The Effect of Intensity Prescription on Individual Responses to Exercise

Samuel Jon Richard Meyler

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School of Life and Medical Sciences

University of Hertfordshire

Hatfield

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ABSTRACT

Following exercise training, evidence demonstrates improvements in exercise capacity, symptoms of disease, quality of life, as well as reductions in hospitalisation, morbidity, and mortality. Notably, cardiorespiratory fitness, measured as maximum oxygen uptake ($\dot{V}O_{2max}$), is associated with all the above. Whilst exercise training increases $\dot{V}O_{2max}$ at the group level, these changes appear to be heterogenous at the individual level. Numerous (non)modifiable factors contribute to response variability. One factor requiring further research is the way exercise intensity is prescribed. The traditional approach is evidenced as inadequate, poorly controlling and normalising exercise intensity among individuals, potentially implicating subsequent acute and chronic responses. Exploring the efficacy of alternative approaches is thus warranted to improve the prescription of exercise intensity and increase the likelihood of individuals experiencing meaningful changes in $\dot{V}O_{2max}$. This was the inherent aim of the thesis. In **Chapter 4**, results of a meta-analysis using individual participant data revealed no difference in $\dot{V}O_{2max}$ response variability following either traditional or threshold-based exercise training. However, greater mean increases in $\dot{V}O_{2max}$ were observed following threshold-based exercise training and increased the likelihood of increasing $\dot{V}O_{2max}$ beyond a predefined response threshold. In **Chapter 5**, it was demonstrated that in response to different exercise bouts, the variability in exercise tolerance and acute physiological responses was lower when exercise intensity was prescribed relative to critical power (a 'threshold-based approach') compared to when prescribed relative to $\dot{V}O_{2max}$ (a 'traditional approach'). In **Chapter 6** it was demonstrated that increases in $\dot{V}O_{2max}$ were superior following exercise training prescribed relative to critical power compared to when prescribed relative to $\dot{V}O_{2max}$. Furthermore, a greater proportion of individuals increased $\dot{V}O_{2max}$ above the predefined response threshold in the threshold group. There was, however, no difference in $\dot{V}O_{2max}$ response variability between exercise groups. The findings of this thesis advocate the use of threshold-based approaches, namely using critical power, to inform and prescribe exercise intensity.

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ABBREVIATIONS

Δ	Delta
[ ]	Denotes concentration
a-vO_2 diff	Arteriovenous oxygen difference
ACSM	American College of Sports Medicine
BF	Bayes factor
BLa	Blood lactate
b·min^{-1}	Beats per minute
BV	Blood volume
Ca-vO_{2max}	Maximum arteriovenous oxygen difference
CI	Confidence intervals
CO_2	Carbon dioxide
CP	Critical power
CrI	Credible intervals
CS	Critical speed
CT	Continuous training
CWR	Constant work rate test
EDV	End-diastolic volume
GET	Gas exchange threshold
GWAS	Genome wide association studies
GXT	Maximal ramp exercise test

H^+	Hydrogen ions
HIIT	High intensity interval training
$HIIT_{THR}$	High intensity interval training prescribed relative to CP
$HIIT_{TRAD}$	High intensity interval training prescribed relative to maximum oxygen uptake
HR	Heart rate
HRR	Heart rate reserve
HR_{max}	Maximum heart rate
HR_{peak}	Peak heart rate
HVY_{THR}	Heavy intensity exercise prescribed relative to gas exchange threshold and critical power
HVY_{TRAD}	Heavy intensity exercise prescribed relative to maximum oxygen uptake
INT	Interval exercise
$kcal \cdot kg^{-1} \cdot wk^{-1}$	Kilocalories per kilogram per week
$L \cdot min^{-1}$	Litres per minute
LT	Lactate threshold
LTP	Lactate turn point
LTv	Velocity at lactate threshold
MICT	Moderate intensity continuous training
MID	Minimum important difference
$min \cdot wk^{-1}$	Minutes per week

$mL \cdot kg^{-1} \cdot min^{-1}$	Millilitres per minute per kilogram
MLSS	Maximal lactate steady state
mmHg	Millimetre of mercury
$mmol \cdot L^{-1}$	Millimoles per litre
MOD_{THR}	Moderate intensity exercise prescribed relative to gas exchange threshold
MOD_{TRAD}	Moderate intensity exercise prescribed relative to maximum oxygen uptake
O_2	Oxygen
P_i	Inorganic phosphates
P_{max}	Maximum power output
PO_2	Partial pressure of oxygen
PP_{GXT}	Peak power attained in maximal ramp exercise test
PPO	Peak power output
PV	Plasma volume
$\dot{Q}$	Cardiac output
$\dot{Q}_{max}$	Maximum cardiac output
RBC	Red blood cell volume
RCP	Respiratory compensation point
SIT	Sprint interval training
SMD	Smallest meaningful difference

SNPs	Single nucleotide polymorphisms
SV	Stroke volume
T1	Physiological threshold one
T2	Physiological threshold two
TE	Technical error of measurement
THR	Exercise prescribed relative to a given physiological threshold
TRAD	Exercise prescribed relative to a given traditional anchor of exercise intensity
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}_E$	Minute ventilation
VER	Verification bout
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_{2peak}$	Peak oxygen uptake
$\dot{V}O_{2max}$	Maximum oxygen uptake
$\dot{V}O_2R$	Oxygen uptake reserve
VT	Ventilatory threshold
W	Watts
W′	Work-prime
WEP	Work above end power output during a three minute all out test

PUBLICATIONS

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CHAPTER 1 – INTRODUCTION

The benefits of aerobic exercise training are unquestionable, positively impacting numerous aspects of both health and endurance performance (Bassett & Howley, 2000; Harber et al., 2017; Jones & Carter, 2000; Warburton & Bredin, 2017). Aerobic exercise training, typically comprised of continuous and/or interval exercise, is typically structured around a series of training principles including training frequency, intensity, duration, and type (Garber et al., 2011), each of which can be manipulated to create a desired training session. As such, recommendations for exercise prescription exist for different populations concerning each training principle (Garber et al., 2011; Pollock et al., 1998; Stefani et al., 2017).

A commonly sought after response to exercise training is an increase in cardiorespiratory fitness, measured as maximum oxygen uptake ($\dot{V}O_{2max}$), which represents the upper limit of cardiopulmonary-muscle oxidative function and quantifies the body's ability to transport and utilise oxygen (Hill & Lupton, 1923; Jones & Carter, 2000). $\dot{V}O_{2max}$ is thus a key measure of cardiovascular, respiratory, and muscular fitness (Millet et al., 2023; R. Ross et al., 2016), changes in which can have important implications on both endurance performance (Bassett & Howley, 2000; Joyner & Coyle, 2008) and health (Ezzatvar et al., 2021; Harber et al., 2017; R. Ross et al., 2016).

From a performance perspective, $\dot{V}O_{2max}$ is one of the key determinants of endurance performance and thus, increasing $\dot{V}O_{2max}$ is a common training goal for endurance athletes (Joyner & Coyle, 2008). As such, successful endurance athletes typically demonstrate some of the highest $\dot{V}O_{2max}$ values recorded and $\dot{V}O_{2max}$ is often used to described someone's training status (Coyle, 1995; Joyner & Coyle, 2008; S. Robinson et al., 1937). From a health perspective, as $\dot{V}O_{2max}$ integrates the functional capacity of numerous bodily systems to transport and utilise oxygen, demonstrating a high $\dot{V}O_{2max}$ requires these systems to be healthy (R. Ross et al., 2016). Importantly, a low $\dot{V}O_{2max}$ has been associated with an elevated risk of cardiovascular disease, all-cause mortality, and disease-specific mortality (e.g.,

mortality attributable to certain cancers) (Blair, 1989; Laukkanen et al., 2004, 2022; R. Ross et al., 2016; Sawada et al., 2014; Sui et al., 2007).

Exercise training, in the form of continuous and/or interval-based exercise, is consistently shown to increase $\dot{V}O_{2max}$ at the group level; however, at the individual level, this effect appears to exhibit a heterogenous distribution (Bouchard et al., 1999; Williams et al., 2019). For example, whilst some individuals experience significant increases in $\dot{V}O_{2max}$ following exercise training, it is estimated that ~20% of individuals will not (Bouchard et al., 1999; Williams et al., 2019). This has contributed to an interest in individual response variability whereby changes in given parameters regarding their magnitude and variation are explored both at the individual and group level, as well as an increased interest in exploring 'response rates' whereby the proportion of individuals demonstrating a change in a given parameter above and below a predefined response threshold are considered (Astorino & Schubert, 2014; Bonafiglia et al., 2016, 2022; Bouchard et al., 1999; Bouchard & Rankinen, 2001; Gurd et al., 2015; Hautala et al., 2006; Hecksteden et al., 2015; Jacques et al., 2021; Karavirta et al., 2011; Mann et al., 2014; Marsh et al., 2020; Maturana et al., 2021; Montero & Lundby, 2017a; Pickering & Kiely, 2017; L. Ross et al., 2019; R. Ross et al., 2019; Walsh et al., 2020; Weatherwax et al., 2019; Williams et al., 2019; Williamson et al., 2017).

The contributing factors to this $\dot{V}O_{2max}$ response variability are complex, comprising influence from various biological, methodological, and statistical factors (Atkinson & Batterham, 2015; Mann et al., 2014; R. Ross et al., 2019; Sarzynski et al., 2017; Williamson et al., 2017). The focus of this thesis concerns the impact that a methodological factor, explicitly, the method used to prescribe exercise intensity, has on response variability regarding the magnitude and variation in $\dot{V}O_{2max}$ changes that manifest following a period of exercise training. This is an area of research that warrants further exploration as it appears that some individuals undertaking a period of exercise training are not attaining the desired benefits whether that be performance- and/or health-related. Previously, studies have focussed on how the manipulation of other training principles, which typically results in an increase in training dose,

may affect response variability (Bonafiglia et al., 2021, 2022; Montero & Lundby, 2017). Such studies have concluded that the incidence of individuals demonstrating changes in $\dot{V}O_{2max}$ which fall short of a predefined response threshold can be abolished when training volume is increased (Montero & Lundby, 2017) and that adopting strategies that increase the mean group change in $\dot{V}O_{2max}$ (again, often by increasing training volume) is the primary attribute of improved response rates (Bonafiglia et al., 2021, 2022). However, simply increasing the volume of exercise training (i.e., 'just do more') is not a feasible overarching answer. Instead, changing the way in which exercise intensity is prescribed might negate this reactive solution and offer a more proactive approach.

Traditionally, exercise intensity is prescribed relative to a maximum physiological marker such as $\dot{V}O_{2max}$ and maximum heart rate (Milanović et al., 2015). Such approaches are, however, evidenced to poorly normalise and control exercise intensity among individuals (Baldwin et al., 2000; Iannetta et al., 2021; Lansley et al., 2011; McLellan & Skinner, 1981; Scharhag-Rosenberger et al., 2010). One postulation might be that when traditionally prescribed exercise sessions are repeated over time by individuals, the inconsistent exercise stimulus experienced among individuals might manifest as a varied chronic adaptive response within the group leading to a wide array of individual changes in $\dot{V}O_{2max}$ (Hofmann & Tschakert, 2011; Mann et al., 2013; Scharhag-Rosenberger et al., 2010). Using an approach that better normalises and controls exercise intensity among individuals might elicit a more consistent exercise stimulus among individuals and increase the likelihood that individuals exercise meaningful changes in $\dot{V}O_{2max}$ following a period of exercise training.

The primary aim of this thesis was, therefore, to investigate the effect that different methods of exercise intensity prescription have on response variability to both acute exercise bouts and to periods of exercise training.

EXERCISE INTENSITY DOMAINS

Exercise intensity is often considered the most important principle of training (Hofmann & Tschakert, 2011; MacInnis & Gibala, 2017; Wenger & Bell, 1986). However, it is also a difficult principle to prescribe due to the complexity between the prescribed 'external' intensity (i.e., the external load of exercise) and the 'internal' stimulus experienced (i.e., physiological stress). To add to this, there are also a multitude of ways in which exercise intensity can be prescribed (Coates et al., 2023; Jamnick et al., 2020). However, regardless of the method used to anchor exercise intensity, exercise ultimately falls into the moderate, heavy, or severe intensity domain (**Figure 1.1**) (Roston et al., 1987). Each of the intensity domains are associated with a myriad of domain-specific physiological responses relating to factors such as the rate of energy turnover, oxygen uptake ($\dot{V}O_2$) kinetics, metabolite accumulation, and ultimately, exercise tolerance (Black et al., 2017; Jamnick et al., 2020; Jones et al., 2008; Vanhatalo et al., 2016; Willingham & McCully, 2017). The acute responses to exercise are thus dictated by the intensity domain in which exercise is being undertaken.

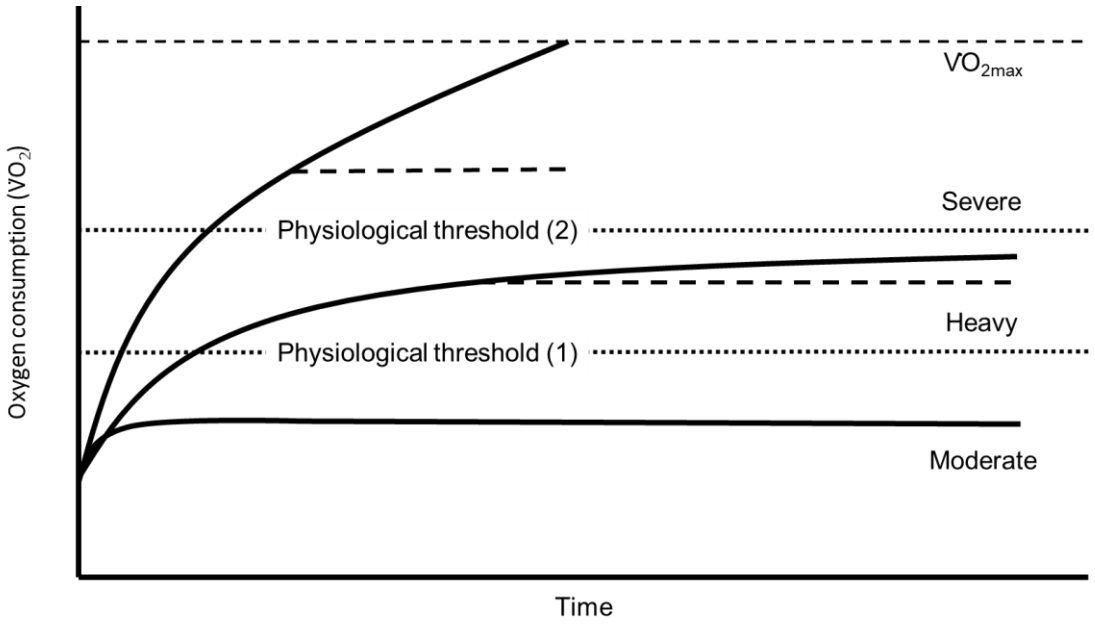

Figure 1.1. Illustration of the three domains of exercise intensity and an example of the associated oxygen uptake ($\dot{V}O_2$) response. Solid curved lines denote the $\dot{V}O_2$ response during constant work rate exercise in the moderate, heavy, and severe intensity domains.

Bold dashed line represents the expected $\dot{V}O_2$ values as interpolated from a test used to determine maximum oxygen uptake ($\dot{V}O_{2max}$; upper dashed line). The space between solid and dashed lines represents the $\dot{V}O_2$ slow component. Dotted lines represent the first and second physiological thresholds that demarcate the boundaries between the moderate-heavy and heavy-severe intensity domains. Adapted from Poole and Jones, (2012).

