

Biological and methodological factors affecting $\dot{V}_{O_2 \max}$ response variability to endurance training and the influence of exercise intensity prescription

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Abstract

Changes in cardiorespiratory fitness (CRF) in response to endurance training (ET) exhibit large variations, possibly due to a multitude of biological and methodological factors. It is acknowledged that ~20% of individuals may not achieve meaningful increases in CRF in response to ET. Genetics, the most potent biological contributor, has been shown to explain ~50% of response variability, whilst age, sex and baseline CRF appear to explain a smaller proportion. Methodological factors represent the characteristics of the ET itself, including the type, volume and intensity of exercise, as well as the method used to prescribe and control exercise intensity. Notably, methodological factors are modifiable and, upon manipulation, alter response rates to ET, eliciting increases in CRF regardless of an individual's biological predisposition. Particularly, prescribing exercise intensity relative to a physiological threshold (e.g., ventilatory threshold) is shown to increase CRF response rates compared to when intensity is anchored relative to a maximum physiological value (e.g., maximum heart rate). It is, however, uncertain whether the increased response rates are primarily attributable to reduced response variability, greater mean changes in CRF or both. Future research is warranted to elucidate whether more homogeneous chronic adaptations manifest over time among individuals, as a result of exposure to more homogeneous exercise stimuli elicited by threshold-based practices.

KEYWORDS

cardiorespiratory fitness, endurance training, exercise prescription, response variability

1 | INTRODUCTION

Cardiorespiratory fitness (CRF), measured as maximum oxygen uptake ($\dot{V}_{O_2 \max}$), represents aerobic capacity and integrates the functional capacity of numerous bodily systems and their ability to deliver and utilise oxygen (Hill & Lupton, 1923). Importantly, $\dot{V}_{O_2 \max}$ is a strong predictor of chronic diseases and all-cause mortality, and increases in

$\dot{V}_{O_2 \max}$ have marked reductions on mortality risk (Harber et al., 2017; Ross et al., 2016). Endurance training (ET) is the most effective intervention for increasing $\dot{V}_{O_2 \max}$; however, the effect of ET on $\dot{V}_{O_2 \max}$ is heterogeneous, whereby some individuals benefit from large changes in $\dot{V}_{O_2 \max}$ whilst others exhibit small, no or even adverse changes (Bouchard et al., 1999; Williams et al., 2019). Understanding why this, herein 'response variability', occurs is important for the development of

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personalised exercise medicine and the pursuit of sporting excellence and may help inform strategies aimed at reducing the current burden associated with low levels of CRF (Myers et al., 2018). Whilst the health benefits attained from ET extend beyond increases in CRF (Warburton & Bredin, 2017), this review exclusively focuses on variable changes to CRF in response to ET.

Studies have typically failed to capture the response variability at the individual level when only reporting measures of central tendency (e.g., mean) and dispersion (e.g., standard deviation) at the group level. The HERITAGE study (Bouchard et al., 1999) was a seminal report highlighting the incidence of response variability at the individual level in a large heterogeneous cohort. Following a 20-week ET programme $\dot{V}_{O_2 \max}$ increased, on average, by 384 ml/min (Bouchard et al., 1999). Notably, some individuals experienced gains in excess of 1000 ml/min whilst others experienced no gain at all (Bouchard et al., 1999). Subsequently, it was concluded that ~20% of individuals undertaking ET may not achieve meaningful increases in $\dot{V}_{O_2 \max}$ (Bouchard et al., 1999). Response variability is now commonly acknowledged following training studies, generating increasing interest in 'trainability' (R. Ross et al., 2019), defined as an individual's adaptive responsiveness to ET (Hoppeler, 2018).

Unfortunately, the mechanisms underpinning response variability are multifaceted and there exist several contributors (Voisin et al., 2019). From a statistical perspective, how training response is defined (e.g., the proportion of individuals that achieve a change above (responders) and below (non-responders) a predefined response threshold), the study design and the statistical model used can each contribute to variability (Atkinson et al., 2019; Hecksteden et al., 2018; R. Ross et al., 2019; Swinton et al., 2018).

This review covers the biological and methodological factors contributing to the response variability reported following ET (Figure 1). Specifically, we appraise how biological factors, consisting of genetics, age, sex, and baseline $\dot{V}_{O_2 \max}$, and methodological factors, consisting of the type, volume and intensity of training, and the method used to prescribe intensity affect response rates to ET. Notably, unlike biological factors, with the exception of baseline $\dot{V}_{O_2 \max}$ methodological factors are modifiable and, upon manipulation, can alter response rates to ET. We contend that altering how exercise intensity is prescribed appears to have a marked impact on response rates. For example, prescribing exercise intensity relative to physiological thresholds (termed herein as threshold-based ET; Table 1), as opposed to prescribing intensity relative to maximum physiological values (termed herein as traditionally prescribed ET; Table 2), appears to have a positive impact on response rates (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015). When intensity is anchored relative to physiological thresholds, a more homogeneous exercise stimulus is elicited among individuals (Baldwin et al., 2000; Black et al., 2017; Lansley et al., 2011). When repeated over time, such responses may manifest as more homogeneous changes in $\dot{V}_{O_2 \max}$ within a group of participants (Mann et al., 2013; Scharhag-Rosenberger et al., 2010).

New Findings

• What is the topic of this review?

Biological and methodological factors associated with the variable changes in cardiorespiratory fitness in response to endurance training.

• What advances does it highlight?

Several biological and methodological factors exist that each contribute, to a given extent, to response variability. Notably, prescribing exercise intensity relative to physiological thresholds reportedly increases cardiorespiratory fitness response rates compared to when prescribed relative to maximum physiological values. As threshold-based approaches elicit more homogeneous acute physiological responses among individuals, when repeated over time, these uniform responses may manifest as more homogeneous chronic adaptations thereby reducing response variability.

2 | BIOLOGICAL FACTORS ASSOCIATED WITH RESPONSE VARIABILITY

2.1 | Genetics

The $\dot{V}_{O_2 \max}$ phenotype is a polygenetic trait influenced by a combination of environmental and genetic factors, and both its baseline and response to ET vary considerably among individuals (Williams et al., 2017). Both twin-sibling and familial-resemblance studies report that ~50% of $\dot{V}_{O_2 \max}$ trainability is attributable to heritability (Bouchard et al., 1999; Hoppeler, 2018). Moreover, compared to adults, heritability of $\dot{V}_{O_2 \max}$ is higher in youths and adolescents with weighted estimates of 59% (ml/min) and 72% (ml/kg/min), respectively (Schutte et al., 2016). However, research implementing candidate gene, gene expression and genome-wide association studies (GWAS) to determine the genetic predictors of $\dot{V}_{O_2 \max}$ trainability has been unable to identify a genome that accurately accounts for the large variation observed in $\dot{V}_{O_2 \max}$ following ET (Hoppeler, 2018).

