilitate insights into  
43 alternative factors that may predict and/or explain *true* observed individual responses to an  
44 exercise training programme.

45

## 46 1. Introduction

47

48 Observations of *inter*-individual variability and ‘non-responders’ to physical activity and  
49 exercise training have been frequently acknowledged (Mann et al., 2014; Bouchard and  
50 Rankinen, 2001). While evidence refuting claims of non-response to both aerobic and  
51 resistance exercise exist (Montero and Lundby, 2017; Bonafiglia et al., 2016; Churchward-  
52 Venne et al., 2015), interest has grown in attempting to quantify, predict and explain observed  
53 *inter*-individual variability in response to interventions (Atkinson, Williamson and Batterham,  
54 2019; Voisin et al., 2018; Sparks, 2017; Hecksteden et al., 2015). Such attempts have involved  
55 the application of genomics (Williams et al., 2017; Bouchard et al., 2015), replicated crossover  
56 designs (Goltz et al., 2019; Goltz et al., 2018; Senn et al., 2011) and statistical methods  
57 (Swinton et al., 2018; Atkinson and Batterham, 2015). Here, we aim to reiterate and  
58 demonstrate the importance to sport and exercise scientists in acknowledging *intra*-individual  
59 variation.

60 We first describe the concept of *intra*-individual variation alongside summarising study  
61 designs and statistical approaches that incorporate *intra*-individual variation to determine  
62 whether true *inter*-individual responses exist. Two examples of common physiological  
63 practices are then outlined to illustrate why *intra*-individual variation should be systematically  
64 explored prior to the implementation of an exercise training programme. This article extends  
65 previous discussions by demonstrating conceptually how *intra*-individual variation in baseline  
66 training parameters (peak or maximum oxygen consumption [ $\dot{V}O_{2\text{peak}}$  and  $\dot{V}O_{2\text{max}}$ ] and  
67 lactate threshold) may impact stratified randomisation and the ‘exercise dose’ prescribed to  
68 individuals. To our knowledge, these considerations of *intra*-individual variation have not  
69 previously been discussed, yet provide clear and relatable examples of how *intra*-individual  
70 variation may contribute to true observed *inter*-individual responses to a training programme.

71

## 72 2. What is *intra*-individual variation?

73

74 *Intra*-individual variation can be defined as the difference in values obtained for an outcome  
75 measure(s) when the same participant is studied under similarly standardised testing conditions  
76 and procedures. It is also referred to as day-to-day or within-subject variation and provides an  
77 indication on the reproducibility or reliability of an observation. Similarly, there is *intra*-  
78 individual variation in response to an intervention i.e. variability of pre-to-post differences  
79 when the same participant is administered the same intervention. These two types of *intra*-  
80 individual variation are inter-connected, derive from three overarching sources and have  
81 implications for the design and interpretation of an intervention (see Figure 1).

82

83 In practice many physiological observations measured on a continuous scale are composed of  
84 a ‘true’ value plus ‘error’ (i.e. noise) (Atkinson and Batterham, 2015; Atkinson and Nevill,  
85 1998). This variability, or error, in an estimate can derive from three overarching sources:  
86 measurement (or technical) error, biological error and biological variation. Measurement error  
87 refers to noise derived from the equipment and protocol used and the experimenter, which  
88 theoretically is identical across all individuals (Voisin et al., 2018). Alternatively, biological  
89 error derives from the influence of environmental factors such as diurnal variation, sleep  
90 quality, diet, or psychological stress (Voisin et al., 2018). Even if such a variable has no  
91 measurement error, test-retest variability will likely be prevalent to some extent, attributable to  
92 biological noise (Atkinson and Batterham, 2015). Importantly, these ‘errors’ are  
93 distinguishable from biological variation that induces a shift in the true score (e.g. adaptations  
94 to training or detraining).