Within the moderate intensity domain, physiological responses, including changes in heart rate, $\dot{V}O_2$ kinetics, inorganic phosphates (P_i), hydrogen ions (H^+), and blood lactate (BLa), reach an early steady state following the onset of exercise. This steady state typically manifests within 3-4 minutes, allowing exercise to be undertaken for prolonged periods of time (Poole & Jones, 2012). In the heavy intensity domain, physiological responses reveal a delayed steady state, and within the severe intensity domain, attainment of physiological stability is prevented which ultimately leads to task failure at a hyperbolic rate if intensity is not reduced (Craig et al., 2018; Jones et al., 2008, 2019; Poole & Jones, 2012). Within the heavy and severe intensity domains, a $\dot{V}O_2$ slow component can also be observed over time which denotes the additional aerobic energy demand required for sustaining such exercise at fixed intensities (**Figure 1.1**) (Jones et al., 2011; Poole & Jones, 2012). Within the heavy intensity domain, this slow component can be stabilised after 10-20 min of exercise, whereas in the severe intensity domain, the slow component does not reach a steady state, instead, $\dot{V}O_2$ is driven to $\dot{V}O_{2max}$ (Poole & Jones, 2012).

METHODS OF INTENSITY PRESCRIPTION

Intensity is prescribed such that exercise is undertaken in an intended exercise intensity domain and thus elicits a desired acute and subsequent physiological response thereafter (Hofmann & Tschakert, 2011). There is, however, a plethora of methods used to prescribe exercise intensity, yet the efficacy of some approaches is questionable (Coates et al., 2023; Hofmann & Tschakert, 2011; Iannetta et al., 2020; Jamnick et al., 2020). For the scope of this thesis, methods of exercise intensity prescription will be categorised into traditional or

threshold-based approaches and will be discussed further in **Chapter 2, Prescription of exercise intensity**. In brief, traditional approaches involve anchoring intensity to a fixed percentage of a maximum physiological value such as $\dot{V}O_{2max}$ or maximum heart rate, whilst threshold-based approaches anchor intensity relative to an individual's physiological thresholds that demarcate the exercise intensity domains (**Figure 1.1**).

In comparison to prescribing exercise intensity relative to traditional intensity anchors, evidence exists demonstrating that using threshold-based approaches to prescribe exercise intensity elicits a more homogeneous exercise stimulus across individuals at the acute level (Baldwin et al., 2000; Lansley et al., 2011; McLellan & Jacobs, 1991). Based on these acute level findings, when threshold-based exercise is repeated over time, such acute responses might manifest as more homogeneous and/or superior changes in $\dot{V}O_{2max}$ thereafter (Mann et al., 2013; Scharhag-Rosenberger et al., 2010). In support of this notion, response rates are shown to increase when threshold-based exercise training is undertaken compared to traditionally prescribed exercise training. In turn, using threshold-based approaches may 1) create a more appropriate exercise stimulus for individuals and 2) reduce the incidence of individuals experiencing non-meaningful changes in $\dot{V}O_{2max}$; however, this idea is currently unconfirmed and will thus be explored in this thesis. The findings of this thesis therefore aim to provide information concerning to the most effective means of informing and prescribing exercise intensity.

CHAPTER 2 – LITERATURE REVIEW

A version of this chapter has been published in Experimental Physiology: Meyler, S., Bottoms, L., & Muniz-Pumares, D. (2021). Biological and methodological factors affecting $\dot{V}O_{2max}$ response variability to endurance training and the influence of exercise intensity prescription. *Experimental Physiology, 106*, 1410-1424.

INTRODUCTION

Maximum oxygen uptake

Over one hundred years ago, the term maximum oxygen uptake ($\dot{V}O_{2max}$) was first introduced when a plateau in oxygen uptake ($\dot{V}O_2$) was observed despite an increase in running intensity (Hill & Lupton, 1923). This was indicative of an upper limit of cardiopulmonary-muscle oxidative function whereby the body is no longer able to meet the oxygen demand placed on it by exercise (Hill & Lupton, 1923).

Since then, $\dot{V}O_{2max}$ has become a key concept in exercise physiology (Millet et al., 2023). Its importance is emphasised when considering it represents the combined functionality of the cardiopulmonary, respiratory, and muscular systems, quantifying their ability to transport and utilise oxygen (Poole & Jones, 2012). In turn, $\dot{V}O_{2max}$ has been shown to be a relevant marker in clinical settings as well as performance related environments. Regarding its importance for health, poor levels of $\dot{V}O_{2max}$ are associated with an increased risk of numerous chronic diseases as well as all-cause and disease-specific mortality (Blair, 1989; Harber et al., 2017; Laukkanen et al., 2004, 2022; R. Ross et al., 2016; Sawada et al., 2014; Sui et al., 2007). Despite being the only major risk factor not routinely assessed in clinical practice, growing epidemiological and clinical evidence suggests that $\dot{V}O_{2max}$ may be a stronger predictor of mortality than other risk factors more commonly assessed, such as smoking, type 2 diabetes mellitus, and obesity (Rose et al., 2022; R. Ross et al., 2016). This is important given $\dot{V}O_{2max}$ is a modifiable risk factor that is highly sensitive to training (Bassett & Howley, 2000; Holloszy & Coyle, 1984; Jones & Carter, 2000; MacInnis & Gibala, 2017; Milanović et al., 2015). As

such, relatively modest increases in $\dot{V}O_{2max}$, typically attained through standard endurance training interventions (Jones & Carter, 2000), can have marked reductions on mortality risk (~10-30%) and health care costs (~5%) (Bachmann et al., 2015; Harber et al., 2017; Myers et al., 2018).

It is also acknowledged that $\dot{V}O_{2max}$ is one of the key determinants of endurance performance along with the positioning of one's lactate threshold and exercise economy, with elite endurance athletes demonstrating some of the highest $\dot{V}O_{2max}$ values ever recorded (Coyle, 1995; Joyner & Coyle, 2008; S. Robinson et al., 1937). As such, $\dot{V}O_{2max}$ can be used to predict endurance performance and is commonly used to describe one's training status (Bassett & Howley, 2000; Joyner, 1991; Joyner & Coyle, 2008; Podlogar et al., 2022). However, whilst $\dot{V}O_{2max}$ is a good predictor of endurance performance in a heterogenous group of individuals, the use of this parameter alone does not predict performance in a relatively homogenous group of individuals (Bassett & Howley, 1997; Jones et al., 2020). For example, among world class athletes with similar marathon performance capabilities, marked differences in $\dot{V}O_{2max}$ were observed (Jones et al., 2020). Additionally, improvements in endurance performance can be realised despite no concomitant increase in $\dot{V}O_{2max}$ (Collins et al., 2022; McLaughlin et al., 2010). It is therefore recommended that $\dot{V}O_{2max}$ be used in conjunction with other parameters of performance when describing and predicting endurance performance (Bassett & Howley, 2000; Joyner & Coyle, 2008; Podlogar et al., 2022; Poole & Jones, 2023). The role of $\dot{V}O_{2max}$ may thus have greater precedence when concerning its importance for health.

Changes in maximum oxygen uptake

The most effective means of increasing $\dot{V}O_{2max}$ is through exercise training, typically in the form of whole-body continuous or interval-based exercise (Milanović et al., 2015). Both forms of training have been shown to be effective in eliciting marked increases in $\dot{V}O_{2max}$, with increases of ~5.5 $mL \cdot kg^{-1} \cdot min^{-1}$ and ~4.9 $mL \cdot kg^{-1} \cdot min^{-1}$ following high intensity interval training and moderate intensity continuous training, respectively (Milanović et al., 2015). Accordingly, $\dot{V}O_{2max}$ is markedly reduced by extended periods of physical inactivity such as prolonged bed

rest (Saltin, Blomqvist, Mitchell, Johnson, Wildenthal, Chapman, et al., 1968). For example, a reduction in $\dot{V}O_{2max}$ of ~28% was observed following three weeks of bed rest and was later increased by 96% following three to six months of exercise training undertaken immediately post-bed rest (an increase of +33% from pre-bed rest values) (Saltin, Blomqvist, Mitchell, Johnson, Wildenthal, Chapman, et al., 1968). Typically, the biggest increases in $\dot{V}O_{2max}$ following endurance training are observed in individuals with the lowest initial $\dot{V}O_{2max}$ values (Kilbom, 1971; Siegel et al., 1970).

The positive effect that exercise training has on increasing $\dot{V}O_{2max}$ is well documented with an abundance of classic studies published from the 1960's onwards. Ekblom et al. (1968) measured $\dot{V}O_{2max}$ in healthy young adult males before and after four months of exercise training comprised of cross-country running, distance running, and interval training. In response, $\dot{V}O_{2max}$ increased by 11% (+0.34 $L \cdot min^{-1}$). An increase of 15% (+0.33 $L \cdot min^{-1}$) in $\dot{V}O_{2max}$ was also observed in six adolescent males following six months of exercise training comprised of two sessions per week of ~45-60 mins of either interval training, sprint training, distance training, strength training, and ball games (Ekblom, 1969). An increase of 14% (+5.34 $mL \cdot kg \cdot^{-1} min^{-1}$) and 23% (+9.00 $mL \cdot kg \cdot^{-1} min^{-1}$) has also been demonstrated in sedentary college females following nine weeks of treadmill exercise (3 sessions per week) performed at 50% and 65% heart rate reserve (HRR; the difference between maximum and resting heart rate), respectively (Kearney et al., 1976). Additionally, female participants of a nine-week supervised endurance training programme consisting of running exercise demonstrated and increase in $\dot{V}O_{2max}$ of 34% (Cunningham & Hill, 1975). Increases of 20% and 9% in $\dot{V}O_{2max}$ have been observed following eight weeks of interval and continuous exercise training, respectively (Cunningham et al., 1979). Hickson et al. (1981) observed a 23% increase in $\dot{V}O_{2max}$ following a nine-week training programme consisting of interval and continuous exercise performed six days a week, where 14% of the increases in $\dot{V}O_{2max}$ were attained in the first three weeks of training. More recently, several meta-analyses have analysed the effect of aerobic-based exercise training on changes in $\dot{V}O_{2max}$ providing further support to this

positive relationship (Bacon et al., 2013; Bonafiglia et al., 2022; Bouaziz et al., 2020; Cao et al., 2019; Carazo-Vargas & Moncada-Jiménez, 2015; Diaz-Canestro & Montero, 2019; Mattioni Maturana et al., 2021; Milanović et al., 2015; Scribbans et al., 2016; Sultana et al., 2019; Wen et al., 2019).

In turn, the efficacy that exercise training has on increasing $\dot{V}O_{2max}$ has encouraged its use across a variety of populations, both healthy and clinical, and the benefits of prescribing exercise for the treatment of various cardiovascular, metabolic, and musculoskeletal disorders and diseases is now well evidenced (Pedersen & Saltin, 2015). For example, exercise training comprised of continuous and/or interval-based exercise is recognised as a key treatment approach for type 2 diabetes (D. Thomas et al., 2006), improving glycaemic control via a reduction in glycated haemoglobin, like that induced by metformin medication, and equating to a ~42% reduction in diabetes-related mortality (Pedersen & Saltin, 2015). Exercise training also has a profound effect on reducing coronary heart disease-related mortality, whereby exercise-based cardiac rehabilitation has been shown to reduce overall and cardiovascular-related mortality (risk ratio: 0.87 and 0.74, respectively), as well as reducing hospital admissions (risk ratio: 0.69) (Heran et al., 2011). Additionally, there is plentiful evidence demonstrating that exercise training consisting of continuous and/or interval-based exercise for cancer patients can have numerous benefits on cardiorespiratory fitness, muscular strength, physical functionality, fatigue reduction, physical well-being, and quality of life (Mcneely et al., 2006; Pedersen & Saltin, 2015). It has been shown that interval-based exercise serves as a safe and time-efficient intervention for increasing $\dot{V}O_{2max}$ in cancer patients across all stages of therapy and aftercare (Mugele et al., 2019; Palma et al., 2021a; Wallen et al., 2020). Whilst it is acknowledged that the benefits of exercise extend beyond changes solely in $\dot{V}O_{2max}$, changes in this marker are the primary focus of the present thesis.

Physiological adaptations underpinning changes in maximum oxygen uptake

Given the well-established effect of exercise training on increasing $\dot{V}O_{2max}$, it is important to understand how such changes manifest. An individuals $\dot{V}O_{2max}$ can be explained by the Fick principle (**Figure 2.1**) (Shapiro, 1972; Willis Hurst et al., 2000) where:

$$\dot{V}O_{2max} = Stroke\ Volume\ x\ Heart\ Rate\ \times\ (a - \bar{v}O_2\ diff)$$

As such, $\dot{V}O_{2max}$ is the product of maximum stroke volume and maximum heart rate (which together equate to maximum cardiac output), and arteriovenous O_2 difference (a-$\bar{v}O_2$ diff). Adaptations influencing stroke volume and heart rate reflect 'perfusive' adaptations whereby phenotypic modifications alter convective O_2 delivery, whereas those influencing a-$\bar{v}O_2$ diff reflect 'diffusive' adaptations, where changes in O_2 extraction and utilisation occur (Ekblom et al., 1968).

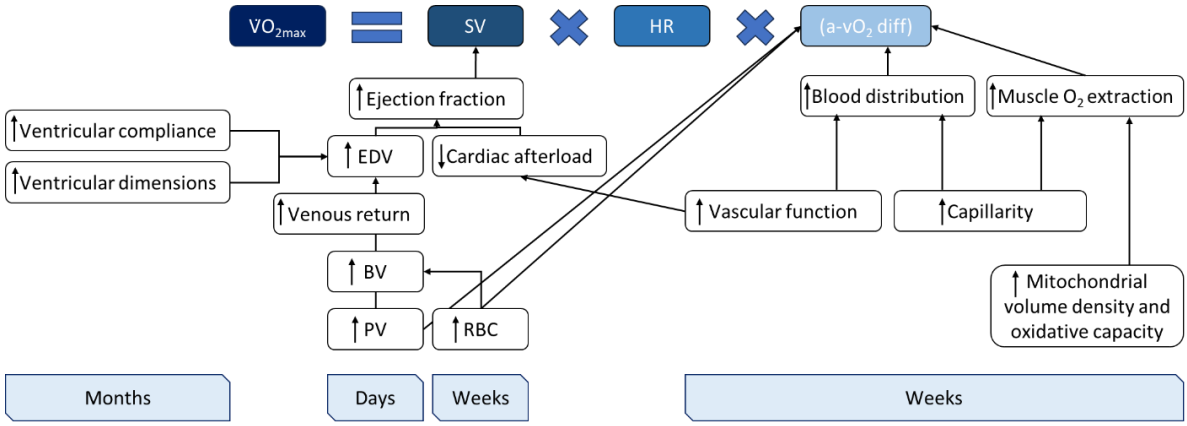

Figure 2.1. Physiological adaptations related to changes in maximum oxygen uptake ($\dot{V}O_{2max}$) induced by exercise training. EDV: end diastolic volume; BV: blood volume; PV: plasma volume; RBC: red blood cell volume; SV: stroke volume; HR: heart rate; (a-$\bar{v}O_2$ diff): arteriovenous difference. Adapted from Lundby et al. (2017).

Accordingly, the use of the 'Wagner diagram' (Wagner, 2008) (**Figure 2.2**) can help facilitate the understanding of how $\dot{V}O_{2max}$ resolves as the product of perfusive (i.e., central) and diffusive (i.e., peripheral) adaptations and illustrates how $\dot{V}O_{2max}$ is increased following exercise training (Poole, Behnke, et al., 2021; Poole et al., 2018; Roca et al., 1992).