In a GWAS of 473 participants of the HERITAGE study, none of the 324,611 single-nucleotide polymorphisms (SNPs) analysed reached genome-wide significance ($P < 5 \times 10^{-8}$) (Bouchard et al., 2011), although, for a GWAS, such a sample size potentially predisposed a lack in statistical power (Spencer et al., 2009). It has been suggested that $\dot{V}_{O_2 \max}$ trainability is determined by the additive effect of multiple small effects from numerous genes rather than a single genetic variant (Sarzynski et al., 2017). Accordingly, 97 SNPs have since been found to predict $\dot{V}_{O_2 \max}$ trainability, of which 13 have been successfully

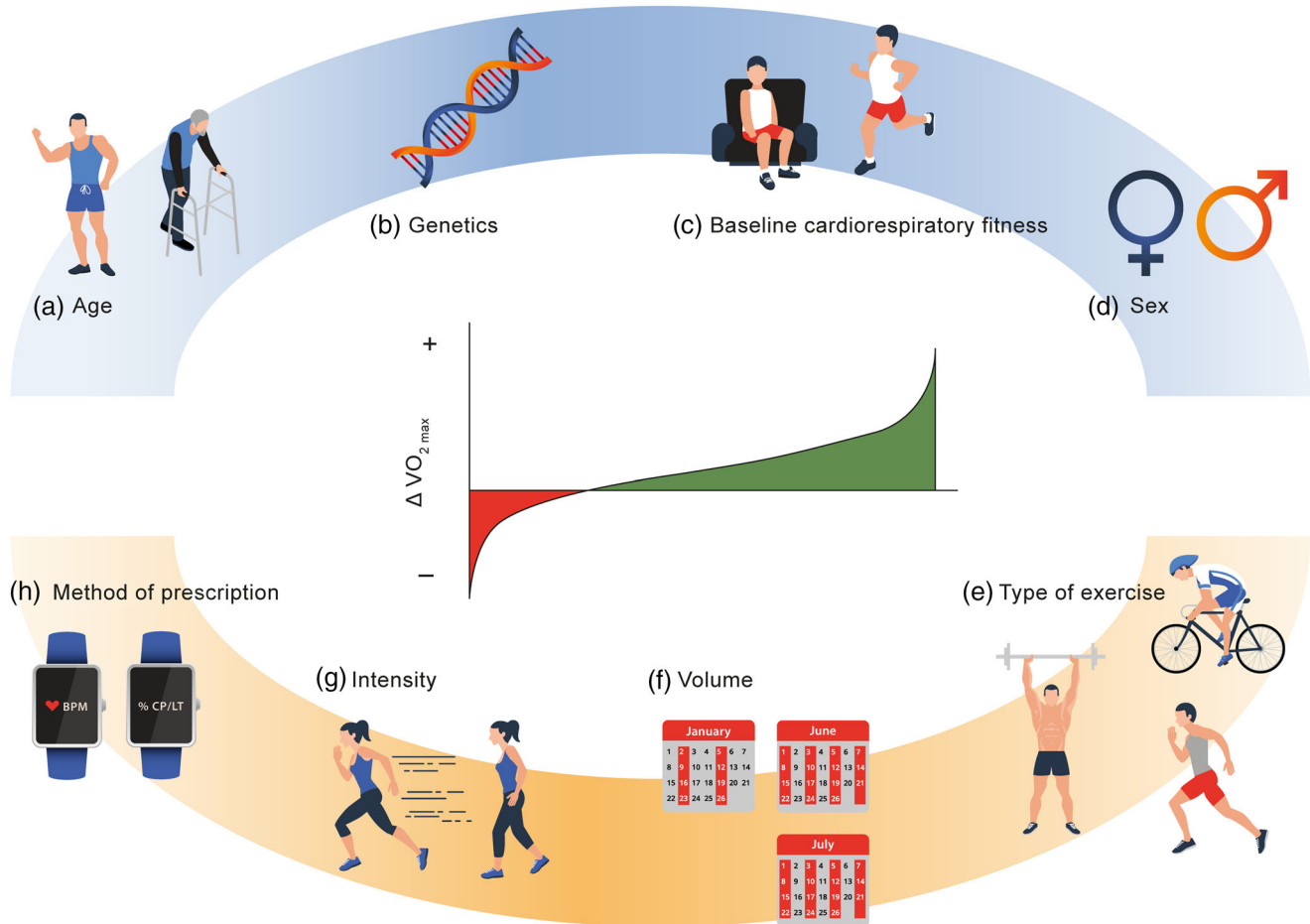


FIGURE 1 Factors affecting $\dot{V}O_{2\max}$ trainability in response to endurance training. Biological factors (blue) include age (a), genetics (b), baseline $\dot{V}O_{2\max}$ (c) and sex (d). Methodological factors (orange) include type (e), volume (f) and intensity (g) of training, and method of exercise intensity prescription (h). Unlike biological factors, with the exception of baseline $\dot{V}O_{2\max}$, methodological factors are modifiable, enabling increases in cardiorespiratory fitness following their manipulation

TABLE 1 Physiological thresholds associated with T_1 and T_2

Threshold	Physiological threshold	Description
T_1	Lactate threshold	Blood lactate concentration begins to rise above baseline levels and represents the upper boundary for nearly exclusive aerobic metabolism (Faude et al., 2009).
	Gas exchange threshold	Transition from steady-state to excess CO_2 production (Beaver et al., 1986).
	Ventilatory threshold	First breakpoint of a systematic increase in $\dot{V}_E/\dot{V}O_2$ (Wasserman & McIlroy, 1964).
T_2	Critical power	Asymptote of the power–duration relationship (Poole et al., 2016).
	Maximum lactate steady-state	Highest constant workload that leads to an equilibrium between lactate production and elimination (Faude et al., 2009).
	Respiratory compensation point	Second breakpoint of a systematic increase in $\dot{V}_E/\dot{V}O_2$ (Beaver et al., 1986).

$\dot{V}_E/\dot{V}O_2$, ventilatory equivalents for oxygen.

replicated (Williams et al., 2017). Additionally, six new SNPs have recently been identified that can distinguish among individuals with high and low $\dot{V}O_{2\max}$ values (Bye et al., 2020).

However, the mechanisms underpinning the role of genetics remain unclear. $\dot{V}O_{2\max}$ is primarily determined by central factors, namely cardiac output and the oxygen-carrying capacity of the blood, but also

by peripheral factors, namely the skeletal muscles' capacity to extract and utilise oxygen (Lundby et al., 2017). However, none of the gene variants currently identified to influence $\dot{V}O_{2\max}$ trainability link to changes in these physiological factors (Joyner & Lundby, 2018).