95

96 To determine the true *intra*-individual variation of an observation, serial measurements over  
97 some time-scale must be conducted (i.e. test-retest, concurrent replicates, day-to-day, trial-to-  
98 trial). Repeated measurements within a trial are also necessary if the aim is to distinguish  
99 between technical and biological sources of *intra*-individual variation. Similarly, if  
100 characterising true *intra*-individual variation in response to an intervention is the aim, then the  
101 same intervention must be repeated at least once in the same participants. Repeated  
102 measurements will conceptually provide a more accurate estimate of a participant's 'true' value  
103 or intervention response, especially when there is no systematic error in measurement (e.g.  
104 learning effects or diminishing returns from a training programme). Furthermore, to obtain a  
105 more valid measurement of *intra*-individual variation, efforts to reduce all sources of error  
106 should be taken, including standardised calibration and testing procedures, appropriate  
107 timeframes between testing and adequate pre-trial standardisation on 'determinants' of the  
108 outcome variable (e.g. physical activity levels and/or dietary intake). (For detailed discussions  
109 on *intra*-individual variation see Swinton et al., 2018; Voisin et al., 2018; Hecksteden et al.,  
110 2015; Atkinson and Batterham, 2015; Atkinson and Nevill, 1998). Therefore, to confidently  
111 capture *intra*-individual variation many aspects need to be considered.

### 112 113 **3. Accounting for *intra*-individual variation to determine whether true *inter*-individual** 114 **responses to an intervention exist**

115  
116 To infer that true *inter*-individual response differences exist, it is imperative to discern between  
117 systematic or 'true' changes (i.e. intervention induced) and *intra*-individual variation (from  
118 measurement and biological error) (Solomon, 2018; Voisin et al., 2018). Indeed, *intra*-  
119 individual variation is in some circumstances large enough to account for all, or a large  
120 proportion of apparent *inter*-individual differences in training responses (e.g. for  $\dot{V}O_2\text{max}$   
121 [Williamson et al., 2017] and weight change [Williamson et al., 2018]). To achieve this  
122 distinction several study designs and/or statistical approaches are available that measure *intra*-  
123 individual variation and accordingly provide information on whether 'true' *inter*-individual  
124 responses are present or if they are an artefact of *intra*-individual variation.

125  
126 The ideal method is to conduct a replicated randomised controlled trial in the same participants,  
127 together with repeated testing within each treatment period (Voisin et al., 2018; Hecksteden et  
128 al., 2015; Senn, 2011). Here, participants are randomly allocated to the intervention or control  
129 (or the order of receiving these conditions if a crossover design) as per a typical randomised  
130 controlled trial (RCT). However, upon completion and after an adequate washout period, the  
131 study is essentially repeated in the same participants to examine if individuals demonstrate a  
132 consistent response to the intervention relative to control. Clearly this poses considerable  
133 logistical and feasibility challenges at both the level of the participant and researcher(s). An  
134 alternative is to implement one of these approaches alone i.e. either replicate the intervention  
135 or have repeated testing pre- and/or post-trial. While such approaches present similar  
136 challenges, several studies have adopted replicated designs (Goltz et al., 2019; 2018; Lindholm  
137 et al., 2016; Senn et al., 2011). . For example, Goltz and colleagues (2018) found in a replicated,  
138 randomized crossover experimental design that true *inter*-individual differences in subjective  
139 appetite and blood hormonal responses to acute exercise were apparent in fifteen healthy males,  
140 exceeding measurement error and biological error. Similarly, a more recent randomised  
141 replicated cross-over study by Goltz and co-workers (2019) also found true *inter*-individual  
142 differences in postprandial appetite responses to a standardised breakfast in eighteen healthy  
143 males. Moreover, a similar elegant design was also employed in a knee extension training  
144 programme where subjects were their own control through exercising one-leg initially followed  
145 by a washout period and then two-leg training (Lindholm et al., 2016). While Lindholm and

146 co-workers (2016) found the response of a large fraction of genes only changed in one training  
147 period, indicating *intra*-individual variation, unfortunately *inter*-individual response  
148 differences were not explored. Nevertheless, the appearance of such study designs shows a  
149 move towards the importance of measuring *intra*-individual variation to determine whether  
150 true *inter*-individual response differences exist.