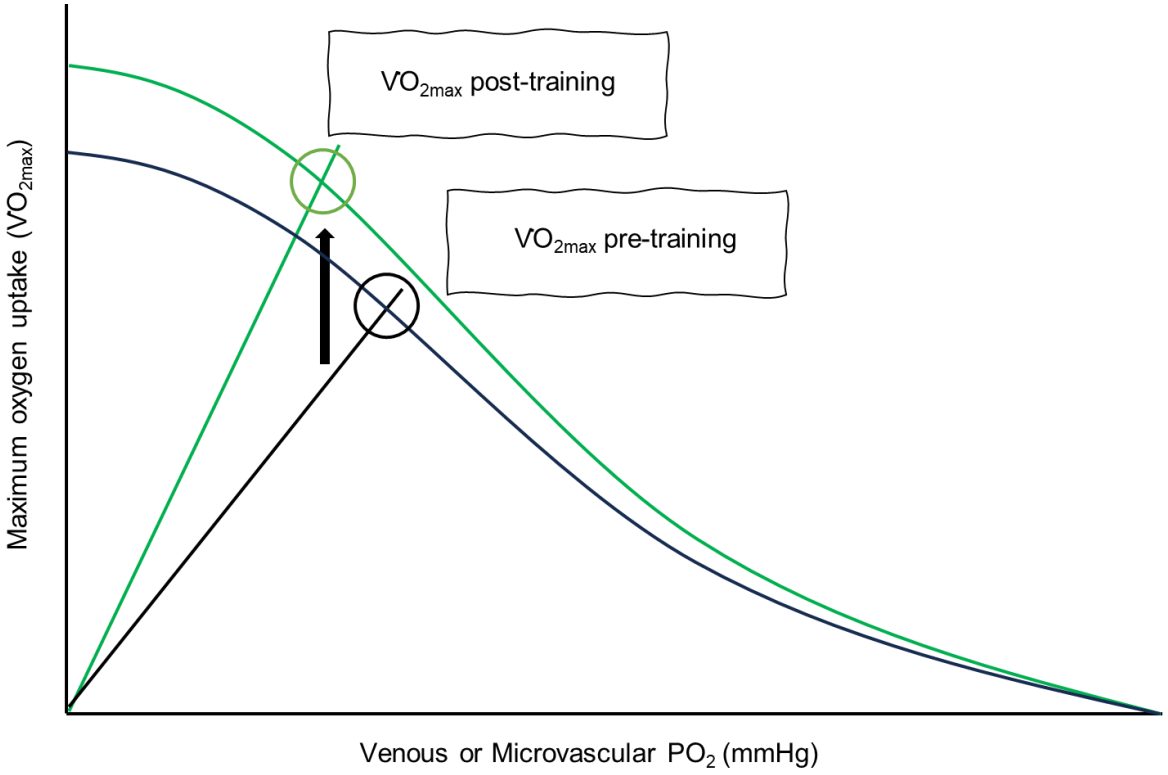

Figure 2.2. Representation of maximum oxygen uptake ($\dot{V}O_{2max}$) plotted as a function of venous or microvascular PO_2. $\dot{V}O_{2max}$ is indicated where perfusive and diffusive lines cross. Perfusive factors indicated by the curved lines and diffusive by straight lines. With training, $\dot{V}O_{2max}$ is increased from pre- (black) to post-training (green). PO_2: partial pressure of oxygen. Adapted from Poole et al. (2021; 2018), Roca et al. (1992), and Wagner (2008b).

Central adaptations

Central adaptations primarily reflect an increase in connective O_2 delivery, which reflect the changes in blood volume, cardiac output, and the O_2-carrying capacity of blood (Lundby et al., 2017). Such factors are demonstrated to be the primary limiting factors of $\dot{V}O_{2max}$ (Bassett & Howley, 2000). The role that augmented blood volume and cardiac output has on increasing $\dot{V}O_{2max}$ is highlighted by clear relationships between $\dot{V}O_{2max}$ and cardiac output, and with red blood cell volume (**Figure 2.3**). Additionally, it is evidenced that conducting phlebotomy after a period of training, i.e., returning blood volume (plasma volume and red blood cell content)

and concomitantly, cardiac output, to pre-training levels, reduces $\dot{V}O_{2max}$ as a result (Bonne et al., 2014; Mandić et al., 2023; Montero et al., 2015). This can be explained by the Frank-Starling mechanism which defines the relationship between the length and tensions of the myocardium. The greater the stretch on the myocardium before systole (preload; augmented by expansions in blood volume) the stronger the ventricular contraction and thus, diastole. This results in a greater stroke volume, leading to a greater cardiac output and thus $\dot{V}O_{2max}$ (Lundby & Montero, 2019). Therefore, following phlebotomy (i.e., the removal of blood), myocardium preload and diastole is reduced, reducing cardiac output and $\dot{V}O_{2max}$ as a result. Additionally, increases in red blood cells and concomitantly their haemoglobin content helps to preserve the blood O_2-carrying capacity which may otherwise be reduced were plasma volume to increase in the absence of changes in red blood cell content (Lundby & Montero, 2019).

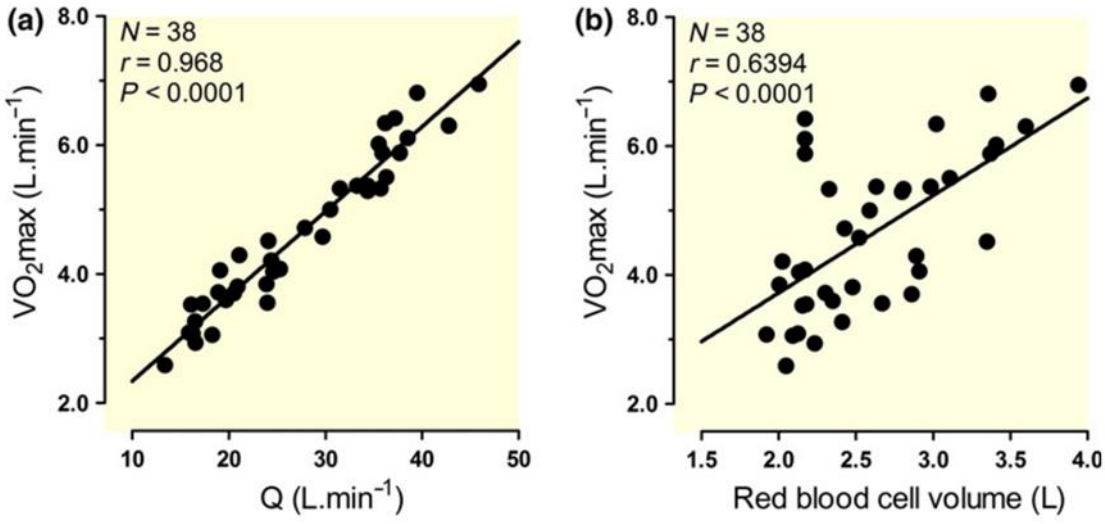

Figure 2.3. Correlations between maximum oxygen uptake ($\dot{V}O_{2max}$) and: a) maximum cardiac output ($\dot{Q}$), and b) red blood cell volume. Taken from Lundby et al. (2017).

Recently, Broxterman et al. (2024) conducted a study investigating the determinants of $\dot{V}O_{2max}$ before and after 8 weeks of single leg knee extensor exercise training in sedentary individuals. Pre-training, when oxygen availability was modified to the muscle using hypoxic (12% O_2;

decreased availability), normoxic (21% O_2; unchanged availability), and hyperoxic conditions (100% O_2; increased availability), convective oxygen delivery increased from hypoxic (0.8 ± 0.3 $L \cdot min^{-1}$) to hyperoxic conditions (1.0 ± 0.3 $L \cdot min^{-1}$) by ~25%. Mean capillary oxygen partial pressure (PO_2) gradient increased from hypoxic (33 ± 5 mmHg) to normoxic conditions (41 ± 4 mmHg) by ~24%, and by ~52% from hypoxic to hyperoxic conditions (50 ± 9 mmHg). Additionally, mean muscle intracellular PO_2 gradient increased by ~90% from hypoxic (3.8 ± 0.6 mmHg) to normoxic conditions (7.2 ± 1.4 mmHg), which was not different from hyperoxic conditions (10.0 ± 6.6 mmHg). Despite this increase in potential for oxygen flux, muscle $\dot{V}O_{2max}$ was unchanged in hypoxic (0.47 ± 0.10 $L \cdot min^{-1}$), normoxic (0.52 ± 0.13 $L \cdot min^{-1}$, and hyperoxic conditions (0.54 ± 0.07 $L \cdot min^{-1}$). This indicates that the capacity to utilise oxygen was the limiting factor of $\dot{V}O_{2max}$ pre-training (**Figure 2.4A**) (Broxterman et al., 2024). Conversely, post-training, $\dot{V}O_{2max}$ did increase from hypoxic (0.59 ± 0.11 $L \cdot min^{-1}$), to normoxic (0.68 ± 0.11 $L \cdot min^{-1}$), and to hyperoxic conditions (0.76 ± 0.09 $L \cdot min^{-1}$) facilitated by an increase in both capillary and intracellular PO_2 gradients. Compared to pre-training, the limiting factor of $\dot{V}O_{2max}$ post-training is thus the capacity to transport oxygen (**Figure 2.4C**) (Broxterman et al., 2024).

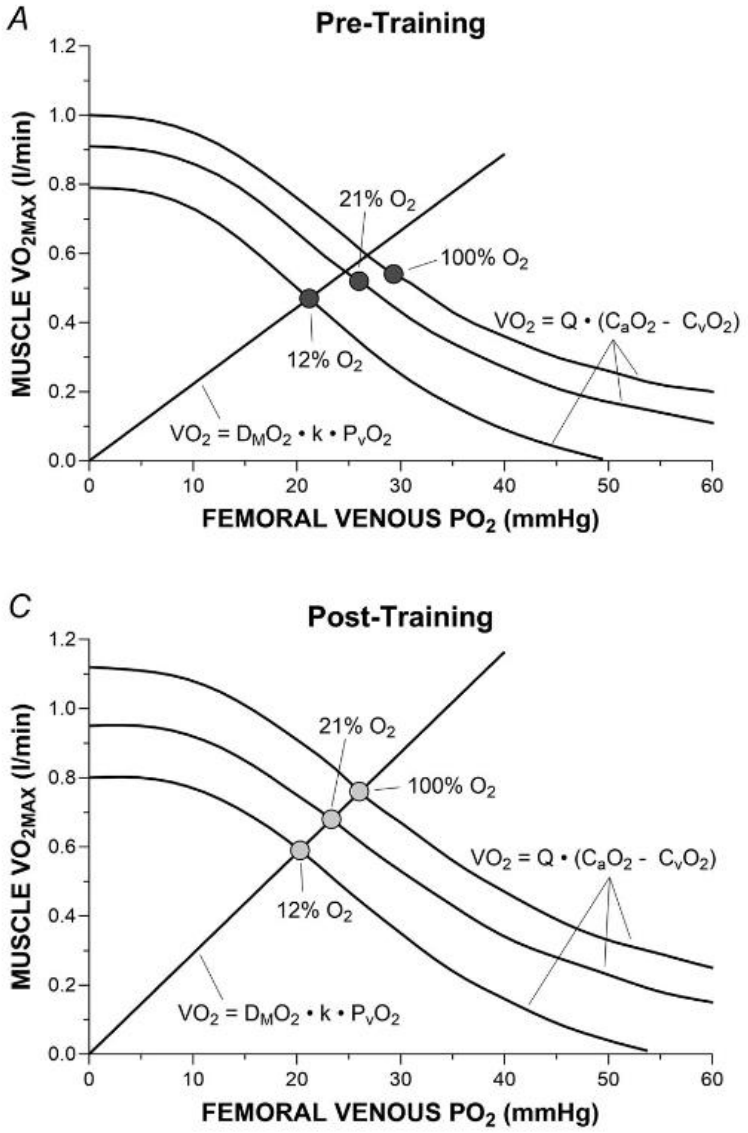

Figure 2.4. Muscle oxygen uptake ($\dot{V}O_{2max}$) as a function of muscle venous oxygen partial pressure (PO_2) during single leg knee extensor exercise pre- (A) and post-training (C) in hypoxia (12% O_2), normoxia (21% O_2), and hyperoxia (100% O_2). $\dot{V}O_2$: oxygen uptake, D_MO_2: muscle diffusional O_2 conductance, k: constant for the proportionality between mean capillary and femoral venous PO_2, P_VO_2: femoral venous PO_2, Q: cardiac output, C_aO_2: arterial O_2 content, C_vO_2: femoral venous O_2 content. Taken from Broxterman et al. (2024).

Peripheral adaptations

Enhancing a-$\bar{v}O_2$ diff is evident following ~12 weeks of training (Montero & Díaz-Cañestro, 2016), potentially explained by improvements in the distribution of blood flow during exercise (Lundby et al., 2008). Whilst the relationship between cardiac output and red blood cell content with $\dot{V}O_{2max}$ is clearly evidenced, the relationship between $\dot{V}O_{2max}$ and a-$\bar{v}O_2$ diff is sometimes unclear indicated by a weaker relationship presented in **Figure 2.5b** (Montero & Díaz-Cañestro, 2016). This highlights the primary driving factor of change in $\dot{V}O_{2max}$ is explained by an enhanced capacity to deliver O_2 (Levine, 2008; Mandić et al., 2023; Montero et al., 2015; Skattebo et al., 2020). Instead, enhanced O_2 extraction fraction appears to be more important for the realisation of $\dot{V}O_{2max}$ in highly trained endurance athletes (Skattebo et al., 2020). As endurance training leads to situations in which O_2 delivery to working muscles becomes limited, improvements in O_2 extraction are vital in order to achieve further improvements in $\dot{V}O_{2max}$ (Skattebo et al., 2020). The role of a-$\bar{v}O_2$ diff thus becomes more important as training status increases, whereas for untrained but healthy individuals, marked improvements in $\dot{V}O_{2max}$ are driven primarily by enhanced O_2 delivery.

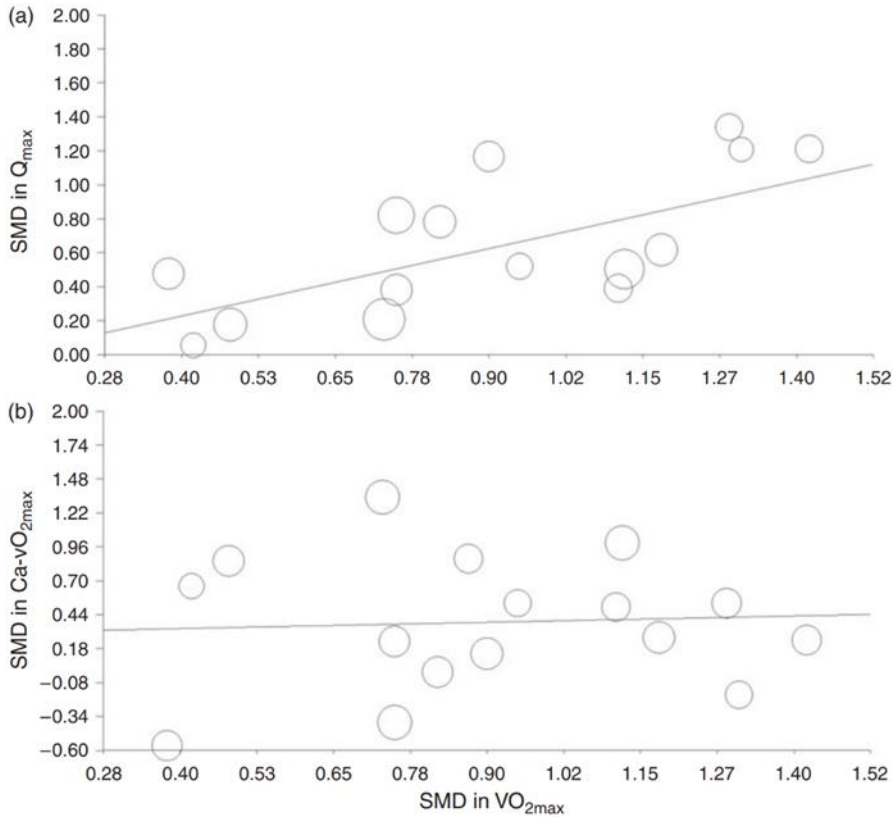

Figure 2.5. Meta-regression plots of the smallest meaningful difference (SMD) in $\dot{V}O_{2max}$ according to the SMD in (a) maximum cardiac output ($\dot{Q}_{max}$ [$L \cdot min^{-1}$]; B = 0.79) and (b) maximum arteriovenous O_2 difference (Ca-$\bar{v}O_{2max}$ [$mL \cdot dL$]; B = 0.79). Size of circles are proportional to the individual study's weight included in the meta-analysis, taken from Montero & Díaz-Cañestro, (2016).