Overall, it is commonly reported that genetics explain ~50% of response variability; however, the molecular basis underpinning

TABLE 2 Exercise intensity domains defined by traditional anchors of exercise intensity

Anchor	Moderate-intensity (moderate)	Vigorous-intensity (heavy)	Near-maximal to maximal intensity (severe)
$\dot{V}_{O_2 \max}$	46–63%	64–90%	≥91%
HR _{max}	64–76%	77–95%	≥96%
$\dot{V}_{O_2 R}$	40–59%	60–89%	≥90%
HRR	40–59%	60–89%	≥90%

HR_{max}, maximum heart rate; HRR, heart rate reserve; $\dot{V}_{O_2 \max}$, maximum oxygen uptake; $\dot{V}_{O_2 R}$, oxygen uptake reserve (American College of Sports Medicine, 2017).

$\dot{V}_{O_2 \max}$ trainability remains to be elucidated (Sarzynski et al., 2017). Indeed, Marsh et al. (2020) reported that the environmental components of twins had a stronger influence on response variability to ET than had genetics. The polygenic nature of the $\dot{V}_{O_2 \max}$ phenotype is also likely modified by the epigenome, responding to environmental cues, such as regular exercise, which alters the transcriptomic network (Hoppeler, 2018). Furthermore, no common genetic profile has been established that can explain variations in $\dot{V}_{O_2 \max}$ (Rankinen et al., 2016), and the disconnect between identified gene variants and the key physiological determinants of $\dot{V}_{O_2 \max}$ (Joyner & Lundby, 2018) highlights that the role of genetics on $\dot{V}_{O_2 \max}$ trainability is not yet fully understood. Results from the ongoing Molecular Transducers of Physical Activity Consortium (MoTrPac) study may further our understanding of the molecular changes that occur in response to ET and how these may influence response variability (Joseph & John, 2020).

2.2 | Age

It is well documented that $\dot{V}_{O_2 \max}$ decreases with ageing (Fleg et al., 2005), primarily driven by a reduction in maximum heart rate (HR_{max}) and maximum cardiac output (Carrick-Ranson et al., 2013). Mechanisms underpinning ET-induced increases in $\dot{V}_{O_2 \max}$ may also differ with ageing. McGuire et al. (2001) found that following ET separated by 30 years, despite similar increases in $\dot{V}_{O_2 \max}$, the primary drivers of increased $\dot{V}_{O_2 \max}$ changed from maximal cardiac output and arteriovenous oxygen difference to exclusive increases in arteriovenous oxygen difference in the 30-year follow-up. However, age did not impact the magnitude of change in $\dot{V}_{O_2 \max}$ following ET. Robinson et al. (2017) reported that both young (18–30 years) and older (65–80 years) adults can substantially increase $\dot{V}_{O_2 \max}$ following ET (~20%), in line with previous findings (Huang et al., 2016; McGuire et al., 2001). Moreover, Kohrt et al. (1991) reported no significant differences in the percentage increase in $\dot{V}_{O_2 \max}$ among older individuals aged between 60 and 71 years, nor was there a relationship between change in $\dot{V}_{O_2 \max}$ and age ($r = -0.13$). There was, however, considerable heterogeneity in the gains in $\dot{V}_{O_2 \max}$ among individuals (0–58%), but differences in age could not explain this variability (Kohrt et al., 1991).

With regards to the effect on response variability, Sisson et al. (2009) reported that age was a strong predictor of non-response rates among a female cohort ($n = 310$; 45–75 years) following 6 months of ET, whereby increments in age of 6.4 years increased the odds of non-response by 35–45%. Hautala et al. (2003) reported that age explained 16% of the response variability following 8 weeks of ET in a male cohort ($n = 39$; 23–52 years). Alternatively, in the HERITAGE cohort, which included a larger age range ($n = 742$; 17–65 years), age was reported to explain only 3% of the response variability following 20 weeks' ET (Sarzynski et al., 2017). Furthermore, Skinner et al. (2001) reported that low, medium, and high responders were present across all age groups within the HERITAGE study.

Overall, whilst an effect of age on response variability has been reported, the age range utilised in such studies was relatively small. Results from the HERITAGE study, which incorporated the largest sample size and age range, suggest that up to 65 years the effect of age on response variability is somewhat minor. Future studies examining large age ranges extending beyond the age of 65 years would further elucidate the influence of age on training response.

2.3 | Sex

The increase in $\dot{V}_{O_2 \max}$ following ET is generally greater in men than in women of a comparable training status (mean difference: 1.95 ml/kg/min; Diaz-Canestro & Montero, 2019). Interestingly, increases in $\dot{V}_{O_2 \max}$ may be attributed to different adaptive pathways between sexes (Ansdell et al., 2020), perhaps explaining why gains in $\dot{V}_{O_2 \max}$ following ET tend to be somewhat superior in men (Diaz-Canestro & Montero, 2019). For example, compared to men, key central adaptations such as increased stroke volume and cardiac filling have been blunted in women following ET (Howden et al., 2015). Instead, women have demonstrated greater training-induced peripheral adaptations such as greater oxygen extraction and mitochondrial respiration (Cardinale et al., 2018; Montero et al., 2018; Spina et al., 1993). Accordingly, women demonstrate a greater exercise capacity during exercises not limited by oxygen delivery, such as single limb exercise, where peripheral factors have a large impact on performance compared to whole-body exercise, which relies heavily on central components (Ansdell et al., 2019). Such peripheral adaptations, potentiated by advantageous metabolic properties of female skeletal muscle, may help compensate for attenuated central adaptations observed in women (Ansdell et al., 2020).

Another explanation for inferior increases in $\dot{V}_{O_2 \max}$ in women is that ET may be informed by training studies dominated by male participants (Ansdell et al., 2020). Compared to men, physiological thresholds such as lactate threshold (LT) and gas exchange threshold occur at higher percentages of $\dot{V}_{O_2 \max}$ in women, and therefore when exercising at the same intensity relative to a maximum physiological value (e.g., $\dot{V}_{O_2 \max}$), women often experience inferior metabolic stress (Ansdell et al., 2020; Iannetta et al., 2021; Vainshelboim et al., 2020). Accordingly, Froberg and Pedersen (1984) found women were able to exercise at 80% $\dot{V}_{O_2 \max}$ for ~17 min longer than men and produced

lower blood lactate levels (5.4 vs. 8.1 mmol/l). Critically, sufficient metabolic stress is required to potentiate a cascade of signalling pathways that manifest as subsequent physiological adaptations (Granata et al., 2018). In turn, when adhering to an ET programme assumed to elicit similar metabolic stress between sexes, particularly when anchoring intensity relative to a maximum physiological value, the relative training intensity may in fact be lower in women (Ansdell et al., 2020; Iannetta et al., 2021). Therefore, women may experience an inferior stimulation of adaptive pathways hindering changes that may influence $\dot{V}_{O_2 \max}$ such as mitochondrial biogenesis and angiogenesis (Ansdell et al., 2020; Bishop et al., 2019; Granata et al., 2018). Thus, how intensity within ET is prescribed may predispose the blunted responses typically observed in women. A threshold-based approach to prescribe exercise intensity may minimise sex differences in response to ET (discussed in section 3.4).