151

152 A further pragmatic compromise is to repeatedly test throughout a trial to act as a surrogate for  
153 a repeated intervention (Hecksteden et al., 2018; Hecksteden et al., 2015). Here, serial  
154 measurements are ideally obtained at similar intervals throughout an intervention (i.e. a time-  
155 series experimental design) where the slope of a linear regression is then fitted to an  
156 individual's measured values to determine their response. *Intra*-individual variation can then  
157 be calculated as the standard error (i.e. typical error) of an individual's slope in which  
158 intervention response (and classification of (non-) responders) can be estimated by pre-  
159 determined thresholds (e.g. zero change, or measured day-to-day variability, minimum  
160 clinically relevant change or smallest worthwhile difference in the respective outcome variable  
161 [Hecksteden et al., 2018; Hecksteden et al., 2015]). This approach can begin to overcome  
162 measurement and biological error in the assessment of the intervention response on that  
163 occasion but cannot discern how individuals would respond if the intervention were repeated.  
164 Furthermore, additional shortcomings to this design exist e.g. the assumption that training  
165 adaptations are linear over a programme (Hecksteden et al., 2015), albeit a non-linear  
166 regression model (e.g. a mono-exponential curve) can be applied in such circumstances  
167 (Bonafiglia et al., 2019), or that the measurement per se does not exhibit a temporal rhythm  
168 independent of the intervention. Moreover, Atkinson and colleagues (2019) have recently  
169 discussed in-depth several further validity concerns in determining *inter*-individual responses  
170 and (non-) responders by counting the number of changes in a sample that exceed or fall below  
171 a pre-determined threshold (e.g. sample comparisons of responder counts have low statistical  
172 power). Recently, Voisin et al (2018) also highlighted using a control period prior to  
173 implementing an intervention. This overcomes potential carry-over effects of exercise training  
174 in a repeated intervention and measurements in the control period can act as the baseline.  
175 However, treatments are not randomly administered, nor can all sources of variability be  
176 disentangled (Voisin et al., 2018).

177

178 An overarching shortcoming is also that many of the designs above are not possible for some  
179 types of outcome. For example, long-term interventions with "hard" end points (such as RCTs  
180 with cardiovascular disease as an end point); or interventions that have learning effects, other  
181 similar biases, or require long washout periods. For instance, unaccustomed exercise that elicits  
182 marked muscle damage should not be performed as a cross-over, since the repeated bout effect  
183 confounds the second-response unless a long washout period is implemented (Goodall et al.,  
184 2017; Betts et al., 2009); or similarly, if an intervention supplements lipid soluble antioxidants,  
185 many months are required for values to return to un-supplemented levels, by which time the  
186 intervention group may no longer be equivalent to the control group. Collectively, this shows  
187 that designing an intervention to incorporate *intra*-individual variation involves many  
188 complexities.

189

190 Alternative statistical approaches can also be applied independently or in adjunct with the  
191 above study designs. Atkinson and Batterham (2015) neatly describe how comparing the  
192 standard deviation of change between the intervention and control groups can act as a measure  
193 of *intra*-individual variation. They demonstrate that *intra*-individual variation can account for  
194 a large proportion, if not all, of apparent individual response differences. True individual

195 responses are only evident, and worth exploring, if the standard deviation for change in the  
196 intervention group is substantially larger than the control group.