Response variability in maximum oxygen uptake

Whilst efficacious at the group level, the effect of exercise training on changes in $\dot{V}O_{2max}$ appears to be largely heterogenous among individuals (Bouchard et al., 1999; Williams et al., 2019). Some individuals experience marked increases in $\dot{V}O_{2max}$, whereas others may not, despite completing the same standardised exercise training programme (Bouchard et al., 1999; Williams et al., 2019). This means that some individuals may not be attaining the intended health- and/or performance-related benefits from their training. Given the current population-wide issue concerning poor levels of cardiorespiratory fitness (R. Ross et al., 2016), increasing individuals' $\dot{V}O_{2max}$ is paramount. Additionally, from a clinical perspective,

increasing or achieving certain level of cardiorespiratory fitness can have critical implications. For example, were someone needing to increase their cardiorespiratory fitness to qualify them for a given surgical procedure, ensuring meaningful increases in $\dot{V}O_{2max}$ are obtained is vital. Typically, individuals demonstrating a $\dot{V}O_{2max}$ <17.5 $mL \cdot kg^{-1} \cdot min^{-1}$ can be considered as high-risk individuals (R. Ross et al., 2016). This can be related to the concept of 'fitness for surgery' which describes an individual's capacity to tolerate and overcome a physiological insult, such as surgery, and is therefore used to assess risk and subsequent care planning (Rose et al., 2022). Understanding why some individuals respond poorly to given exercise training programmes is thus important, and interventions aiming to increase the proportion of individuals experiencing meaningful increase in $\dot{V}O_{2max}$ are highly warranted. If the likelihood of individuals experiencing meaningful improvements in their $\dot{V}O_{2max}$ is increased, this could have profound implications across a variety of settings, for example positively impacting public health, reducing health care costs, and increasing athletic performance associated with improved functional and exercise capacity. G.H. Huang et al. (2016) demonstrated that exercise training increased $\dot{V}O_{2max}$ prior to major cancer surgery; however, only 50% of the cohort were classified as exercise 'responders' whereby an increase of ≥10% at the anaerobic threshold was observed. Patients with a lower baseline $\dot{V}O_2$ at the anaerobic threshold were most likely to be classified as responders, and notably, responders were less likely to experience major postoperative complications (G. H. Huang et al., 2016a). A similar finding was observed by West et al. (2019) who observed a 62% response rate in the change in $\dot{V}O_2$ at the anaerobic threshold in cancer patients following six weeks of preoperative exercise training. In this cohort, an increase of ≥2.0 $mL \cdot kg \cdot^{-1} min^{-1}$ at the anaerobic threshold was used to classify responders and non-responders (West et al., 2019). Developing interventions or strategies that effectively increases response rates in pre-surgical markers of cardiorespiratory fitness, and thus reduce the number of non-responders, is highly warranted.

Following periods of exercise training, studies have typically failed to capture this response variability at the individual level when only reporting group level measures of central tendency

(e.g., mean) and dispersion (e.g., standard deviation). 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 exercise training programme, $\dot{V}O_{2max}$ increased, on average, by 384 $mL \cdot min^{-1}$. Notably, some individuals experienced gains in excess of 1000 $mL \cdot min^{-1}$ whilst other experienced no gain at all. Subsequently, it was concluded that ~20% of individuals undertaking exercise training may not achieve meaningful increases in $\dot{V}O_{2max}$ (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 exercise training (Hoppeler, 2018).

The mechanisms underpinning response variability are multifaceted and there exist several contributors (Noone et al., 2024; Voisin et al., 2019). Some of the factors that contribute to $\dot{V}O_{2max}$ response variability relate to *unmodifiable* 'biological' factors such as individual characteristics, some to *modifiable* 'methodological' factors (**Figure 2.6**), such as training characteristics, and others simply relate to measurement error and biological variability (Bonafiglia et al., 2022). It also is worth noting that there has been an increase in studies analysing response counts when aiming to evaluate individual response variability, something that has been highlighted as a cause for concern (Atkinson et al., 2019; Atkinson & Batterham, 2015; Bonafiglia et al., 2018). Importantly, whether an individual is deemed as a 'responder' following a training programme depends largely on the study design and the statistical model used to classify said individuals (Atkinson et al., 2019; Bonafiglia et al., 2018; Hecksteden et al., 2018; R. Ross et al., 2019; Swinton et al., 2018).

Whilst the contribution of biological and methodological factors will be discussed below, the primary focus of this literature review is the method used to prescribe exercise intensity, falling under the bracket of modifiable methodological factors. The reason for this is that evidence demonstrates that the most commonly used methods of exercise intensity prescription elicits largely heterogenous acute physiological responses to exercise among individuals, thus

individuals following the same exercise training programmes are experiencing markedly different exercise- and adaptive-stimuli (Baldwin et al., 2000; Egger et al., 2016; Iannetta et al., 2020; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). It is supposed that this acute response heterogeneity might manifest as chronic response heterogeneity, thus contributing to the observation of response variability following a period of exercise training. Therefore, if an alternative method can be used to prescribe exercise intensity that reduces the variability in the exercise stimuli experienced among individuals, this may elicit more homogenous training-induced adaptations (i.e., changes in $\dot{V}O_{2max}$). In turn, this might reduce the incidence of individuals experiencing negligible changes in $\dot{V}O_{2max}$.

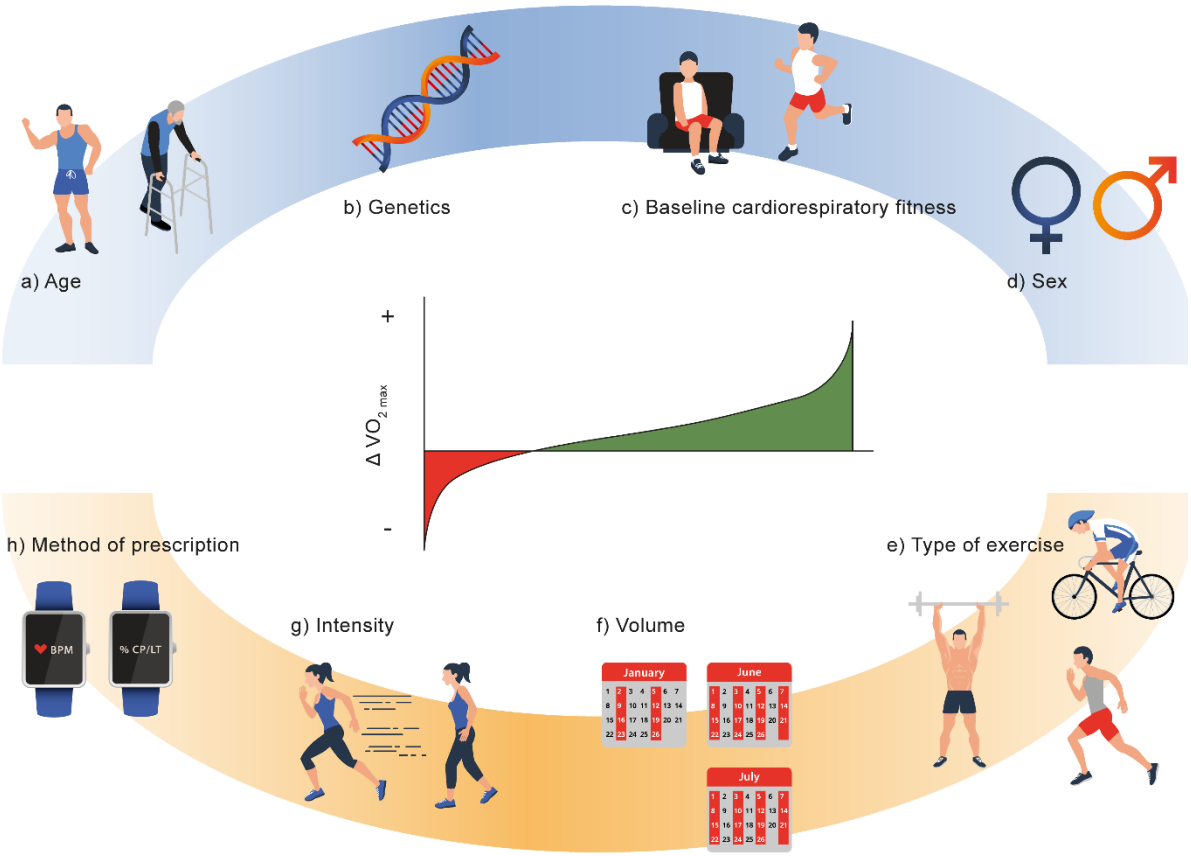

Figure 2.6. Factors affecting $\dot{V}O_{2max}$ trainability in response to endurance training. Biological factors (blue) include age (a), genetics (b), baseline $\dot{V}O_{2max}$ (c), and sex (d). Methodological factors (orange) include type (e), volume (f), and intensity (g) of training, and method of exercise intensity prescription (h). Δ $\dot{V}O_{2max}$: Change in maximum oxygen uptake.

PART 1 – BIOLOGICAL FACTORS ASSOCIATED WITH MAXIMUM OXYGEN UPTAKE RESPONSE VARIABILITY

In this section, individual characteristics that may contribute to $\dot{V}O_{2max}$ response variability are discussed. This includes the influence of Genetics, Age, Sex, and Baseline $\dot{V}O_{2max}$.

Genetics

The $\dot{V}O_{2max}$ phenotype is a polygenetic trait influenced by a combination of environmental and genetic factors, and both its baseline and response to exercise training vary considerably among individuals (Williams et al., 2017). Both twin-sibling and familial-resemblance studies

report that ~50% of $\dot{V}O_{2max}$ trainability is attributable to heritability (Bouchard et al., 1999). Moreover, compared to adults, heritability of $\dot{V}O_{2max}$ is higher in youths and adolescents with weighted estimates of 59% ($mL \cdot min^{-1}$) and 72% ($mL \cdot kg^{-1} \cdot min^{-1}$), respectively (Schutte et al., 2016). However, research implementing candidate gene, gene expression and genome-wide association studies (GWAS) to determine the genetic predictors of $\dot{V}O_{2max}$ trainability has been unable to identify a genome that accurately accounts for the large variation observed in $\dot{V}O_{2max}$ following exercise training (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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ trainability, of which 13 have been successfully replicated (Williams et al., 2017). Additionally, six new SNPs have recently been identified that can distinguish among individuals with high and low $\dot{V}O_{2max}$ values (Bye et al., 2020).

However, the mechanisms underpinning the role of genetics remain unclear. $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 exercise training than had genetics. The polygenic nature of the $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ (Rankinen et al., 2016), and the disconnect between identified gene variants and the key physiological determinants of $\dot{V}O_{2max}$ (Joyner & Lundby, 2018) highlights that the role of genetics on $\dot{V}O_{2max}$ 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 exercise training and how these may influence response variability (Joseph & John, 2020; Noone et al., 2024).

Age

It is well documented that $\dot{V}O_{2max}$ 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 training-induced increases in $\dot{V}O_{2max}$ may also differ with ageing. McGuire et al. (2001), found that following exercise training separated by 30 years, despite similar increases in $\dot{V}O_{2max}$, the primary drivers of increased $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ following exercise training. Robinson et al. (2017), reported that both young (18–30 years) and older (65–80 years) adults can substantially increase $\dot{V}O_{2max}$ following interval (~17%; +3.5 mL·kg·$^{-1}$min^{-1}) and continuous (~20%; 4.4 mL·kg·$^{-1}$min^{-1}) exercise training, in line with previous findings (G. Huang et al., 2016; McGuire et al., 2001). Moreover, Kohrt et al. (1991), reported no significant differences in the percentage increase in $\dot{V}O_{2max}$ among older individuals aged between 60 and 71 years, nor was there a relationship between change in $\dot{V}O_{2max}$ and age ($r = -0.13$). There was, however, considerable heterogeneity in the gains in $\dot{V}O_{2max}$ 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 exercise training, 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 exercise training in a male cohort (n = 39; 23–52 years). Alternatively, in the HERITAGE cohort, which included a larger sample and age range (n = 742; 17–65 years), age was reported to explain only 3% of the response variability following 20 weeks' exercise training (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.

Sex

The increase in $\dot{V}O_{2max}$ following exercise training is generally greater in men than in women of a comparable training status (mean difference: 1.95 $mL \cdot kg^{-1} \cdot min^{-1}$; (Diaz-Canestro & Montero, 2019). Interestingly, increases in $\dot{V}O_{2max}$ may be attributed to different adaptive pathways between sexes (Ansdell et al., 2020), perhaps explaining why gains in $\dot{V}O_{2max}$ following exercise training tend to be somewhat superior in men (Diaz-Canestro & Montero, 2019).

One thing to consider, however, is the potential impact of the female menstrual cycle on exercise performance which was not controlled for in the study by Diaz-Canestro & Montero (2019). Whilst more research is needed to determine the effect of the menstrual cycle and indeed oral contraceptive use on exercise performance, currently, exercise performance appears to be relatively consistent across the oral contraceptive pill cycle (Elliott-Sale et al., 2020). Furthermore, the current evidence does not warrant guidelines on modulating exercise

across the menstrual cycle with most research being classified as low in quality, necessitating further, better-quality, studies to be conducted (McNulty et al., 2020). Recently, results of the 'FENDURA' project (Taylor et al., 2024) found that peak oxygen uptake ($\dot{V}O_{2peak}$), $\dot{V}O_2$ at 4 $mmol \cdot L^{-1}$, time to exhaustion, running economy, and mean 30 s power output were not affected by menstrual cycle phase or the serum concentrations of oestrogen and progesterone. Overall, it was concluded that despite the observation of some individual patterns, no single menstrual cycle phase was associated with a change in $\dot{V}O_{2peak}$ (Taylor et al., 2024). Finally, as demonstrated by James et al. (2023), critical power (discussed below) is not influenced by the menstrual cycle phase and the reproducibility of critical power was similar to that observed in males. In turn, the authors concluded that when conducting exercise interventions, the phase of the menstrual cycle does not need to be controlled for when including eumenorrheic females with no menstrual dysfunction (James et al., 2023).

Regarding the observation of greater changes in $\dot{V}O_{2max}$ in males compared to females, compared to men, key central adaptations such as increased stroke volume and cardiac filling have been blunted in women following exercise training (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). For example, females typically demonstrate a greater proportion of type I muscle fibres which are more fatigue resistant than type II muscle fibres (Schiaffino & Reggiani, 2011; Simoneau & Bouchard, 1989), greater capillary density and capillarisation relative to muscle mass (Roepstorff et al., 2006), and greater muscle oxygenation (Mantooth et al., 2018). Of note, the

difference in adaptations between sexes are not fully understood (S. K. Hunter et al., 2023) but the blunted adaptations in cardiac characteristics may be explained by the lack of ventricular remodelling and blood volume expansion particularly in older females (Barnes & Fu, 2018). It may be that reductions in oestrogen induced by menopause might also contribute but this relationship is currently unclear (Spina et al., 1993).

Another explanation for inferior increases in $\dot{V}O_{2max}$ in women is that exercise training 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 $\dot{V}O_{2max}$ in women, and therefore when exercising at the same intensity relative to a maximum physiological value (e.g., $\dot{V}O_{2max}$), 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% $\dot{V}O_{2max}$ for ~17 min longer than men and produced lower blood lactate levels (5.4 vs. 8.1 $mmol \cdot L^{-1}$). 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 exercise training 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 $\dot{V}O_{2max}$ such as mitochondrial biogenesis and angiogenesis (Ansdell et al., 2020; Bishop et al., 2019; Granata et al., 2018). Thus, how intensity within exercise training 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 exercise training.