Surprisingly, despite differences in the magnitude of $\dot{V}_{O_2 \max}$ changes in response to ET, the effect of sex on response variability is reported to be relatively minor (Kohrt et al., 1991; Sarzynski et al., 2017; Williams et al., 2019). For example, sex explained only ~3% of the variability in $\dot{V}_{O_2 \max}$ changes in the HERITAGE study (Sarzynski et al., 2017). Furthermore, when assessing $\dot{V}_{O_2 \max}$ trainability subsequent to high-intensity interval training (HIIT) and moderate intensity continuous training (MICT), sex played no role in response variation (Williams et al., 2019). Indeed, the American College of Sports Medicine (ACSM) has concluded that sex and age have little influence on $\dot{V}_{O_2 \max}$ response variability (Garber et al., 2011).

Overall, increases in $\dot{V}_{O_2 \max}$ following ET tend to be somewhat superior in men. For men increases in $\dot{V}_{O_2 \max}$ may be primarily attributed to central adaptations compared to enhanced peripheral adaptations observed in women; however, more research is required to elucidate sex-specific adaptations (Barnes & Fu, 2018). Surprisingly, whilst sex may influence the magnitude of change in $\dot{V}_{O_2 \max}$ following ET, it is reported that sex explains only a small proportion of $\dot{V}_{O_2 \max}$ response variability.

2.4 | Baseline cardiorespiratory fitness

Those initially presenting in the lowest quintile of $\dot{V}_{O_2 \max}$ appear to have a potentiated capacity to experience the greatest health reward in response to increases in $\dot{V}_{O_2 \max}$ (Harber et al., 2017). It appears that baseline $\dot{V}_{O_2 \max}$ affects subsequent response to training whereby a higher baseline $\dot{V}_{O_2 \max}$ hinders the potential for further adaptation (Astorino & Schubert, 2014; Saltin et al., 1969; Sisson et al., 2009). Sisson et al. (2009) concluded that baseline $\dot{V}_{O_2 \max}$ was among the strongest predictors of $\dot{V}_{O_2 \max}$ non-response following ET. Specifically, increments in baseline $\dot{V}_{O_2 \max}$ of 0.24 l/min increased the odds of non-response by 2-fold. A number of studies have further reported a negative association between baseline $\dot{V}_{O_2 \max}$ and increases in $\dot{V}_{O_2 \max}$ (Astorino & Schubert, 2014; Hautala et al., 2006; Maturana et al., 2021). It is plausible that a ceiling may exist in those with an already developed phenotype whereby the ability to elicit a

metabolic strain potent enough to invoke adaptive signalling becomes diminished.

Whilst baseline $\dot{V}_{O_2 \max}$ can impact the magnitude of change in $\dot{V}_{O_2 \max}$, it appears to have little effect on response variability. For example, in the HERITAGE study, only 2% of the response variability was concluded to be attributable to baseline $\dot{V}_{O_2 \max}$ (Sarzynski et al., 2017). In an analysis of 633 subjects from the same cohort, no association ($r = 0.08$) was found between the baseline and change in $\dot{V}_{O_2 \max}$ (ml/kg/min), although there was a negative association with relative changes in $\dot{V}_{O_2 \max}$ (%) ($r = -0.38$; Skinner et al., 2001). Moreover, low, medium, and high responders were present across all levels of baseline $\dot{V}_{O_2 \max}$ (Skinner et al., 2001). The lack of association could be explained by the relatively untrained nature of the participants. For example, in the HERITAGE study, the mean baseline $\dot{V}_{O_2 \max}$ was ~31 ml/kg/min (Skinner et al., 2001). A large proportion may have possessed modestly developed $\dot{V}_{O_2 \max}$ phenotypes at most, and thus scope for further increases in $\dot{V}_{O_2 \max}$ may not have been hindered in this cohort.

Overall, evidence suggests that baseline $\dot{V}_{O_2 \max}$ may influence $\dot{V}_{O_2 \max}$ trainability. It is plausible that the likelihood of non-response may increase among individuals who already possess a highly developed $\dot{V}_{O_2 \max}$ phenotype, in which room for further improvement becomes limited. However, considering the equivocal evidence resulting from the HERITAGE study, this conclusion warrants further investigation.

3 | METHODOLOGICAL FACTORS ASSOCIATED WITH RESPONSE VARIABILITY

3.1 | Type of training

The type of training appears to affect the variability in $\dot{V}_{O_2 \max}$ following ET as it has been shown that changing the type of training can alter subsequent response outcomes and 'rescue' individuals previously identified as non-responders (Hautala et al., 2006; Marsh et al., 2020). In the STRUETH study, non-response was salvaged when non-responders converted from ET to resistance training (RT), and vice versa (Marsh et al., 2020). The newly elicited responses were primarily training type-specific, whereby individuals who did not exhibit a change in $\dot{V}_{O_2 \max}$ following ET attained increases in strength following RT, and vice versa (Marsh et al., 2020). Surprisingly, ~50% of participants showed non-training type-specific responses, and reported increases in strength following ET (51%), and increases in $\dot{V}_{O_2 \max}$ following RT (57%) (Marsh et al., 2020). Hautala et al. (2006) also observed that subjecting individuals who failed to increase $\dot{V}_{O_2 \max}$ following ET to RT could counteract previous non-response and elicit increases in $\dot{V}_{O_2 \max}$. Whilst positive responses to training are primarily training type-specific, changing the type of exercise (e.g., from ET to RT) may be an effective strategy for some individuals to provoke subsequent adaptation in other parameters of interest and, to a lesser extent, in $\dot{V}_{O_2 \max}$.