197  
198 When a control group is not feasible, a second approach is to calculate the typical error of a  
199 measurement (or the within-subject standard deviation) (Solomon, 2018; Swinton et al., 2018).  
200 This can be calculated through using difference scores derived from either testing a single  
201 participant multiple times or a single test-retest in a group of participants (Swinton et al., 2018).  
202 Importantly, repeated testing must occur in a time-frame where the ‘true’ value should remain  
203 theoretically stable (Swinton et al., 2018). Assuming data are normally distributed, the pre-to-  
204 post change should be no less than 1.96 standard deviations of the group-level within-subject  
205 mean to be 95% confident that the apparent intervention-induced change is not simply *intra*-  
206 individual variation (Solomon, 2018). Arguably, alternative reliability statistics could also be  
207 used in place of the typical error such as 95% limits of agreement (Bland and Altman, 1986).  
208

209 Importantly, there are overarching considerations for the above statistical approaches. For  
210 example, *intra*-individual variation must be consistent across time (e.g. pre- and post-  
211 intervention) and sub-groups / different populations (i.e. display no heteroscedasticity)  
212 (Solomon, 2018; Swinton et al., 2018). Similarly, if no true comparator arm is available,  
213 standard deviations or typical errors from prior reliability studies can be used (Atkinson and  
214 Batterham, 2015), albeit generalisability must then be assumed, which may be troublesome  
215 given laboratory specific practices and the often-small sample sizes of such studies (Voisin et  
216 al., 2018; Solomon et al., 2018). Moreover, while confounders such as socio-environmental  
217 influences, natural variations and certain biases are in principle controlled for by  
218 randomisation, it must be assumed no changes in behaviour or other biases have driven any  
219 potential pre-to-post differences in the control group. Indeed, controlling for familiarisation  
220 effects may pose substantial challenges (e.g. muscle damage induced by unaccustomed  
221 exercise [Goodall et al., 2016; Betts et al., 2009]). Furthermore, trial effects (i.e. the Hawthorne  
222 effect) can lead to conscious or unconscious changes in behaviour. Such scenarios may skew  
223 change scores and misinform interpretations of *intra*-individual variation and subsequently  
224 whether true *inter*-individual response differences exist. Nevertheless, the above statistical  
225 approaches adjust for error uncertainty in pre-to-post changes, where apparent *inter*-individual  
226 response differences are easily able to be encapsulated by *intra*-individual variation.  
227

#### 228 **4. The consideration of *intra*-individual variation prior to a training programme to** 229 **explain true *inter*-individual responses**

230 The above statistical approaches to quantify *intra*-individual variation employ these methods  
231 after data collection. While applying this step is essential to interpret whether further  
232 exploration of *inter*-individual responses to an intervention are warranted, if these criteria are  
233 met, *intra*-individual variation should not then be neglected. As demonstrated below, *intra*-  
234 individual variation should also be considered much earlier in the design and implementation  
235 of a training programme as it may be an underlying factor contributing to observed true *inter*-  
236 individual responses.

##### 237 **4.1 Example 1: Stratified randomisation**

238 Randomised control trials frequently use stratified randomisation to control for *a priori*  
241 identified parameter(s) of importance. This helps reduce confounding influences of co-variables  
242 that may mask, attenuate or intensify potential intervention effects and jeopardise conclusions  
243 (e.g. regression to the mean or ceiling effects). Consequently, establishing ‘true’ baseline  
244 estimates are imperative (Swinton et al., 2018).

245

246 Alongside representing a common outcome measure, cardiorespiratory fitness can be an  
247 important baseline characteristic for stratification in an exercise training RCT. Typically, a one-  
248 off incremental graded exercise test (GXT) is used to estimate  $\dot{V}O_{2peak}$  or  $\dot{V}O_{2max}$  as a marker  
249 of cardiorespiratory fitness. However, obtaining only a one-off estimate for cardiorespiratory  
250 fitness could conceptually threaten stratification. For example, if an individual's estimate of  
251  $\dot{V}O_{2peak}$  is assessed only once at baseline, but large variability is unknowingly evident in this  
252 estimate, this participant could be categorised into the wrong strata. Repeated assessment at  
253 baseline (or the inclusion of a shorter verification protocol [Poole and Jones, 2017]) would in  
254 principle provide a more confident estimate of their cardiorespiratory fitness and increase the  
255 researcher's confidence that this participant meets the pre-defined strata thresholds. This would  
256 consequently attenuate the influence of potential confounding biases (such as selection bias  
257 and ceiling effects) that may otherwise be introduced if *intra*-individual variation at baseline  
258 was not assessed. In principle this would help to more precisely determine whether true *inter*-  
259 individual response differences are apparent and/or facilitate the identification of further  
260 contributing factors.