Surprisingly, despite differences in the magnitude of $\dot{V}O_{2max}$ changes in response to exercise training, 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 $\dot{V}O_{2max}$ changes in the HERITAGE study (Sarzynski et al., 2017). Furthermore, when assessing $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ variability (Garber et al., 2011).

Overall, increases in $\dot{V}O_{2max}$ following exercise training tend to be somewhat superior in men. For men increases in $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ following exercise training, it is reported that sex explains only a small proportion of $\dot{V}O_{2max}$ response variability.

Baseline maximum oxygen uptake

Those initially presenting in the lowest quintile of $\dot{V}O_{2max}$ appear to have a potentiated capacity to experience the greatest health reward in response to increases in $\dot{V}O_{2max}$ (Harber et al., 2017). It appears that baseline $\dot{V}O_{2max}$ affects subsequent response to training whereby a higher baseline $\dot{V}O_{2max}$ hinders the potential for further adaptation (Astorino & Schubert, 2014; Saltin et al., 1969; Sisson et al., 2009). Sisson et al. (2009) concluded that baseline $\dot{V}O_{2max}$ was among the strongest predictors of $\dot{V}O_{2max}$ non-response following exercise training. Specifically, increments in baseline $\dot{V}O_{2max}$ of 0.24 $L \cdot min^{-1}$ increased the odds of non-response by 2-fold. A number of studies have further reported a negative association between baseline $\dot{V}O_{2max}$ and increases in $\dot{V}O_{2max}$ (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 $\dot{V}O_{2max}$ can impact the magnitude of change in $\dot{V}O_{2max}$, 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 $\dot{V}O_{2max}$ (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 $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$), although there was a negative association with relative changes in $\dot{V}O_{2max}$ (%) (r = −0.38) (Skinner et al., 2001). Moreover, low, medium, and high responders were present across all levels of baseline $\dot{V}O_{2max}$ (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 $\dot{V}O_{2max}$ was ~31 $mL \cdot kg^{-1} \cdot min^{-1}$ (Skinner et al., 2001). A large proportion may have possessed modestly developed $\dot{V}O_{2max}$ phenotypes at most, and thus scope for further increases in $\dot{V}O_{2max}$ may not have been hindered in this cohort.

Overall, evidence suggests that baseline $\dot{V}O_{2max}$ may influence $\dot{V}O_{2max}$ trainability. It is plausible that the likelihood of non-response may increase among individuals who already possess a highly developed $\dot{V}O_{2max}$ phenotype, in which room for further improvement becomes limited. However, considering the equivocal evidence resulting from the HERITAGE study, this conclusion warrants further investigation.

PART 2 – METHODOLOGICAL FACTORS ASSOCIATED WITH MAXIMUM OXYGEN UPTAKE RESPONSE VARIABILITY

In this section, methodological factors contributing to $\dot{V}O_{2max}$ response variability will be discussed. This includes a discussion on how the manipulation of the principles of training might affect $\dot{V}O_{2max}$ response variability. This section will then go into more depth on the different methodological approaches to exercise intensity prescription, covering the different intensity anchors, and also the influence that the method used to prescribe exercise intensity might have on $\dot{V}O_{2max}$ response variability.

Type of training

The type of training appears to affect the variability in $\dot{V}O_{2max}$ following traditional endurance training (i.e., continuous and/or interval-based exercise training) 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 exercise training to resistance training, 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 $\dot{V}O_{2max}$ following exercise training attained increases in strength following resistance training, and vice versa (Marsh et al., 2020). Surprisingly, ~50% of participants showed non-training type-specific responses and reported increases in strength following exercise training (51%) and increases in $\dot{V}O_{2max}$ following resistance training (57%) (Marsh et al., 2020). Hautala et al. (2006) also observed that subjecting individuals who failed to increase $\dot{V}O_{2max}$ following exercise training to resistance training could counteract previous non-response and elicit increases in $\dot{V}O_{2max}$. Whilst positive responses to training are primarily training type-specific, changing the type of exercise (e.g., from exercise training to resistance training) may be an effective strategy for some individuals to provoke subsequent adaptation in other parameters of interest and, to a lesser extent, in $\dot{V}O_{2max}$.

Volume of training

It has been argued that the non-response phenomenon to exercise training 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 $\dot{V}O_{2max}$ (Montero & Lundby, 2017a). 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 $\dot{V}O_{2max}$ 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% $\dot{V}O_{2max}$, targeted 12 versus 4 kcal·kg^{-1}·wk^{-1}. Ross et al. (2015) reported that when exercising at 50% $\dot{V}O_{2max}$, 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 (Montero & Lundby, 2017a) observed similar findings whereby in response to 60, 120, 180, 240 and 300 min·wk^{-1} of exercise training 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' exercise training with an additional two sessions per week. A common finding in the studies that investigated response rates to exercise training following the manipulation of training volume is that for a given intensity, greater volumes induced greater mean changes in $\dot{V}O_{2max}$ compared to the lower volume protocols (Montero & Lundby, 2017; R. Ross et al., 2015; Sisson et al., 2009). Increased response rates may therefore be driven more so by greater mean changes in $\dot{V}O_{2max}$ than a narrowing in response variability (Atkinson et al., 2019; Bonafiglia et al., 2021).

Whilst a seemingly efficacious strategy to increase $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ following 10 weeks of strenuous exercise training, yet, despite marked gains in $\dot{V}O_{2max}$, the strenuous nature of the exercise training 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. In turn, an approach which elicits meaningful changes to the initial stimulus, without the need to exhaust training volume, would be of interest and may link to how exercise intensity is prescribed to begin with (discussed in **Chapter 2, Prescription of exercise intensity**). Simply increasing training volume to increase response rates is not sustainable.

Intensity of training

Intensity of training is another key variable influencing adaptations in $\dot{V}O_{2max}$ (MacInnis & Gibala, 2017). Whilst increases in $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ following 6 months' exercise training matched by training volume at an intensity corresponding to the ventilatory threshold (VT, **Table 2.2**) compared to training 20% <VT (10.4 vs. 6.1 $mL \cdot kg^{-1} \cdot min^{-1}$). Surprisingly, Gaskill et al. (2001) and Guio de Prada et al. (2019) reported similar changes in $\dot{V}O_{2max}$ following exercise training <VT and >VT, yet training at intensities >VT resulted in greater increases in the VT. Ross et al. (2015) reported that following exercise training completed at 50% and 75% $\dot{V}O_{2max}$, 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 $\dot{V}O_{2max}$ should be minimal, if not non-existent (Montero & Lundby, 2017a). 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%, like the ~20% rate typically reported following exercise training (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 $\dot{V}O_{2max}$ (Margaritelis et al., 2018; Tamura et al., 2014). Tamura et al. (2014) demonstrated that reactive oxygen species accumulating in the myocytes is a key signal for the upstream regulation of PGC-1α. Margaritelis et al. (2018) also reported that when individuals experienced low exercise-induced oxidative stress, subsequent increases in $\dot{V}O_{2max}$ were inferior compared to individuals who experienced high oxidative stress (12% vs. 19%, respectively). For low-intensity exercise training, 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 and vice versa, if training volume is low, intensity must be increased in order to elicit a potent adaptive stimulus (Cosaburi, 1992). As such, a 'critical' intensity has been asserted whereby there is a threshold intensity which needs to be exceeded in order to elicit a training effect (Garber et al., 2011; Pollock et al., 1998). When using heart rate as an anchor of exercise intensity, this critical threshold is ~60% maximum heart rate (HR_{max}) or ~50% heart rate reserve (HRR; the percentage difference between HR_{max} and resting heart rate) (Cosaburi, 1992; Garber et al., 2011; Pollock et al., 1998). Notably, it is considered that if exercising below this threshold, no training effect will be induced regardless of the duration or frequency of time spent exercising at the given intensity (Cosaburi, 1992); however, it has been demonstrated that exercising below this threshold for prolonged periods of time can elicit a significant training effect (Casaburi et al., 1990; Sharkey, 1970). Regarding $\dot{V}O_2$, the threshold is asserted to be ~50% $\dot{V}O_{2max}$ (Cosaburi, 1992); however, training effects have again been observed despite

exercising below this intensity threshold (Casaburi et al., 1990; Gaesser & Rich, 1984; Shephard, 1968). In a recent study by Inglis et al. (2024), it was demonstrated that exercise intensity was a key determinant of changes in $\dot{V}O_{2max}$ following training whereby exercising in the heavy or severe domains increased $\dot{V}O_{2max}$ whereas exercising in the moderate domain did not. This highlights the importance of exercising at a high intensity in order to elicit marked increases in $\dot{V}O_{2max}$. This echoes the findings of Collins et al. (2022) who found that exercising at higher intensities when expressed relative to critical power had the greatest influence on training-induced changes in endurance parameters.

Prescription of exercise intensity

Traditional exercise intensity prescription

A multitude of methods can be used to prescribe exercise intensity (Jamnick et al., 2020). The most commonly used approaches, termed herein 'traditional' approaches, anchor intensity relative to a maximum physiological value (**Table 2.1**) and can be used to prescribe exercise intensity for both healthy and unhealthy individuals (e.g., recreationally active and trained individuals and those undergoing cardiac rehabilitation or secondary prevention programmes). These approaches are characterised by using fixed percentages of the chosen physiological value or using this in combination with their equivalent resting value (American College of Sports Medicine, 2017; Giada et al., 2008; Mezzani et al., 2009; Milanović et al., 2015; Stefani et al., 2017; Williams et al., 2019). Currently, these approaches dominate when prescribing whole-body aerobic based exercise in both applied and research settings (Milanović et al., 2015). It is assumed that traditionally prescribed exercise training will elicit homogeneous acute physiological responses among individuals, yet this is not always the case (Iannetta et al., 2020; Katch et al., 1978; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010).

Table 2.1. Exercise intensity domains defined by traditional anchors of exercise intensity.

Anchor	Moderate intensity (moderate)	Vigorous intensity (heavy)	Near-maximal to maximal intensity (severe)
$\dot{V}O_{2max}$	46-63%	64-90%	≥91%
HR_{max}	64-76%	77-95%	≥96%
$\dot{V}O_2R$	40-59%	60-89%	≥90%
HRR	40-59%	60-89%	≥90%

HR_{max}, maximum heart rate; HRR, heart rate reserve [difference between maximum and resting heart rate]; $\dot{V}O_{2max}$, maximum oxygen uptake; $\dot{V}O_2R$, oxygen uptake reserve [difference between maximum and resting oxygen uptake] (American College of Sports Medicine, 2017).

Methodological approaches of traditional exercise intensity prescription

Maximum oxygen uptake

The gold standard approach to $\dot{V}O_{2max}$ determination involves an incremental exercise test completed to task failure (GXT), typically performed on a treadmill or stationary cycle ergometer (**Figure 2.7**) (Poole & Jones, 2017). The protocol can be performed either in a ramp (continuous increase in work rate over time) or stepwise manner (step increases over time) until the individual cannot sustain the applied external work rate. Pulmonary $\dot{V}O_2$ is analysed breath by breath throughout the test via an online gas analyser and the highest $\dot{V}O_2$ averaged over a given period of time (i.e., 10, 20, or 30 s) or the highest recorded measure of $\dot{V}O_2$ during the GXT is taken as $\dot{V}O_{2max}$ or $\dot{V}O_{2peak}$, respectively.

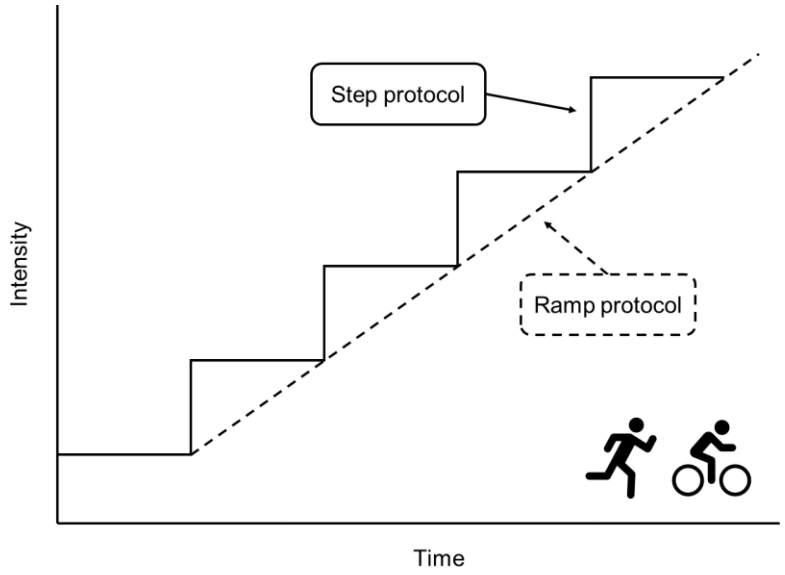

Figure 2.7. Illustration of an incremental exercise test to determine maximum oxygen uptake ($\dot{V}O_{2max}$) and maximum heart rate (HR_{max}). Step protocol represents an increase in work rate in a stepwise fashion whereas a ramp protocol represents a constant increase in work rate over time.

Once $\dot{V}O_{2max}$ is determined, exercise can be prescribed at different percentages of this value to prescribe moderate (46-63%), vigorous/heavy (64-90%), or near-maximal to maximal/severe (≥91%) intensity exercise (American College of Sports Medicine, 2017). One issue with using this approach is that prescribing intensity as a fixed percentage of $\dot{V}O_{2max}$ necessitates the continuous monitoring of $\dot{V}O_2$ during an exercise bout to ensure the desired response is observed and maintained (Jamnick et al., 2020; Scharhag-Rosenberger et al., 2010). Furthermore, when exercise is intended to take place at intensities exceeding that of the moderate domain, reductions in exercise intensity might be required over time to compensate for the $\dot{V}O_2$ slow component which drives $\dot{V}O_2$ up despite no increase in external work rate (Jamnick et al., 2020; Scharhag-Rosenberger et al., 2010).

Alternatively, exercise intensity can be prescribed based off the extrapolation of a specific work rate with a corresponding $\dot{V}O_2$ from the GXT (Jamnick et al., 2020). This removes the need to constantly monitor $\dot{V}O_2$ and instead a fixed work rate can be used to define the

intensity of the exercise bout. However, an inherent flaw in this approach is that it assumes a linear relationship exists between $\dot{V}O_2$ and work rate during a GXT (Jamnick et al., 2020). This relationship is more so reflective of a curvilinear relationship, particularly in the latter stages of the GXT (Zoladz et al., 1995, 1998). At higher intensities, the relationship between $\dot{V}O_2$ and work rate becomes more disparate and variable, augmenting the shift from a linear increase in $\dot{V}O_2$ and work rate (Keir et al., 2016). Using a fixed percentage of $\dot{V}O_{2max}$ to control and normalise exercise intensity may thus only be of use when low to moderate intensity exercise is intended.

Maximum heart rate

Like $\dot{V}O_{2max}$, HR_{max} is typically determined from a GXT or estimated from equations, for example 220 – age or 208 – 0.7 x age (Tanaka et al., 2001). As recommended, percentages of HR_{max} values can be used to prescribe moderate (64-76%), heavy (77-95%), and severe (≥96%) intensity exercise (American College of Sports Medicine, 2017). If exercise intensity is informed by a given HR, constant monitoring of HR is thus needed. Like the issues of using $\dot{V}O_{2max}$, the HR response to exercise undertaken above the moderate intensity domain is subject to a HR slow component and thus, work rate will need to be adjusted over time (Baldassarre et al., 2022; Jamnick et al., 2020). This is why different modes on cycle ergometers exist, for example the Lode Excalibur Sport (Groningen, Netherlands), whereby a HR clamping mode can be selected such that power output changes in order to maintain a given HR. However, as opposed to requiring a gas analyser, means by which HR can be monitored are more accessible. With the increased popularity of smart-watches and exercise-related digital applications, measuring and using HR to define training zones and exercise intensities remains a popular approach among the public (El-Amrawy & Nounou, 2015; Montalvo et al., 2023). As such, using HR to anchor exercise intensity persists as a popular approach to intensity prescription in research settings (Milanović et al., 2015).