3.2 | Volume of training

It has been argued that the non-response phenomenon to ET is a modifiable outcome (Pickering & Kiely, 2019). Non-responders may simply experience an insufficient training dose (product of training intensity and volume, where volume is the product of the training frequency and exercise duration), as required to induce physiological adaptations that manifest as increased $\dot{V}_{O_2 \max}$ (Montero & Lundby, 2017). Accordingly, Williams et al. (2019) investigated the response rates following high- and low-volume HIIT and MICT, reporting that high-volume HIIT, which involved the greatest training dose, produced the fewest $\dot{V}_{O_2 \max}$ non-responders (35%), followed by MICT (42%) and low-volume HIIT (52%). Indeed, increasing training volume has consistently shown to increase response rates. Astorino and Schubert (2014) found an increase in response rates following 12 weeks' high-volume HIIT compared to 2 weeks' low-volume sprint interval training (SIT), whereby non-response rates were 5% and 35%, respectively. In addition to a greater training volume, the 12-week programme may have also allowed a greater time course for adaptations to manifest, thus resulting in increased response rates. Sisson et al. (2009) reported the likelihood of non-response was 74% lower when weekly training volume, at 50% $\dot{V}_{O_2 \max}$, targeted 12 versus 4 kcal/kg/wk. Ross et al. (2015) reported that when exercising at 50% $\dot{V}_{O_2 \max}$, increasing training volume from 180 to 360 kcal per session and from 300 to 600 kcal per session for women and men, respectively, reduced the number of non-responders by 50%. Montero and Lundby (2017) observed similar findings whereby in response to 60, 120, 180, 240 and 300 min/wk of ET at ~60% maximum work rate, the incidence of non-response was 69%, 40%, 29%, 0% and 0%, respectively. Furthermore, the authors reported that non-response was abolished following completion of a further 6 weeks' ET with an additional two sessions per week. A common finding in the studies that investigated response rates to ET following the manipulation of training volume is that for a given intensity, greater volumes induced greater mean changes in $\dot{V}_{O_2 \max}$ compared to the lower volume protocols (Montero & Lundby, 2017; Ross et al., 2015; Sisson et al., 2009). Increased response rates may therefore be driven more so by greater mean changes in $\dot{V}_{O_2 \max}$ than a narrowing in response variability (Atkinson et al., 2019; Bonafiglia et al., 2021).

Whilst a seemingly efficacious strategy to increase $\dot{V}_{O_2 \max}$ responses, increasing training volume may be unfeasible for a large proportion of the population endeavouring to obtain the health benefits of exercise. Lack of time is the main barrier to exercise (Godin et al., 1994), and thus simply increasing the training volume to achieve beneficial adaptations may not be a feasible strategy for many individuals. The strenuous nature of increasing training volume may also prove detrimental to training adherence (Joyner, 2017). For example, Hickson et al. (1977) demonstrated linear increases in $\dot{V}_{O_2 \max}$ following 10 weeks of strenuous ET, yet, despite marked gains in $\dot{V}_{O_2 \max}$, the strenuous nature of the ET deterred participants from continuing with the protocol beyond the study.

Moreover, ensuring adherence to the current exercise guidelines has proven a challenge in itself (Du et al., 2019). Therefore, whilst increasing training volume is efficacious in reducing the incidence of non-response, simply increasing training volume to achieve greater responses may be challenging in certain populations and not a realistic solution.

3.3 | Intensity of training

Intensity of training is another key variable influencing adaptations in $\dot{V}_{O_2 \max}$ (MacInnis & Gibala, 2017). Whilst increases in $\dot{V}_{O_2 \max}$ can be achieved via MICT, the gains observed following HIIT tend to be somewhat superior, with a substantially diminished time commitment (Milanović et al., 2015). Farah et al. (2014) reported a superior increase in $\dot{V}_{O_2 \max}$ following 6 months' ET matched by training volume at an intensity corresponding to the ventilatory threshold (VT) compared to training 20% <VT (10.4 vs. 6.1 ml/kg/min). Surprisingly, Gaskill et al. (2001) and Guio de Prada et al. (2019) reported similar changes in $\dot{V}_{O_2 \max}$ following ET <VT and >VT, yet training at intensities >VT resulted in greater increases in the VT. Ross et al. (2015) reported that following ET completed at 50% and 75% $\dot{V}_{O_2 \max}$, incidence of non-response was 17.6% and 0%, respectively, despite the two programmes being matched by training volume. Manipulation of the training dose thus has a strong influence on response rates and can be used as a tool to increase the likelihood of observing meaningful responses. Indeed, it has been suggested that providing the training dose is sufficient to elicit a potent exercise stimulus, the absence of positive changes in $\dot{V}_{O_2 \max}$ should be minimal, if not non-existent (Montero & Lundby, 2017). As such, the exercise stimulus must evoke potent challenge to the bodily systems and metabolic signalling pathways that provoke adaptation in aerobic capacity (Bishop et al., 2019).

Metcalfe and Vollaard (2021) reported that after SIT, which may elicit consistently high metabolic perturbations associated with the severe-intensity domain (Black et al., 2017), the non-response rate was 18%, similar to the ~20% rate typically reported following ET (Bouchard et al., 1999). Moreover, Bonafiglia et al. (2016) and Gurd et al. (2015) also reported marked response variability following SIT. Importantly, oxidative stress is an essential signal for metabolic pathways and adaptations in $\dot{V}_{O_2 \max}$ (Margaritelis et al., 2018). Margaritelis et al. (2018) reported that when individuals experienced low exercise-induced oxidative stress, subsequent increases in $\dot{V}_{O_2 \max}$ were inferior compared to individuals who experienced high oxidative stress (12% vs. 19%, respectively). For low-intensity ET, it may thus be important to ensure that intensity is high enough to create such a stress, below which simply increasing training volume may not be effective in stimulating adaptation. Overall, a sufficient exercise stimulus is required to activate signalling pathways that when repeated over time manifest into chronic adaptations. If training intensity is low, training volume must be increased to elicit an adaptive stimulus, provided that the intensity is potent enough.

3.4 | Prescription of exercise intensity

A multitude of methods can be used to prescribe intensity for ET, the most common practices anchor intensity relative to maximum physiological values (Table 2), which will be termed traditionally prescribed ET. Traditional methods are commonly used to control exercise intensity defined by the current exercise guidelines (150 min/week of moderate-intensity (3–6 metabolic equivalents) or 75 min/week of vigorous-intensity (≥ 6 metabolic equivalents) exercise) (American College of Sports Medicine, 2017; Bull et al., 2020). It is assumed that traditionally prescribed ET will elicit homogeneous acute physiological responses among individuals, yet this is not the case (Iannetta et al., 2020, 2021; Katch et al., 1978; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010).