261

262 The relevance of this example is apt given findings from studies that have explored the  
263 reproducibility of  $\dot{V}O_{2peak}$  estimates from GXTs. While high intra-class correlations (0.92–  
264 0.99) and low within-subject coefficient of variations (CVs) (3–5%) are typically reported  
265 (Edgett et al., 2018; Dideriksen and Mikkelsen, 2017; Midgley et al., 2007), evidence exists  
266 that  $\dot{V}O_{2peak}$  may be underestimated from an initial or first GXT compared to an identical  
267 second and third GXT (Edgett et al., 2018). This learning effect may be particularly evident in  
268 individuals inexperienced to maximal testing and importantly influenced the classification of  
269 individual responses in  $\dot{V}O_{2peak}$  following exercise training (Edgett et al., 2018). Additionally,  
270 within-subject CVs and a typical error of up to 9 % and  $4.27 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , respectively, for  
271  $\dot{V}O_{2max}$  estimates were reported in eleven male amateur runners who completed four identical  
272 treadmill GXTs (Lourenço et al., 2011). This demonstrates that *intra*-individual variability in  
273  $\dot{V}O_{2peak}$  estimates from one-off GXTs could influence fitness classifications (such as those  
274 outlined by Decroix et al. [2016] and De Pauw et al. [2013]). Moreover, a recent study showed  
275 group mean estimates of  $\dot{V}O_{2peak}$  varied by  $\sim 1\text{--}5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  alongside within-subject CVs  
276 between 2.0 – 5.2 %, when five different GXT protocols employing varying stage lengths were  
277 compared in seventeen trained male cyclists (Jamnick et al., 2018).

278

279 To further demonstrate the potential impact that *intra*-individual variation in a baseline  
280 characteristic may have for stratified randomisation, a theoretical example is provided in Figure  
281 2. This figure reflects a hypothetical scenario where participants  $\dot{V}O_{2peak}$  ( $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) has  
282 been estimated at baseline on three separate occasions (GXT 1, 2 and 3) from the same  
283 treadmill GXT. The within-subject variability of  $\dot{V}O_{2peak}$  is within the typical error reported  
284 by Lourenco and colleagues (2011) i.e.  $4.27 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , where stratified randomisation is to  
285 be performed for participants who have a  $\dot{V}O_{2peak}$  threshold of  $< 45 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (threshold  
286 derived from performance level 1 fitness classification in males as outlined by De Pauw et al.  
287 (2013)). As illustrated, for participant's 1, 4, 5, 6 and 10, if  $\dot{V}O_{2peak}$  was assessed only once  
288 at baseline (i.e. GXT 1), the researcher(s) would assume these participants are similarly  
289 matched for cardiorespiratory fitness and would believe stratified randomisation, to say an  
290 exercise RCT, is appropriate. However, if *intra*-individual variability was accounted for by  
291 repeated assessment at baseline (i.e. obtaining an average from each individual's GXT 1, GXT  
292 2 and GXT 3 values), a more precise estimate of the participant's true fitness levels (e.g. the  
293 within-subject mean on Figure 2) would conceptually be obtained. The researcher(s) would  
294 then see that they would be incorrect to perform stratified randomisation on participant 1, 4