Oxygen uptake reserve and heart rate reserve

Instead of using a fixed percentage of a maximum physiological value, the intensity of exercise can be prescribed relative to the difference between a maximum and resting physiological value, for example, the difference between $\dot{V}O_{2max}$ and resting $\dot{V}O_2$ (oxygen uptake reserve, $\dot{V}O_2R$) or the difference between HR_{max} and resting HR (heart rate reserve, HRR) (F. A. da Cunha et al., 2011; F. Cunha et al., 2010). However, this approach also relies upon the assumption that a linear relationship exists between $\dot{V}O_2$ or HR and work rate (F. A. da Cunha et al., 2011; F. Cunha et al., 2010). Results from a study by Weltman et al. (1990a) indicate that such approaches do not have the capacity to delineate the exercise intensity domains among individuals. For example, exercising at 85% HRR resulted in 35% of participants exercising below their lactate threshold, and 65% of participants above their lactate threshold (i.e., above the moderate intensity domain) (Weltman et al., 1990a). Using such approaches to control and normalise exercise intensity among individuals is thus not recommended (Jamnick et al., 2020).

Acute and chronic responses to traditionally prescribed exercise

Prescribing exercise intensity using traditional approaches appears 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 2.1**), exercise performed at 60–80% $\dot{V}O_{2max}$ results in considerable differences in $\dot{V}O_{2max}$, 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% $\dot{V}O_{2max}$ 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 exercise training has also been observed. In the DREW study (Church et al., 2007), >30% of participants experienced no increase in $\dot{V}O_{2max}$ following exercise training prescribed at 50%

$\dot{V}O_{2max}$ (Pandey, Ayers, et al., 2015). In the HART-D study (Church et al., 2010), it was reported that 57% of individuals experienced an increase in $\dot{V}O_{2max}$, and only 37% an increase of ≥5% (Pandey, Swift, et al., 2015). Similarly, in the STRRIDE studies (Kraus et al., 2001; Slentz et al., 2011), the change in $\dot{V}O_{2max}$ ranged substantially, between −37–77% (L. Ross et al., 2019). Hautala et al. (2006) reported a range of changes in $\dot{V}O_{2max}$ from −5–22% following exercise training prescribed at 70–80% HR_{max}. Williams et al. (2019) concluded that despite positive aggregate changes in $\dot{V}O_{2max}$ following traditionally prescribed HIIT, SIT and MICT, each protocol produced considerable heterogeneity in changes in $\dot{V}O_{2max}$ among individuals. Whilst response rates are influenced by various factors, the commonality of varied responses following traditionally prescribed exercise training appears to be relevant.

The use of HRR and $\dot{V}O_2R$, not to be used interchangeably (Ferri Marini et al., 2021), have been proposed to create more homogeneous exercise training programmes. However, these methods still produce dissimilar responses to exercise. Weltman et al. (1990b) reported that at 85% HRR, only 65% of individuals were exercising above T1 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 $\dot{V}O_{2max}$ of ∼5 $mL \cdot kg^{-1} \cdot min^{-1}$ in both groups; however, ∼60% of individuals increased $\dot{V}O_{2max}$ by <5 $mL \cdot kg^{-1} \cdot min^{-1}$. Scharhag-Rosenberger et al. (2012) reported that following 1 year of exercise training at 60% HRR, the mean increase in $\dot{V}O_{2max}$ was ∼14%, but changes ranged from −3–37%, and 22% of the participants were deemed non-responders. Moreover, a series of studies implementing exercise training 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., 2015a). It is acknowledged that chronic adaptations from exercise training 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 exercise training does not elicit a uniform exercise intensity among individuals despite aiming to prescribe standardised exercise training. This may contribute to the varied chronic responses commonly observed following traditionally prescribed exercise training. 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).

Threshold-based exercise intensity prescription

Exercising at a fixed percentage of $\dot{V}O_{2max}$ or HR_{max} appears to elicit a heterogenous exercise stimulus among individuals, as discussed above (Hofmann & Tschakert, 2011; Katch et al., 1978; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). (Hofmann & Tschakert, 2011; Katch et al., 1978; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). One reason for this mismatch between what is prescribed and what is subsequently elicited is that traditional approaches do not account for individual metabolic differences; for example, where the transitional boundary between each intensity domain occurs as a percentage of one's $\dot{V}O_{2max}$ or HR_{max} (**Figure 2.8**) (Iannetta et al., 2020). When prescribing exercise intensity relative to such markers, the resultant exercise stimulus experienced among individuals can span across different intensity domains (Gaskill et al., 2001). Despite being the most used prescription approach, traditional approaches are in fact poor in controlling and normalising exercise intensity among individuals.

Instead of using a 'top down' approach whereby exercise intensity is anchored relative to a maximum physiological value, exercise intensity can be anchored relative to an individual's physiological thresholds (**Table 2.2**).

Table 2.2. Physiological thresholds associated with T1 and T2.

Threshold	Physiological threshold	Description
T1	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	First point at which $\dot{V}CO_2$ increases disproportionately to $\dot{V}O_2$ (Beaver et al., 1986).
	Ventilatory threshold	First breakpoint of a systematic increase in $\dot{V}_E/\dot{V}O_2$ (Wasserman & McIlroy, 1964).
T2	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).

$\dot{V}O_2$: oxygen uptake, $\dot{V}CO_2$: carbon dioxide production, $\dot{V}_E/\dot{V}O_2$: ventilatory equivalents or oxygen

The first physiological threshold delineates the moderate and heavy intensity domain (T1), and the second threshold (T2) delineates the heavy and severe intensity domain (Poole & Jones, 2012; Poole & Richardson, 1997). Using such markers avoids the assumption that intensity domains occur, and transition, at roughly the same percentage of $\dot{V}O_{2max}$ or HR_{max} between individuals and instead, these thresholds are determined based on each individual's own unique metabolic response to exercise. This is typically done using measures such as BLa, $\dot{V}O_2$ kinetics, and self-assessment tools such as rating of perceived exertion (RPE) (Jamnick et al., 2020). Prescribing intensity relative to physiological thresholds ensures that when exercise is prescribed below the first threshold, between the first and second threshold,

or above the second threshold, then moderate, heavy, and severe intensity exercise is in fact undertaken, respectively (**Figure 2.8**).

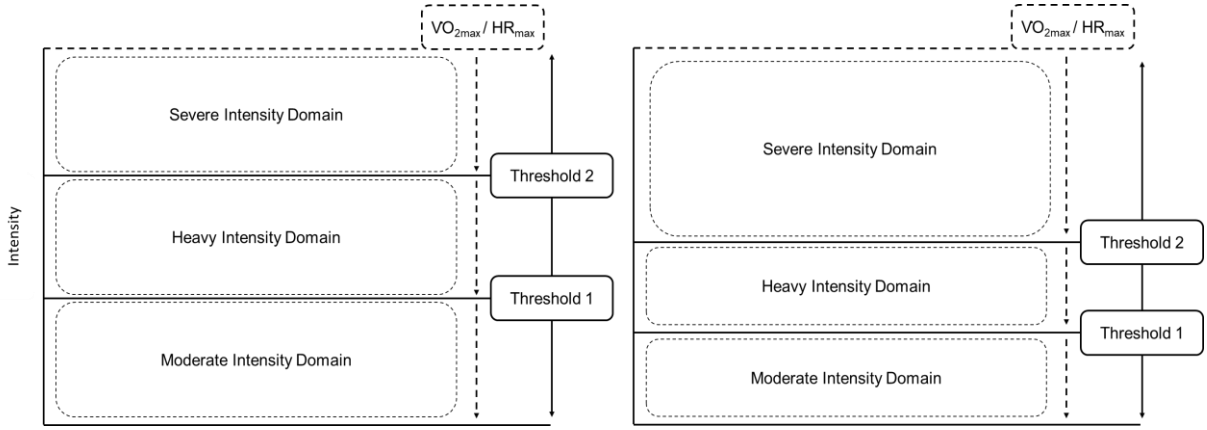

Figure 2.8. Demonstration of the potential mismatch between prescribing exercise intensity relative to a fixed percentage of a maximum physiological value and relative to physiological thresholds when targeting moderate, heavy, or severe intensity exercise.

Methodological approaches of threshold-based exercise intensity prescription

The various thresholds discussed below all aim to estimate the boundary between the moderate and heavy intensity domain (T1) or the heavy and severe intensity domain (T2); however, they are not to be used synonymously (Caen et al., 2018).

Lactate threshold

The lactate threshold (LT), defined as the first rise in BLa above baseline levels, represents the upper boundary for nearly exclusive aerobic metabolism (Faude et al., 2009). Above this intensity, the supply of energy from maximal fat oxidation is inadequate to that demanded by working muscles causing an increase in energy turnover via anaerobic glycolysis and a increased demand of pyruvate oxidation which ultimately cannot be matched by the mitochondria leading to a build-up of BLa and H^+ (Holloszy & Coyle, 1984; Roston et al., 1987).

The LT is determined invasively during a GXT or by some means of incremental exercise where samples of blood are taken throughout the test and are plotted on a graph to produce a BLa curve (**Figure 2.9**) (Costill, 1970). There are, however, around 25 different methods

used to calculate an individual's LT and thus, estimations of LT can vary considerably depending on which method is chosen as well as which exercise protocol is used (**Figure 2.9**) (Faude et al., 2009; Jamnick et al., 2018). The visual inspection of the BLa response profile the first breakpoint in BLa, the Log-log method, the D_{max} method, or the first given increase in BLa above baseline are primarily used to determine an individual's LT (Jamnick et al., 2018). The Log-log method involves dividing the BLa response (i.e., log of BLa vs intensity) into two segments and identifying the breakpoint in the BLa curve as the intersection of two lines with the lowest residual sum of squares (Beaver et al., 1985). The D_{max} method establishes the point on the third order polynomial regression curve yielding the maximum perpendicular distance to the straight line joining the start and end of the BLa curve (Cheng et al., 1992). Alternatively, an absolute, arbitrarily established, increase in BLa above baseline values (e.g., an increase of 0.5, 1.0, or 1.5 $mmol \cdot L^{-1}$) can be used to determine the LT (Jamnick et al., 2018). Exercising below the LT should elicit exercise that induces no meaningful change in BLa or a steady state response in BLa, reflecting a matching of lactate accumulation and disposal, and exercise in the moderate intensity domain (Faude et al., 2009). If this profile is not observed and BLa reaches either a delayed steady state or continues to increase, exercise is being undertaken in the heavy or severe intensity domain, respectively.

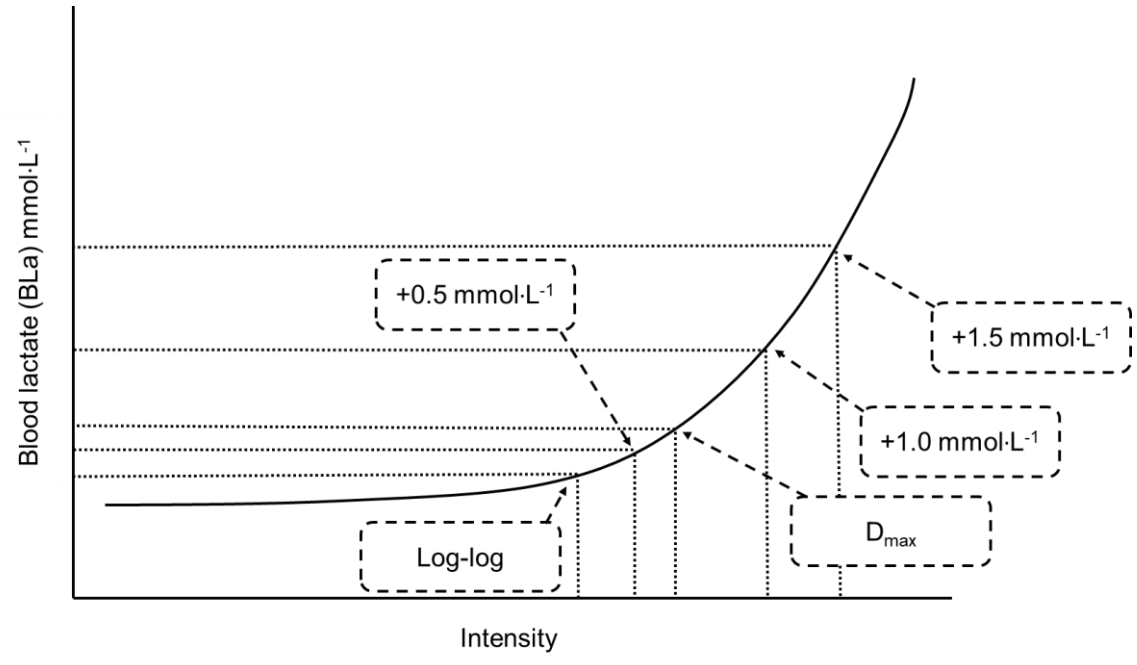

Figure 2.99. Example of different methods used to determine the lactate threshold (LT) and resultant differences in intensity at which the LT occurs. Adapted from Jamnick et al. (2018).

Gas exchange threshold

The gas exchange threshold (GET) reflects the point at which $\dot{V}CO_2$ increases disproportionately to $\dot{V}O_2$ and is determined non-invasively during a GXT via gas analysis (Beaver et al., 1986; Wasserman, 2002). At this point, muscle cells regenerate a greater amount of adenosine triphosphate via substrate-level metabolism resulting in an increase in BLa and subsequently, CO_2 production, driven by an increase in the buffering of hydrogen ions (H^+) by bicarbonate (HCO_3^-) (Wasserman, 2002). When $\dot{V}O_2$ and $\dot{V}CO_2$ are plotted against one another (**Figure 2.10**), GET can be identified by drawing two lines of best fit on the data points, the intersection of which identifies the point at which $\dot{V}CO_2$ increases disproportionately compared to $\dot{V}O_2$ (Wasserman, 2002).

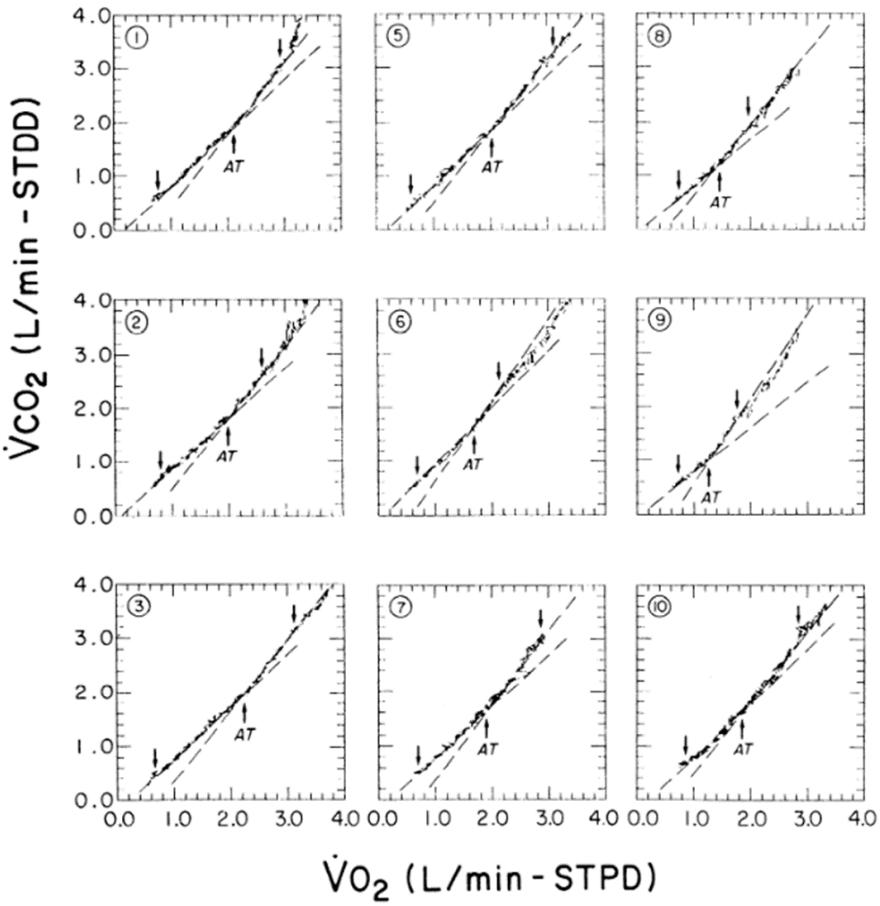

Figure 2.10. CO_2 production ($\dot{V}CO_2$) plotted against oxygen uptake ($\dot{V}O_2$) for individuals having undertaken an incremental exercise test to task failure (GXT). Gas exchange threshold (in this figure, the AT: 'anaerobic threshold') is identified as the intersection between the two lines of best fit. From Beaver et al. (1986).