Acute physiological responses to exercise are dictated by two physiological thresholds which delineate three domains of exercise intensity (moderate, heavy and severe; Jamnick et al., 2020), each of which elicit distinctive homeostatic perturbations (Black et al., 2017; Carter et al., 2002). Within the literature, the varied nomenclature for these two physiological thresholds can be confusing (Poole et al., 2020). Whilst acknowledging that each of the various physiological thresholds are not synonymous and should not be used interchangeably (Caen et al., 2018), for this review, thresholds are categorised into two tipping points: T_1 and T_2 (Table 1). Crucially, among individuals, T_1 and T_2 vary in their position relative to $\dot{V}_{O_{2\max}}$ (Iannetta et al., 2020). It has been shown that T_1 can vary between 40 and 60% $\dot{V}_{O_{2\max}}$ among individuals with similar $\dot{V}_{O_{2\max}}$ values (Lansley et al., 2011); T_2 , estimated by critical power (CP), ranged between 53–80% peak work rate in young healthy males (Van Der Vaart et al., 2014); and in elite marathon athletes, T_1 and T_2 occurred at extremely high fractions of $\dot{V}_{O_{2\max}}$ ($\sim 85\%$ and $\sim 95\%$, respectively; Jones et al., 2020). In the HERITAGE study, the position of T_1 occurred at various percentages of $\dot{V}_{O_{2\max}}$ among individuals, and consequently the standardisation of exercise intensity (55–75% $\dot{V}_{O_{2\max}}$) resulted in exercise undertaken $<T_1$ and $>T_1$ among individuals (Gaskell et al., 2001). Thus, unsurprisingly, when exercising at an intensity fixed to a maximum physiological value, individuals may be exercising above, or below, T_1 and T_2 (Dwyer & Bybee, 1983; Iannetta et al., 2020; Katch et al., 1978; Meyer et al., 1999; Weltman et al., 1989, 1990). As diverse physiological response profiles are elicited at such intensities, traditionally prescribed ET does not appropriately control the exercise intensity and stimuli experienced among individuals despite prescribing 'standardised' exercise (Iannetta et al., 2020, 2021; Jamnick et al., 2020).

3.4.1 | Traditional approaches to exercise intensity prescription

Traditionally prescribed ET programmes appear to elicit a heterogeneous response to an acute exercise stimulus among individuals. For example, despite all corresponding to the heavy-intensity domain according to the ACSM guidelines (Table 2), exercise

performed at 60–80% $\dot{V}_{O_{2\max}}$ results in considerable differences in \dot{V}_{O_2} , HR and blood lactate concentrations among individuals (Katch et al., 1978; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). Moreover, tolerable exercise duration varies considerably between such intensities, for example, some participants appear to be able to sustain exercise at 75% $\dot{V}_{O_{2\max}}$ for 60 min, while others are unable to do so (range: 10–50 min) (Scharhag-Rosenberger et al., 2010).

Chronically, substantial heterogeneity in the adaptations to traditionally prescribed ET has also been observed. In the DREW study (Church et al., 2007), >30% of participants experienced no increase in $\dot{V}_{O_{2\max}}$ following ET prescribed at 50% $\dot{V}_{O_{2\max}}$ (Pandey et al., 2015a). In the HART-D study (Church et al., 2010), it was reported that 57% of individuals experienced an increase in $\dot{V}_{O_{2\max}}$, and only 37% an increase of $\geq 5\%$ (Pandey et al., 2015b). Similarly, in the STRRIDE studies (Kraus et al., 2001; Slentz et al., 2011), the change in $\dot{V}_{O_{2\max}}$ ranged substantially, between -37 – 77% (L. Ross, et al., 2019). Hautala et al. (2006) reported a range of changes in $\dot{V}_{O_{2\max}}$ from -5 – 22% following ET prescribed at 70–80% HR_{\max} . Williams et al. (2019) concluded that despite positive aggregate changes in $\dot{V}_{O_{2\max}}$ following traditionally prescribed HIIT, SIT and MICT, each protocol produced considerable heterogeneity in changes in $\dot{V}_{O_{2\max}}$ among individuals. Whilst response rates are influenced by various factors, the commonality of varied responses following traditionally prescribed ET appears to be relevant.

The use of heart rate reserve (HRR) and oxygen uptake reserve ($\dot{V}_{O_{2R}}$), not to be used interchangeably (Marini et al., 2021), have been proposed to create more homogeneous ET programmes. However, these methods still produce dissimilar responses to exercise. Weltman et al. (1990) reported that at 85% HRR, only 65% of individuals were exercising above T_1 and thus exercising in the intended heavy intensity domain. Following HIIT (90% HRR) and MICT (60–70% HRR), Rowan et al. (2017) reported a mean increase in $\dot{V}_{O_{2\max}}$ of ~ 5 ml/kg/min in both groups; however, $\sim 60\%$ of individuals increased $\dot{V}_{O_{2\max}}$ by <5 ml/kg/min. Scharhag-Rosenberger et al. (2012) reported that following 1 year of ET at 60% HRR, the mean increase in $\dot{V}_{O_{2\max}}$ was $\sim 14\%$, but changes ranged from -3 – 37% , and 22% of the participants were deemed non-responders. Moreover, a series of studies implementing ET progressing from 40–65% HRR evoked non-response rates ranging from ~ 30 – 60% (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015). It is acknowledged that chronic adaptations from ET are composed of 'micro-adaptations' experienced over time (Flück, 2006), and thus it is plausible, but not yet demonstrated, that heterogeneous acute responses to exercise, when repeated over time, may manifest as heterogeneous chronic responses (Mann et al., 2013; Scharhag-Rosenberger et al., 2010).

Overall, traditionally prescribed ET does not elicit a uniform exercise intensity among individuals despite aiming to prescribe standardised ET. This may contribute to the varied chronic responses commonly observed following traditionally prescribed ET. Despite these shortcomings, traditional methods remain the dominant means of intensity prescription within both the scientific literature and the

field, most likely due to their practicality and availability to be used by the general population (e.g., HR monitors and smartwatches).

3.4.2 | Threshold-based exercise intensity prescription

An alternative method of exercise intensity prescription implements the use of physiological thresholds as anchors in an attempt to account for metabolic differences among individuals (Mann et al., 2013; Scharhag-Rosenberger et al., 2010). Specifically, threshold-based ET has been reported to elicit more homogeneous physiological responses to an exercise bout among individuals (Baldwin et al., 2000; Black et al., 2017; Lansley et al., 2011). Therefore, when repeated over time, threshold-based ET is proposed to result in more homogeneous chronic adaptations and reduced response variability (Mann et al., 2013; Scharhag-Rosenberger et al., 2010). An increase in response rates following threshold-based ET has indeed been reported in some studies (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015). Nonetheless, Karavirta et al. (2011) reported a considerable range of changes in $\dot{V}_{O_2 \max}$ following ET prescribed above and below T_1 combined with RT (−8 to 42%). The authors of this study, however, did not report the specific intensities of the training sessions preventing a full explanation for this variability.

The LT can be used as an anchor to prescribe the intensity of exercise (Edge et al., 2006) and appears to produce a more homogeneous exercise stimulus among individuals than that elicited by traditional methods (Baldwin et al., 2000). Baldwin et al. (2000) demonstrated that performing a similar exercise dose at 70% $\dot{V}_{O_2 \max}$ compared to 95% LT elicited observable differences in the acute physiological responses among trained and untrained individuals. When performed at 95% LT, the perturbations were more homogeneous both within and between trained and untrained groups (Baldwin et al., 2000). Such results support the superiority of threshold-based ET in its ability to control exercise intensity. A recent study demonstrated higher response rates following HIIT at 90% HR_{\max} (95%) compared to MICT at 90% LT (53%), despite the range of $\dot{V}_{O_2 \max}$ changes being similar between groups (Maturana et al., 2021). Notably, in the HIIT group the intensity of 90% HR_{\max} was sufficient to ensure that all individuals were exercising above T_2 . In this instance, information of physiological thresholds helped inform the prescription of traditionally prescribed HIIT, without which it would have been uncertain whether the prescribed intensity provoked exercise pertaining to the intended severe-intensity domain among all individuals.