295 and 10. Equally, the reverse is true for participant 2 and 8, who initially would be excluded  
296 from stratified randomisation based on the observed value from GXT 1, but in actual fact could  
297 be appropriately stratified were repeated assessment to be performed. While the  
298 meaningfulness of  $\pm 4.27 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in  $\dot{V}\text{O}_2\text{peak}$  could be questioned, the relevance of this  
299 variability is highlighted by a meta-analysis of  $n = 34$  studies that reported sprint interval  
300 training (mean intervention length of 5-weeks) improved  $\dot{V}\text{O}_2\text{peak}$  by 8 % (Vollaard et al.,  
301 2017), which equates to  $3.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  with the  $\dot{V}\text{O}_2\text{peak}$  threshold used above. This  
302 hypothetical example shows how overlooking *intra*-individual variation in a baseline  
303 characteristic could in principle lead to inappropriate stratified randomisation and introduce  
304 biases that may affect analysis techniques (e.g. skew the standard deviation of change in the  
305 intervention and/or control groups) and mask, attenuate or intensify intervention effects and  
306 *inter*-individual response differences to exercise training.  
307 Collectively, this suggests repeated assessment (or verification tests) are necessary to obtain  
308 more confident estimates of baseline characteristics to stratify upon. Moreover, given the  
309 potential influence of learning effects, researchers and practitioners may wish to determine the  
310 number of assessments required for this bias to dissipate (and consequently exclude initial  
311 measurements as appropriate) and/or then obtain the average of the remaining repeated  
312 measurements. This arguably would facilitate a more confident assessment of baseline  
313 parameters, where acknowledging *intra*-individual variation prior to randomisation may assist  
314 with participant group allocation and consequently help remove further confounding biases  
315 that may contribute to observed true *inter*-individual responses.

316

#### 317 **4.2 Example 2: Standardisation of prescribed exercise dose**

318

319 Many exercise training programmes and RCTs ‘standardise’ the exercise dose i.e. the workload  
320 performed by participants, by fixing the exercise intensity, duration and/or frequency of  
321 sessions between participants. However, the method used to standardise exercise programmes  
322 varies considerably, leading to concerns over whether the exercise dose standardisation  
323 procedure allows precise quantification of *inter*-individual responses (Ross et al., 2019). In a  
324 similar manner, *intra*-individual variation in training prescription parameters may pose a  
325 concern not only for the standardisation of exercise dose between-subjects but also within a  
326 participant during an exercise programme. To our knowledge, the potential implication of  
327 *intra*-individual variation in training parameters that are used to prescribe exercise dose has not  
328 previously been highlighted but may contribute to observed true *inter*-individual response  
329 differences.

330

331 To demonstrate the importance of acknowledging *intra*-individual variation in training  
332 prescription parameters, a hypothetical example is provided whereby a training programme  
333 prescribes participants a ‘set’ relative intensity to exercise at derived from a one-off GXT. As  
334 issues of prescribing exercise intensity based on a percentage of  $\dot{V}\text{O}_2\text{max}$ , or a percentage /  
335 beats below maximum heart rate ( $\text{HR}_{\text{MAX}}$ ) have been discussed elsewhere (Piatrikova et al.,  
336 2019; Mann et al., 2013; Meyer et al., 1999), this example focuses on the recommendation to  
337 prescribe exercise upon indices that elicit more similar physiological responses between-  
338 subjects such as the lactate threshold or critical speed.

339

340 Before describing this scenario, it is important to acknowledge that the precise prescription of  
341 exercise intensity is particularly important given that the physiological responses to exercise  
342 intensity are not necessarily linear. If the physiological stress displayed a linear relationship  
343 across all exercise intensities, then (non-systematic) variability could be reduced simply with  
344 randomisation and a sufficient sample size. However, since the metabolic stress response to

345 exercise is non-linear, an over-estimation of exercise intensity could disproportionately affect  
346 the physiological response compared to an equivalent under-estimate, and therefore balance  
347 would not necessarily be achieved by randomisation. Accordingly, repeated assessment at  
348 baseline to accurately prescribe exercise intensity (and at time-points throughout a training  
349 programme to recalibrate the prescribed exercise intensity to account for any training  
350 adaptations) can be important to ensure that the adaptive stimuli is similar across people within  
351 each group of an intervention.