To highlight the issue of using fixed percentages of $\dot{V}O_{2max}$ to anchor exercise intensity, take the individual data from Beaver et al. (1986) (**Table 2.3**). In this cohort of ten healthy males, GET, determined from a GXT, occurred at 55±7% $\dot{V}O_{2max}$ (43% to 67% $\dot{V}O_{2max}$). Were a training session prescribed at, say 50%, $\dot{V}O_{2max}$, seven individuals would be exercising above (likely heavy intensity exercise), and three below (moderate intensity exercise), their GET (**Table 2.3**). The experienced exercise stimulus may thus vary markedly among the individuals despite undertaking what(Hofmann & Tschakert, 2011; Mann et al., 2013; Scharhag-

Rosenberger et al., 2010)harhag-Rosenberger et al., 2010). Prescribing exercise intensity relative to GET would thus negate this issue.

Table 2.3. Gas exchange threshold determined during an incremental exercise test (GXT), expressed relative to $\dot{V}O_{2max}$.

Individual	$\dot{V}O_2$ at GET ($L \cdot min^{-1}$)	$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	$\dot{V}O_2$ at GET (% $\dot{V}O_{2max}$)
1	2.08	3.1	67
2	1.96	3.36	58
3	2.25	3.95	57
4	1.84	3.2	58
5	2.02	3.4	59
6	1.67	3.5	48
7	1.92	3.6	53
8	1.45	3.0	48
9	1.26	2.9	43
10	1.86	3.45	54
MEAN	**1.83**	**3.35**	**55**
SD	**0.30**	**0.31**	**7**

$\dot{V}O_2$: oxygen uptake, $\dot{V}O_{2max}$: maximum oxygen uptake, GET: gas exchange threshold. Data from Beaver et al. (1986).

Maximum lactate steady state

The MLSS is used to determine the maximum work rate sustainable over time without an increase in BLa accumulation (Beneke, 1995). At intensities exceeding the MLSS, the rate of glycolysis exceeds the rate of oxidative phosphorylation, resulting in a net excess of BLa (Heck et al., 1985). A series of 30-min, constant work rate tests, performed on separate days and at different intensities, is the conventional approach to MLSS determination (**Figure 2.11**) (Beneke, 1995, 2003). The intensity at MLSS is determined as the highest work rate where

BLa does not increase ≥1.0 mmol·L^{-1} during minutes 10 and 30 (Beneke & von Duvillard, 1996).

The are, however, several methodological concerns regarding the accuracy of MLSS determination and its ability to identify the maximum metabolic steady state, a threshold that separates steady and non-steady state exercise (Jones et al., 2019). These are highlighted in a review by Jones et al. (2019) and concern issues such as, but not limited to, the measurement error of commonly used BLa analysers, the reliability of BLa measurement, and whether the measured BLa is representative of the metabolic status of the working muscle. Furthermore, due to the nature of BLa kinetics whereby BLa change is typically greater in the first 10 min compared to the last 10 min of the 30-min test, exercise intensity might be concluded to be above the MLSS despite BLa reaching a steady state over the latter portion of the test (i.e., a delayed steady state, indicative of heavy intensity exercise) (Jones et al., 2019). Finally, due to the nature of the 30-min test protocol, the MLSS must underestimate the maximum metabolic steady state as the work rate at MLSS is always taken as the prior work rate to the test where BLa increases ≥1.0 mmol·L^{-1}. The true work rate likely falls between the two work rates and further refined tests would need to be conducted to find the true work rate demarcating the heavy and severe intensity domain (Jones et al., 2019). It is also worth noting that steady state $\dot{V}O_2$ responses have been observed at work rates exceeding the MLSS, indicating that the MLSS might not accurately define the maximum metabolic steady state and relying solely on BLa measurements may not reflect systemic metabolic rate (Nixon et al., 2021). Whilst the MLSS is shown to demarcate the heavy and severe intensity domain, there appear to be more accurate means of doing so.

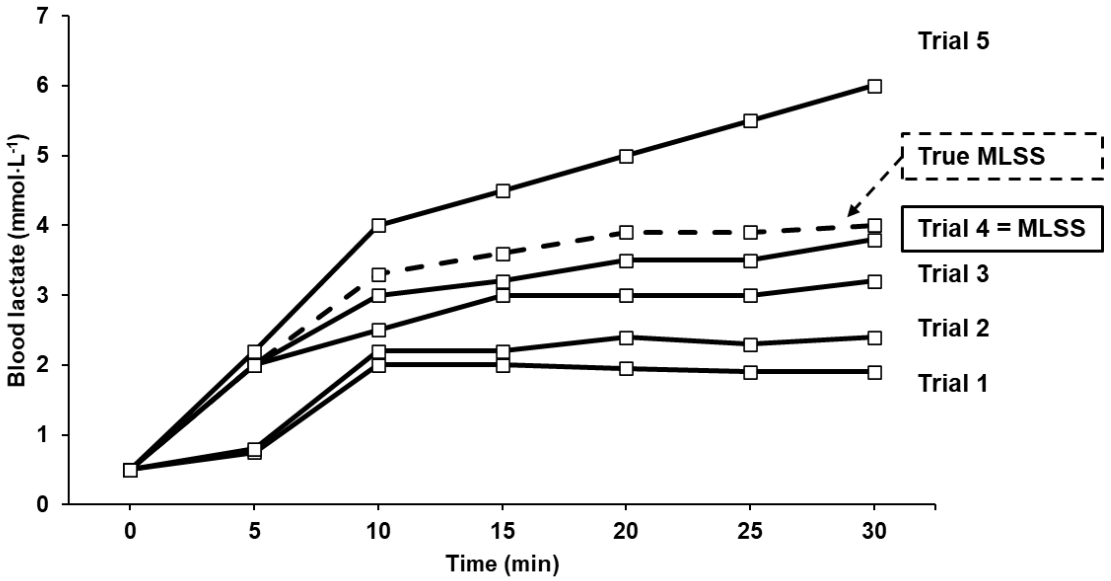

Figure 2.11. A series of 30-min constant work rate tests to determine maximal lactate steady state (MLSS). Trial 4 taken as the highest work rate where an increase ≥1.0 mmol·L^{-1} is not observed during the last 20 minutes of the test. However, were further testing conducted (dashed line), a higher MLSS might have been observed. Adapted from Jones et al. (2019).

Respiratory compensation point

The respiratory compensation point (RCP) is determined non-invasively during a GXT (Pettitt et al., 2013) and is identified as: the second breakpoint in $\dot{V}_E$ (**Figure 2.12a**), the breakpoint in $\dot{V}_E/\dot{V}CO_2$ (**Figure 2.12b**), or when end-tidal partial pressure for CO_2 ($P_{ET}CO_2$) falls following a period of stability (**Figure 2.12c**) (Whipp et al., 1989). This reflects the point at which hyperventilation occurs induced by the accumulation of H^+ resulting from an increased demand on anaerobic energy metabolism (Whipp et al., 1989).

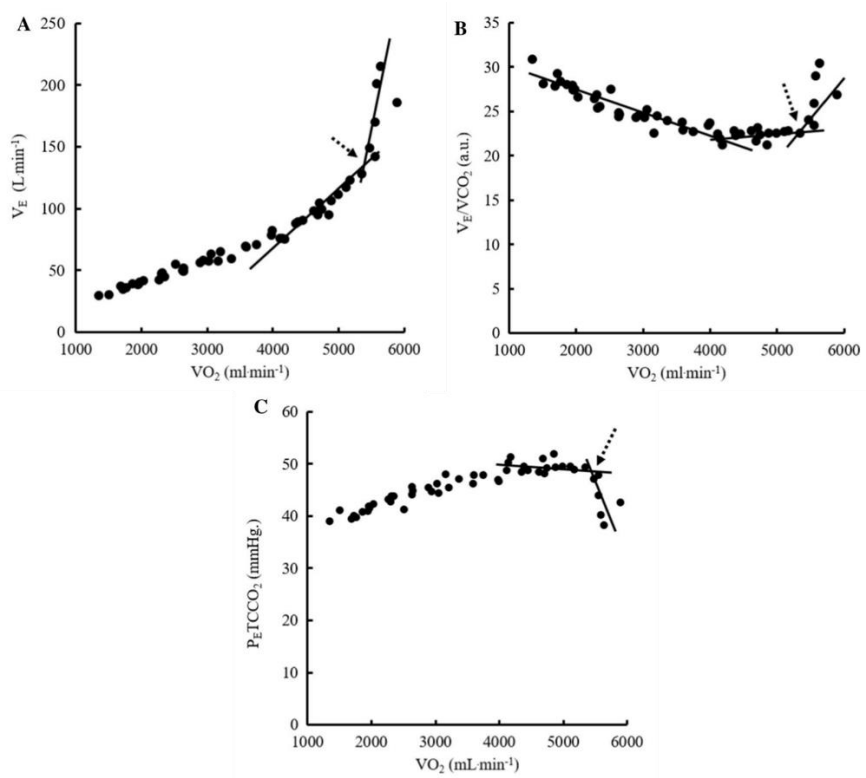

Figure 2.12. Illustration of expired air data collected during an incremental exercise test (GXT) used to determine the respiratory compensation point (RCP). RCP estimated at the second breakpoint in $\dot{V}_E$ (A), the breakpoint in $\dot{V}_E/\dot{V}CO_2$ (B), or when end-tidal partial pressure for CO_2 ($P_{ET}CO_2$) falls following a period of stability (C). From Jamnick et al. (2020).

There has been recent debate as to whether RCP is a valid marker of the boundary between the heavy and severe intensity domain (i.e., maximum metabolic steady state) (Caen et al., 2018; Galán-Rioja et al., 2020; Keir et al., 2018; Leo et al., 2017). Keir et al. (2015) demonstrated that $\dot{V}O_2$ at MLSS, critical power (discussed below), and RCP, were not different among a group of healthy participants, concluding that each threshold represents the same underlying phenomenon. Furthermore, Pessoa Filho et al. (2012) demonstrated a delayed steady state in $\dot{V}O_2$ kinetics at swimming intensities below the RCP, indicative of heavy intensity exercise, and a continuous increase in $\dot{V}O_2$ kinetics above the RCP, indicative of severe intensity exercise. These data thus support the use of RCP to delineate the heavy and severe intensity domains (Pessoa Filho et al., 2012). However, the association between critical power and RCP remains unclear and may be 'coincidental' (Cross & Sabapathy, 2012). It is

evidenced that RCP occurs at lower intensities when slower vs faster ramp GXTs are undertaken (Scheuermann & Kowalchuk, 1998) indicating that RCP may not represent a discrete external work rate (Leo et al., 2017). It has also been shown that a progressive decline in $P_{ET}CO_2$, indicative of respiratory compensation, can be observed during heavy intensity exercise (Poole et al., 1988; Simon et al., 1983). Nevertheless, if RCP is deemed to estimate the boundary between heavy and severe intensity exercise, the boundary between the moderate and heavy, and heavy and severe intensity domain can all be determined from a single non-invasive GXT.

Critical power

The power-duration relationship, when considering exercise tolerance, denotes that as exercise intensity increases, the ability to sustain such exercise reduces at a hyperbolic rate (A. V. Hill, 1925; Monod & Scherrer, 1965; Poole et al., 2016). The power-asymptote of this relationship is represented by critical power (CP) and the curvature constant by W prime (W′) (**Figure 2.13**) (Poole et al., 2016). CP is considered to represent the highest metabolic rate that results in wholly oxidative energy metabolism and the body is in a state of homeostasis regarding the balance between BLa production and clearance (Poole et al., 2016). CP is therefore argued to be an accurate representation of the maximum metabolic steady state and the boundary between the heavy and severe intensity domain (Jones et al., 2019; Nixon et al., 2021; Poole et al., 2016; Poole, Rossiter, et al., 2021) whereby exercising below and above CP can delineate between sustainable and non-sustainable exercise, respectively (Poole et al., 2016). As such, utilisation of the CP model as a tool for exercise intensity prescription is becoming more apparent (Chorley & Lamb, 2020; Clark et al., 2013; Collins et al., 2022; B. Hunter et al., 2023; Pettitt, 2016; Pettitt et al., 2015).

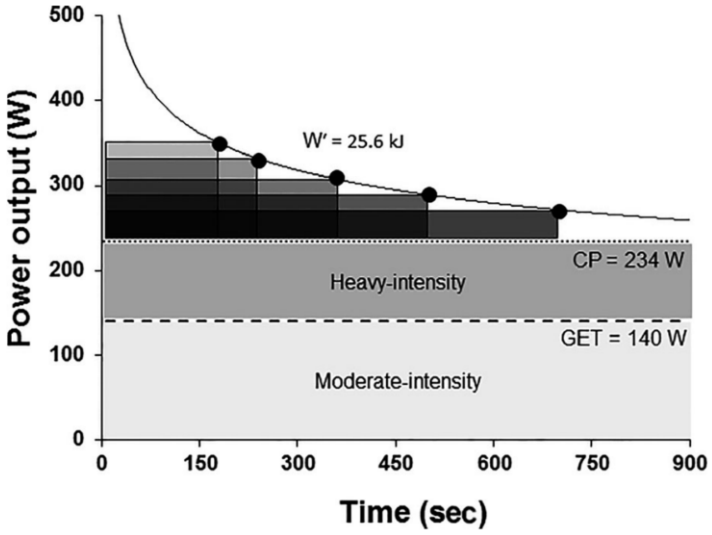

Figure 2.13. Representation of the power-duration relationship with reference to the moderate and heavy intensity domain delineated by the gas exchange threshold in this instance (GET). Boundary representing the upper limit of the heavy intensity domain represented by the asymptote of the power-duration relationship i.e., critical power (CP). The CP and the finite work capacity for exercise above the CP (i.e., W prime [W′]) are determined via a series of constant work rate tests (CWR). From Poole et al. (2016).

The conventional approach to CP determination involves a series of constant work rate exercise tests (CWR) performed to task failure (Muniz-Pumares et al., 2019). It is recommended that the duration of the CWRs should be between 2-15 min, with at least 5 min difference between the shortest and longest CWR. Power output and exercise time are recorded from each test and used to calculate CP using one of three models:

1) non-linear *power-time model*

$$T_{lim} = \frac{W'}{(P - CP)}$$

where, T_{lim} is time to task failure (s), P is power output (W), CP is the asymptote of the hyperbolic relationship, and W′ is the curvature constant;

2) linear *work-time model*

$$W = W' + CP \times T_{lim}$$

using linear regression analysis where, W is work (kJ), the y-intercept represents W′, and the slope represents CP;

3) linear *1·time^{-1} model*

$$P = CP + W' \times {T_{lim}}^{-1}$$

where the y-intercept represents CP, and the slope represents W′. For each individual, the standard error of estimate (SEE) is typically determined for CP and W′ and the model producing the lowest combined SEE is used.