Prescribing intensity using the delta (Δ) concept has been proposed based on its ability to reduce the variability in the acute physiological perturbations experienced by individuals compared to traditionally prescribed ET (Lansley et al., 2011). The Δ method prescribes intensity as a percentage of the difference between a sub-maximum (T_1) and maximum physiological value (Casaburi et al., 1987). Yan et al. (2017) prescribed intensity equating to the power at LT plus 40–70% of the difference between LT and peak aerobic power (i.e. 40–70% Δ). However, preliminary findings do demonstrate variable changes in

$\dot{V}_{O_2 \max}$ following 4 weeks of HIIT (−455 to 1521 ml/min). Casaburi et al. (1987) did however report 100% response rates following ET prescribed at 50–75% Δ with a mean increase in $\dot{V}_{O_2 \max}$ of ~15% (7–30%). It has been suggested that 50% Δ approximates CP (i.e., T_2 ; de Souza et al., 2016), and therefore exercising at intensities above this threshold should elicit consistently high metabolic stress among individuals, increasing the likelihood of stimulating subsequent adaptation and increased response rates. Lansley et al. (2011) observed significantly lower individual variability in a variety of acute physiological responses following exercise prescribed at 40%, 60% and 80% Δ compared to 50%, 70% and 90% $\dot{V}_{O_2 \max}$. Additionally, at 70% $\dot{V}_{O_2 \max}$, four individuals attained $\dot{V}_{O_2 \max}$ and were unable to sustain the exercise for 20 min (Lansley et al., 2011), consistent with a work intensity within the severe-intensity domain (Black et al., 2017), demonstrating an inability of traditional approaches to accurately control the exercise stimulus among individuals (Iannetta et al., 2020).

It is generally accepted that T_2 represents the upper boundary at which metabolic stability may be achieved, thus demarcating the heavy- and severe-intensity domain. It has recently been proposed that CP is the gold-standard representation of this threshold (Jones et al., 2019; Poole et al., 2020). However, unlike its common application to determine endurance performance (Craig et al., 2018; Jones et al., 2020), the efficacy of using CP to prescribe training has not been readily demonstrated within the literature despite its recognition as a potentially efficacious anchor for intensity prescription. This may relate to the arduous nature of determining CP, although alternative methods have now been developed to overcome this issue (Muniz-Pumares et al., 2019).

Working at an intensity <CP enables the consistent attainment of metabolic stability and stabilised \dot{V}_{O_2} kinetics, allowing for prolonged exercise to be completed (Craig et al., 2018; Jones et al., 2008, 2019). Working >CP prevents the attainment of metabolic stability, which ultimately results in task failure at a hyperbolic rate (Craig et al., 2018; Jones et al., 2008, 2019). In particular, exercising >CP is associated with discrete acute responses and predictable exercise tolerances (Black et al., 2017). Accordingly, CP is a strong candidate as a key anchor of intensity (Poole et al., 2020). Training programmes specifically informed by the running derivative of CP, critical speed, have proven effective in the prescription of HIIT, eliciting an increase in both critical speed and $\dot{V}_{O_2 \max}$ (Clark et al., 2013; Pettitt, 2016; Pettitt et al., 2015; Thomas et al., 2020). However, response variability is yet to be investigated following CP-informed ET. As exercising relative to CP is associated with predictable physiological perturbations (Black et al., 2017), future research might aim to investigate whether the CP-based ET elicits more homogeneous chronic adaptations in $\dot{V}_{O_2 \max}$ than that of traditional approaches as a result of exposure to more homogeneous acute exercise responses among individuals.

In addition to marked increases in $\dot{V}_{O_2 \max}$, prescribing volume-matched ET relative to VT (T_1) and the respiratory compensation point (T_2) resulted in 100% response rates compared to 40–70% response rates when ET was prescribed relative to HRR (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015). Thresholds derived from gas exchange data are likely to