352

353 Take a hypothetical situation where *intra*-individual variability in the GXT used to determine  
354 the lactate threshold, for which exercise training sessions are prescribed upon, is unknowingly  
355 large. The metabolic stress (i.e. ‘training stimuli’) induced by each acute exercise bout may  
356 consequently vary session-to-session. In support of this example, the corresponding speed and  
357 heart rate at which the lactate threshold (first significant elevation of blood lactate  
358 concentration above resting levels) and fixed 4 mmol·L<sup>-1</sup> blood lactate concentration were  
359 detected, showed 95% limits of agreement of  $\pm 1.5$  and 1.3 km·h<sup>-1</sup> and 16 and 12 beats per  
360 minute, respectively in twenty males and sixteen females who were young, healthy and active  
361 (Grant et al., 2002). This variability in running speed at “lactate threshold” is equivalent to  
362 ~10%, which is therefore substantial. Similar low reproducibility in several blood lactate  
363 markers during GXTs have also subsequently been reported, albeit partly moderated by factors  
364 such as analysis method, stage duration and training status (Gavin et al., 2014; Morton et al.,  
365 2012). Training status is particularly important given that sedentary individuals are often  
366 recruited to training programmes, where reproducibility of lactate measures are speculated to  
367 be lower (Gavin et al., 2014; Grant et al., 2002). Further support for the realism of the above  
368 example derives from a recent study that found substantial *inter*-method variability when  
369 estimating the lactate threshold via five one-off GXT protocols of various stage lengths and  
370 fourteen analysis techniques in seventeen trained males (Jamnick et al., 2018).

371

372 Echoing the issue of prescribing relative exercise intensity upon  $\dot{V}O_2$ max or HR, the potential  
373 variability in ‘training stimuli’ session-to-session may induce different training adaptations,  
374 supporting previous speculations and potentially accounting for observations of ‘responders’  
375 and ‘non-responders’ to a training programme (Mann et al., 2013; 2014). Moreover, this  
376 potential variability in training stimuli may influence the standard deviation of change in the  
377 intervention group and have important implications for data interpretation (Voisin et al., 2018).  
378 Further complications may also derive from individuals potentially having different capacities  
379 to work aerobically and anaerobically (Piatrikova et al., 2018; Buchheit and Laursen, 2013).  
380 The applicability of this example is apt given preliminary findings that acute differences in  
381 metabolic stress to the first exercise training session (mean blood lactate concentrations) were  
382 positively associated (via a simple linear regression) with increases in  $\dot{V}O_{2peak}$  after 4-weeks  
383 of exercise training (Preobrazenski et al., 2018), albeit approaches to adjust for *intra*-individual  
384 variation in pre-to-post changes were not employed. Nevertheless, the above collectively  
385 suggests that a more confident estimate of the selected parameter to prescribe training upon  
386 would conceptually provide more assurance that participants are exercising at an intensity that  
387 elicits similar physiological responses both within- and between-subjects. This can be achieved  
388 by repeated testing prior to the implementation of and during a training programme, which  
389 would arguably lead to a more precise standardisation of the exercise dose prescribed.  
390 Collectively, this would attenuate any potential confounding bias introduced by *intra*-  
391 individual variation that may contribute to true observed *inter*-individual responses to a training  
392 programme.

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394

## 395 5. Conclusion

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397 This perspective piece highlights the importance that *intra*-individual variation in baseline and  
398 training parameters may have on the implementation of a training programme and  
399 consequently, how this may dictate apparent group and true *inter*-individual responses to a  
400 training programme. Ultimately, the reasons behind *true* heterogeneous training adaptations  
401 are likely multi-dimensional (Solomon, 2018; Swinton et al., 2018; Hecksteden et al., 2015)  
402 and there is unlikely one universal solution to incorporate *intra*-individual variation  
403 (Hecksteden et al., 2015). Nevertheless, while quantifying and controlling for *intra*-individual  
404 variation through repeated testing is undoubtedly challenging, researchers who do this will be  
405 better placed to: a) identify *true* effects of a training programme and b) more confidently and  
406 appropriately prescribe ‘personalised’ training programmes on an individual basis. Moreover,  
407 while examples specific to aerobic endurance training were used, the implications of *intra*-  
408 individual variation highlighted here are highly applicable and transferable to all domains of  
409 sport and exercise science (e.g. resistance exercise, biomechanics and / or psychology).  
410 Overall, acknowledging *intra*-individual variation will attenuate a potential confounding  
411 variable and facilitate greater insights into alternative variables that may predict and/or explain  
412 true observed *inter*-individual responses to exercise training.