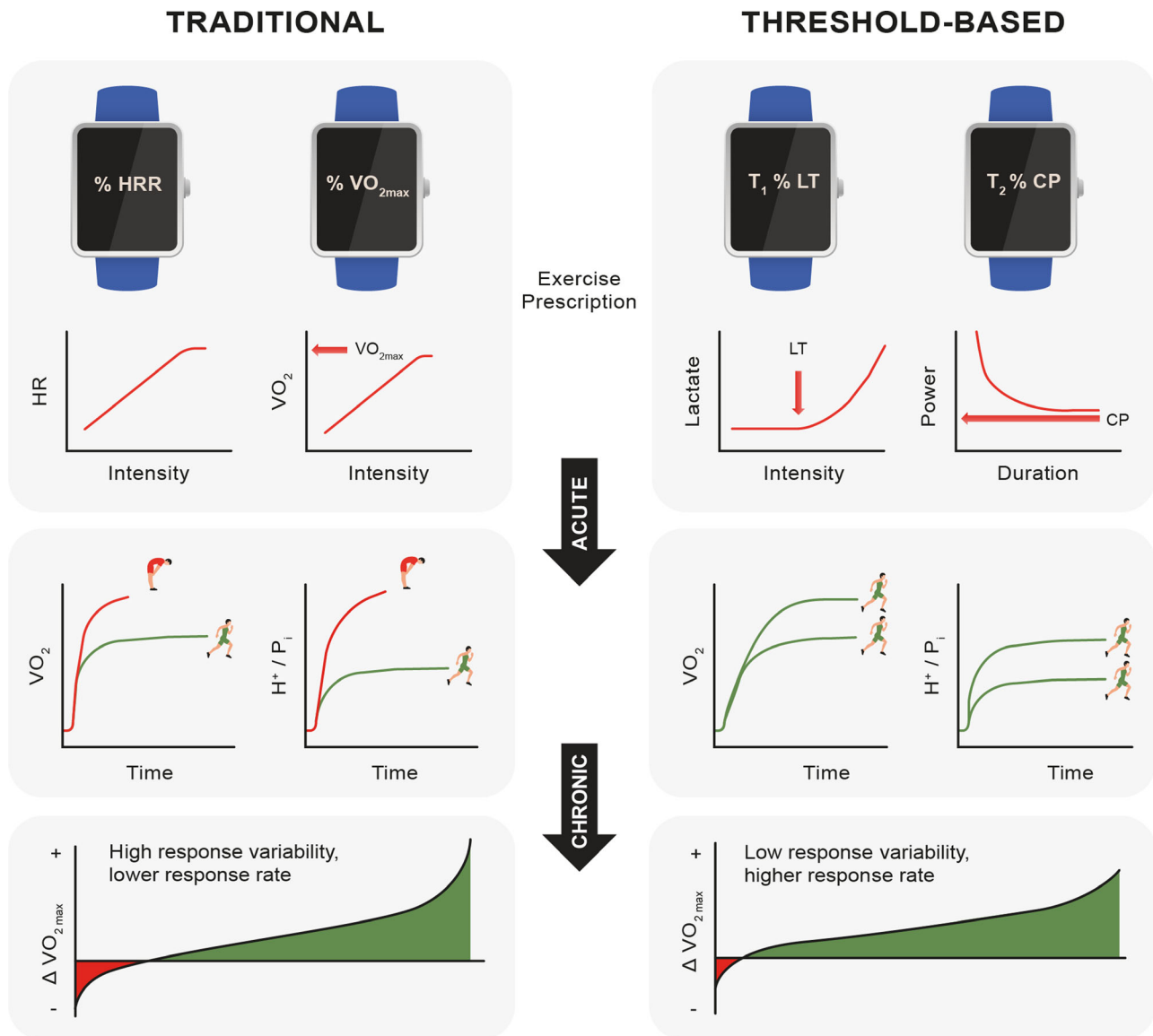


FIGURE 2 Theoretical pathway for varied response following traditional versus threshold-based intensity prescription within an endurance training programme. Some examples are provided of traditional and threshold-based anchors of intensity. Compared to traditional approaches (where intensity is relative to a maximum physiological value), threshold-based approaches (where intensity is relative to a physiological threshold) elicit more homogeneous responses to an acute exercise bout. When repeated over time, more homogeneous chronic adaptations may manifest resulting in reduced response variability and increased response rates. CP, critical power; H^+ , hydrogen ion concentration; HRR, heart rate reserve; LT, lactate threshold; P_i , inorganic phosphate concentration; T_1 , tipping point 1; T_2 , tipping point 2; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2\max}$, maximum oxygen uptake

reflect changes in metabolic rate and substrate utilization in response to different exercise intensities (Keir et al., 2015). Therefore, the increased response rates may have been driven by repeated exposure to more homogeneous exercise stimuli, as evidenced herein when using physiological thresholds to prescribe intensity. However, as this was not determined, it is unclear whether increased response rates were, in fact, the result of reductions in response variability, greater mean changes in $\dot{V}O_{2\max}$ or both.

Overall, most studies have demonstrated greater response rates following threshold-based ET compared to traditionally prescribed ET (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al.,

2019; Wolpern et al., 2015). As threshold-based ET elicits more homogeneous acute physiological stress among individuals, increased response rates following such ET may be driven by the manifestation of more homogeneous chronic adaptations (Figure 2). In contrast to attributing increased response rates to greater mean changes in $\dot{V}O_{2\max}$, as typically observed following the manipulation of training dose within traditionally prescribed ET, future research might aim to determine whether increased response rates following threshold-based ET are, in fact, driven by a reduction in response variability exclusively, or in addition to the elicitation of greater mean changes in $\dot{V}O_{2\max}$.

4 | SUMMARY

In summary, considerable individual variability in $\dot{V}_{O_2 \max}$ response rates occurs following ET. This is concerning as ~20% of the population may not increase CRF in response to ET, even when adhering to the exercise guidelines. As increases in CRF are associated with improved health and reduced risk of disease and all-cause mortality, understanding the factors which may influence response variability and how to minimise the incidence of non-response is important. This review has explored the biological contributors of CRF response variability following a period of ET, and the methodological sources of variation that, upon manipulation, can influence subsequent CRF training responses.

Biological factors including genetics, age, sex and baseline $\dot{V}_{O_2 \max}$ appear to contribute to varied individual responses, with the most potent being genetics, explaining ~50% of response variability. However, the molecular basis underpinning $\dot{V}_{O_2 \max}$ trainability remains unclear. The influence of age, sex and baseline $\dot{V}_{O_2 \max}$ appears to be smaller, accounting for <10% of response variability when combined. Men appear to be somewhat more responsive than women and increases in $\dot{V}_{O_2 \max}$ are attributed primarily to central adaptations. In contrast, increases in $\dot{V}_{O_2 \max}$ in women appear to be attributed to a greater extent to peripheral adaptations. Lastly, whilst the effect of baseline $\dot{V}_{O_2 \max}$ on response variability remains inconclusive, individuals possessing an already well-developed $\dot{V}_{O_2 \max}$ phenotype are at a higher risk of non-response due to a physiological 'ceiling', whereby scope for further adaptation becomes diminished.

The manipulation of methodological factors appears to have a potent influence on $\dot{V}_{O_2 \max}$ response variability. Changing the type of exercise can salvage previous non-response to training in some individuals; however, these improvements are primarily training-type specific. Increasing training dose, and thus the physiological stress elicited by the exercise within an ET programme, has consistently been shown to increase $\dot{V}_{O_2 \max}$ response rates. However, whilst efficacious, such a strategy may be unfeasible for the wider population.

The method of intensity prescription implemented within ET can influence subsequent $\dot{V}_{O_2 \max}$ response rates and, notably, could explain a significant proportion of response variability to ET. Whilst increases in $\dot{V}_{O_2 \max}$ can be achieved via traditionally prescribed ET, the unpredictable and heterogeneous physiological stress experienced among individuals assumed to be exercising at the same standardised intensity likely promotes variable chronic adaptations. The mechanisms explaining the observed reduction, or even abolishment, of non-response to ET following threshold-based ET likely stems from the ability of such methods to better control the acute physiological stress elicited by such exercise. It is plausible that, when repeated over time, the accumulation of more homogeneous micro-adaptations among individuals may manifest as more homogeneous chronic adaptations and thus increased response rates as a result of reduced response variability.

5 | FUTURE DIRECTIONS

Future research may endeavour to investigate whether threshold-based ET reduces the incidence of non-response via the elicitation of more homogeneous responses to exercise among individuals, and whether such increases in response rates are attributable to reduced individual response variability exclusively or in addition to greater mean changes in $\dot{V}_{O_2 \max}$. Such findings may help inform future training interventions which aim to obtain increases in $\dot{V}_{O_2 \max}$ in as many individuals as possible, increasing the number of individuals attaining meaningful health benefits from exercise.

COMPETING INTERESTS

S.M., L.B. and D.M.-P. declare that they have no conflicting interests.

AUTHOR CONTRIBUTIONS

S.M. drafted the manuscript. D.M.-P. and L.B. were involved in the editing of the manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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