413 **Figures**

414

415 Figure 1. Sources and potential implications of *intra*-individual variation

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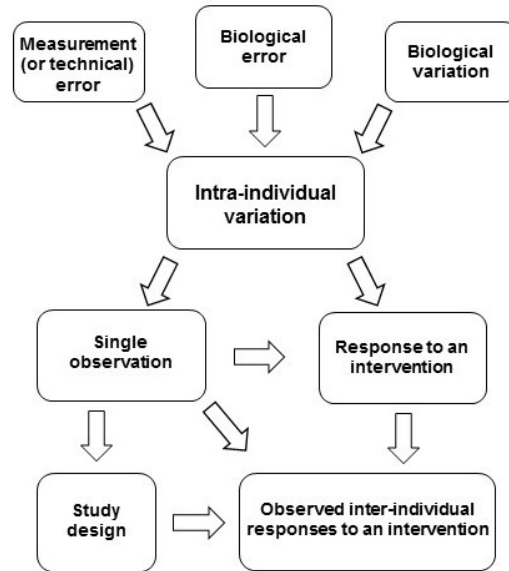
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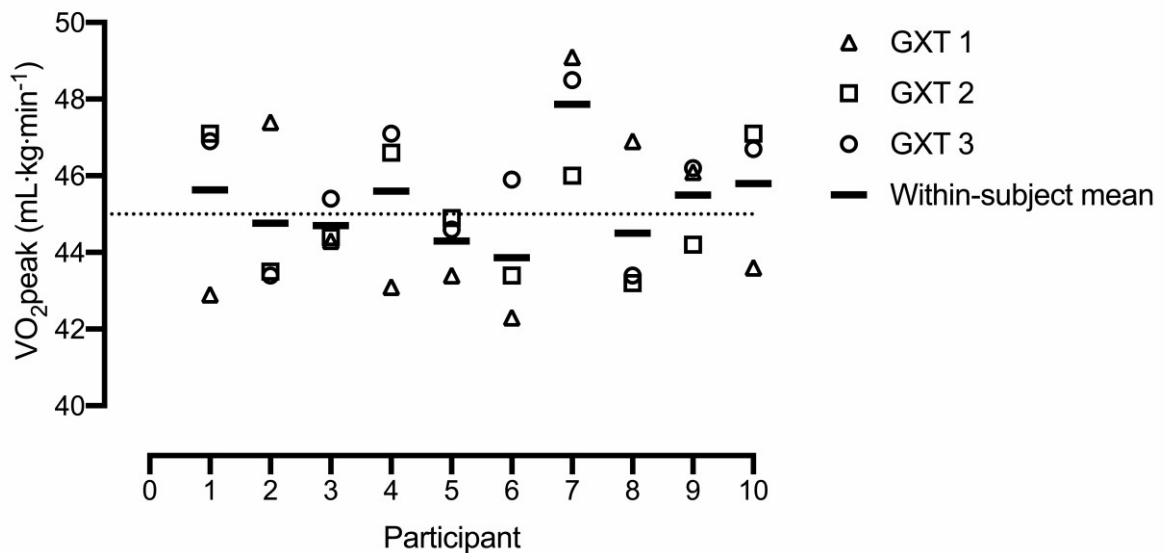
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438 Figure 2. A hypothetical scenario to demonstrate the influence *intra*-individual variation at  
439 baseline may have for stratified randomisation



440 **Author Contributions**

441

442 The manuscript was written by O.C-S. All authors (E.P., J.B., S.W. and J.G.) contributed to  
443 each section and revised and approved the final manuscript.

444

445 **Conflict of Interest Statement**

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447 The authors declare no conflicts of interest.

448

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450

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