Acute and chronic responses to threshold-based exercise

Crucially, among individuals, T1 and T2 vary in their position relative to $\dot{V}O_{2max}$ (Iannetta et al., 2020). It has been shown that T1 can vary between 40 and 60% $\dot{V}O_{2max}$ among individuals with similar $\dot{V}O_{2max}$ values (Lansley et al., 2011); T2, estimated by CP, ranged between 53–80% peak work rate in young healthy males (Van Der Vaart et al., 2014); and in elite marathon athletes, T1 and T2 occurred at extremely high fractions of $\dot{V}O_{2max}$ (~85% and ~95%, respectively) (Jones et al., 2020). In the HERITAGE study, the position of T1 occurred at various percentages of $\dot{V}O_{2max}$ among individuals, and consequently the standardisation of exercise intensity (55–75% $\dot{V}O_{2max}$) resulted in exercise undertaken <T1 and >T1 among individuals (Gaskill et al., 2001)2001). Thus, unsurprisingly, when exercising at an intensity fixed to a maximum physiological value, individuals may be exercising above, or below, T1 and T2 (Dwyer & Bybee, 1983; Iannetta et al., 2020; Katch et al., 1978; Meyer et al., 1999; Weltman et al., 1989, 1990b). As diverse physiological response profiles are elicited at such intensities, traditionally prescribed exercise training does not appropriately control the exercise intensity and stimuli experienced among individuals despite prescribing ‘standardised’ exercise (Iannetta et al., 2020; Jamnick et al., 2020).

Using physiological thresholds to prescribe intensity thus attempts to account for such metabolic differences among individuals (Mann et al., 2013; Scharhag-Rosenberger et al., 2010). As such, the observation of increased response rates, i.e., those demonstrating an increase in $\dot{V}O_{2max}$ above a predefined response threshold, following threshold-based exercise training compared to traditionally prescribed exercise training might be influenced by this notion (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015a). Nonetheless, Karavirta et al. (2011) reported a considerable range of changes in $\dot{V}O_{2max}$ following exercise training prescribed above and below T1 combined with resistance training (−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% $\dot{V}O_{2max}$ compared to 95% LT elicited observable differences in the acute physiological responses among trained and untrained individuals. When performed at 95% LT, the perturbations in plasma lactate and ammonia were more homogeneous both within and between trained and untrained groups (Baldwin et al., 2000). Such results support the superiority of threshold-based exercise training in its ability to control exercise intensity. A recent study demonstrated higher response rates following HIIT at 90% HRmax (95%) compared to MICT at 90% LT (53%), despite the range of $\dot{V}O_{2max}$ changes being similar between groups (Maturana et al., 2021a). Notably, in the HIIT group the intensity of 90% HR_{max} was sufficient to ensure that all individuals were exercising above T2. 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 (∆) concept has been proposed based on its ability to reduce the variability in the acute physiological perturbations experienced by individuals

compared to traditionally prescribed exercise training (Lansley et al., 2011). The Δ method prescribes intensity as a percentage of the difference between a sub-maximum (T1) and maximum physiological value (Casaburi et al., 1987a). 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 $\dot{V}O_{2max}$ following 4 weeks of HIIT (−455 to 1521 mL·min^{-1}). Casaburi et al. (1987a) did however report 100% response rates following exercise training prescribed at 50–75% Δ with a mean increase in $\dot{V}O_{2max}$ of ~15% (7–30%). It has been suggested that 50% Δ approximates CP (i.e., T2) (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% $\dot{V}O_{2max}$. Additionally, at 70% $\dot{V}O_{2max}$, four individuals attained $\dot{V}O_{2max}$ 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 T2 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).

CP represents the asymptote of the power-duration relationship denoting the highest work rate, or $\dot{V}O_2$, that can be sustained for prolonged periods of time (Poole & Jones, 2012). Working at an intensity <CP enables the consistent attainment of stabilised $\dot{V}O_{2max}$ kinetics (revealing a reduced slow component) (Craig et al., 2018; Jones et al., 2008, 2019) and also of metabolic stability (e.g., stabilised levels of intramuscular creatin(Poole & Jones, 2012)gen ions) (Poole & Jones, 2012). 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). 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 $\dot{V}O_{2max}$ (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 exercise training. 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 exercise training elicits more homogeneous chronic adaptations in $\dot{V}O_{2max}$ than that of traditional approaches as a result of exposure to more homogeneous acute exercise responses among individuals.

In addition to marked increases in $\dot{V}O_{2max}$, prescribing volume-matched exercise training relative to VT (T1) and the respiratory compensation point (T2) resulted in 100% response rates compared to 40–70% response rates when exercise training was prescribed relative to HRR (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015a). Thresholds derived from gas exchange data are likely to 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 $\dot{V}O_{2max}$ or both.

Overall, most studies have demonstrated greater response rates following threshold-based exercise training compared to traditionally prescribed exercise training (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015a). As threshold-based exercise training elicits more homogeneous acute physiological stress among individuals, increased response rates following such exercise training may be driven by the manifestation of more homogeneous chronic adaptations (**Figure 2.14**). In contrast to attributing increased response rates to greater mean changes in $\dot{V}O_{2max}$, as typically observed following the manipulation of training dose within traditionally prescribed exercise training, future research might aim to determine whether increased response rates following threshold-based exercise training are, in fact, driven by a reduction in response variability exclusively, or in addition to the elicitation of greater mean changes in $\dot{V}O_{2max}$.

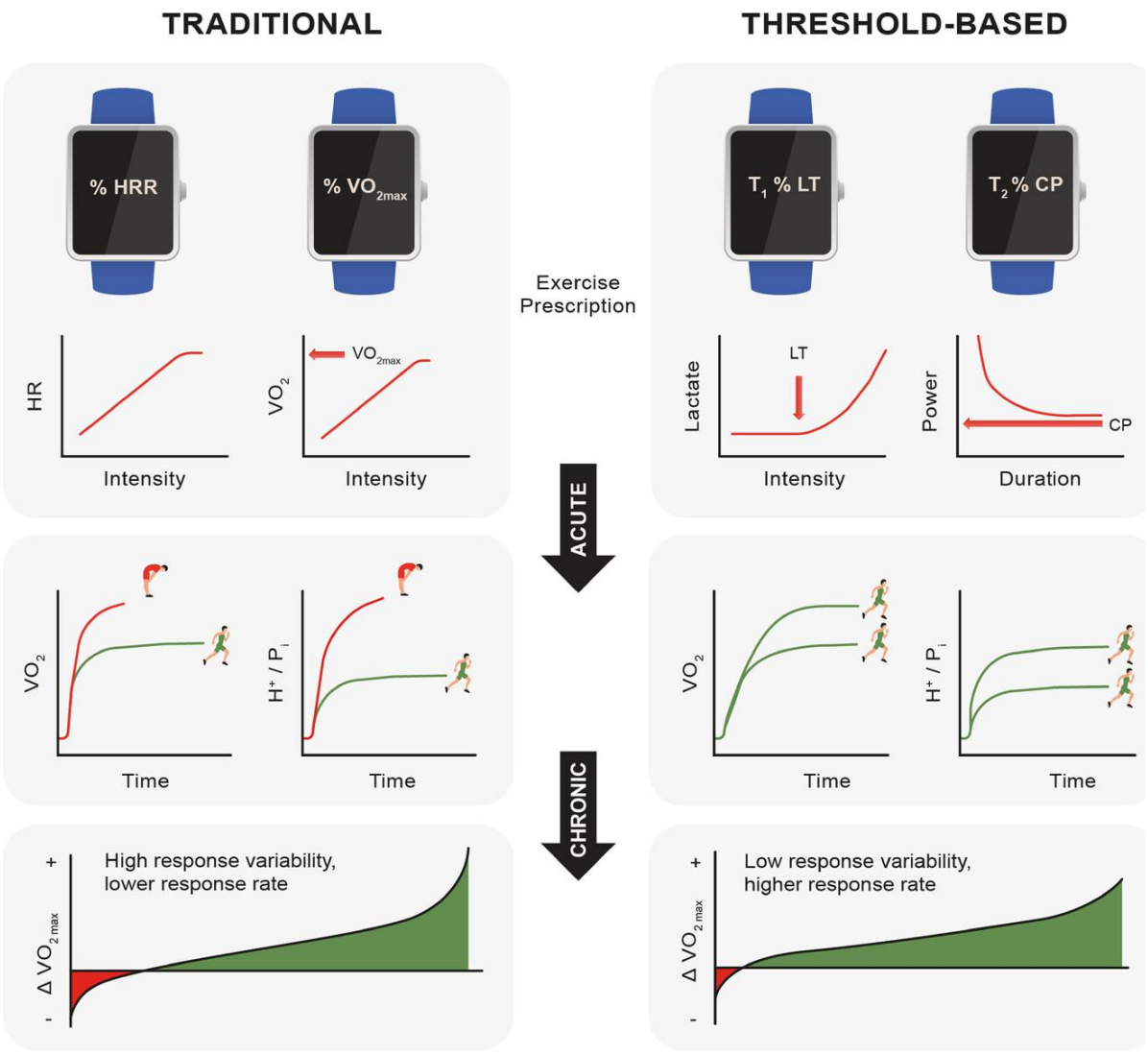

Figure 2.14. Theoretical pathway for varied response following traditional versus threshold-based intensity prescription within an endurance training programme. Some examples are provided of traditional and threshold-based anchors of intensity. Compared to traditional approaches (where intensity is relative 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; Pi, inorganic phosphate concentration; T1, physiological threshold 1; T2, physiological threshold 2; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2max}$, maximum oxygen uptake.

Implications of exercise intensity prescription

Moderate, heavy, and severe intensity exercise can thus be prescribed in a multitude of ways; however, the ability of certain approaches to control and normalise exercise intensity among individuals have come into question (Jamnick et al., 2020). Currently, compared to when traditional approaches are used, prescribing exercise relative to physiological thresholds has shown promise regarding the inducement of more homogeneous physiological responses and greater adaptations to exercise training, namely in markers of cardiorespiratory fitness (i.e., $\dot{V}O_{2max}$) (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015a). Regarding the acute response to exercise, more homogeneous acute responses to exercise among individuals have been reported using a threshold-based approach (Baldwin et al., 2000; Lansley et al., 2011). This, however, has only been demonstrated when the LT (Baldwin et al., 2000), onset of blood lactate accumulation (McLellan & Jacobs, 1991), and GET (Lansley et al., 2011) are used as the key physiological threshold(s).

Whilst the use of such thresholds is rational, particularly for prescribing moderate intensity exercise (i.e., below the lactate threshold and/or gas exchange threshold), using an accurate threshold that differentiates higher intensity exercise between the heavy and severe intensity domains may be of more precedence. This stems from the notion that just small differences in external work rate at intensities approaching or crossing the transition from heavy to severe intensity exercise can induce marked differences in the elicited physiological demand and exercise tolerance. Controlling exercise at such intensities is thus important.

An approach currently under-utilised within the scientific literature that may fulfil this role is using CP as a tool for exercise intensity prescription. Evidence demonstrates the precision of CP in demarcating sustainable (heavy intensity exercise) and unsustainable exercise (severe intensity exercise) whereby metabolic perturbations can and cannot be stabilised, respectively (Jones et al., 2019; Nixon et al., 2021; Poole et al., 2016, 2020). As physiological responses, and exercise tolerance, can be accurately predicted using the CP model, it thus seems appropriate to use such a marker when prescribing exercise intensity. Furthermore, Collins et

al. (2022) recently demonstrated that physiological variability and adaptations to training are more appropriately explained when exercise intensity is related to CP compared to when related to $\dot{V}O_{2max}$. Despite this, the use of CP as an anchor of exercise intensity remains relatively absent literature (Poole & Jones, 2023). As such, with the continued use of traditional approaches to implement exercise intensity prescription, otherwise well controlled research studies are potentially confounded by poorly controlled exercise and exercise training.

SUMMARY

Considerable individual variability in $\dot{V}O_{2max}$ response rates occurs following exercise training. This is concerning as ~20% of the population may not increase CRF in response to exercise training, 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 exercise training, and the methodological sources of variation that, upon manipulation, can influence subsequent CRF training responses.

Biological factors including genetics, age, sex, and baseline $\dot{V}O_{2max}$ appear to contribute to varied individual responses, with the most potent being genetics, explaining ~50% of response variability. However, the molecular basis underpinning $\dot{V}O_{2max}$ trainability remains unclear. The influence of age, sex and baseline $\dot{V}O_{2max}$ appears to be smaller, accounting for <10% of response variability when combined. Men appear to be somewhat more responsive than women and increases in $\dot{V}O_{2max}$ are attributed primarily to central adaptations. In contrast, increases in $\dot{V}O_{2max}$ in women appear to be attributed to a greater extent to peripheral adaptations. Lastly, whilst the effect of baseline $\dot{V}O_{2max}$ on response variability remains inconclusive, individuals possessing an already well-developed $\dot{V}O_{2max}$ 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 $\dot{V}O_{2max}$ 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 exercise training programme, has consistently been shown to increase $\dot{V}O_{2max}$ response rates. However, whilst efficacious, such a strategy may be unfeasible for the wider population.

The method of intensity prescription implemented within exercise training can influence subsequent $\dot{V}O_{2max}$ response rates and, notably, could explain a significant proportion of response variability to exercise training. Whilst increases in $\dot{V}O_{2max}$ can be achieved via traditionally prescribed exercise training, 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 exercise training following threshold-based exercise training 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.

Further research may endeavour to investigate whether threshold-based exercise training 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 $\dot{V}O_{2max}$. Such findings may help inform future training interventions which aim to obtain increases in $\dot{V}O_{2max}$ in as many individuals as possible, increasing the number of individuals attaining meaningful health benefits from exercise.

AIMS AND HYPOTHESES

The overarching aim of this thesis was to elucidate on the effect that prescribing exercise training relative to physiological thresholds has on both the magnitude and variability of acute and chronic responses to exercise.

The aims and hypotheses of the three experimental chapters were as follows:

1. To compare the variability in exercise tolerance and physiological responses to acute exercise bouts prescribed relative to the gas exchange threshold and critical power, and relative to maximum oxygen uptake ($\dot{V}O_{2max}$).
    1.1 Hypothesis: The variability in exercise tolerance and acute physiological responses to exercise bouts prescribed relative to the gas exchange threshold and critical power will be lower than those elicited by exercise prescribed relative to $\dot{V}O_{2max}$.
2. To compare the magnitude and variability in changes to cardiorespiratory fitness following exercise training prescribed relative to critical power and to $\dot{V}O_{2max}$.
    2.2 Hypothesis: The variability in training-induced changes in physiological parameters, namely in $\dot{V}O_{2max}$, will be lower when exercise training is prescribed relative to critical power compared to when training is prescribed relative to $\dot{V}O_{2max}$.
    2.3 Hypothesis: The proportion of individuals increasing their $\dot{V}O_{2max}$ beyond a predefined threshold (i.e., technical error of measurement [TE] and minimum important difference [MID]) will be greater in those exercising relative to critical power.
3. To systematically review and meta-analyse, using individual participant data, the magnitude and variability in $\dot{V}O_{2max}$ change scores to exercise training prescribed relative to physiological thresholds and to traditional intensity anchors.
    3.1 Hypothesis: Threshold-based exercise training would elicit greater mean changes in $\dot{V}O_{2max}$ to that of traditionally prescribed exercise.

3.2 Hypothesis: The variability in $\dot{V}O_{2max}$ change scores would be less following exercise training prescribed relative to physiological thresholds compared when prescribed relative to traditional intensity anchors.

3.3 Hypothesis: A larger proportion of individuals will demonstrate increases in $\dot{V}O_{2max}$ beyond the minimum important difference following threshold-based exercise training compared to traditionally prescribed exercise training.

CHAPTER 3 – GENERAL METHODS

ETHICS

All experimental procedures presented in this thesis were approved by the Health, Science, Engineering & Technology Ethics Committee with Delegated Authority of the University of Hertfordshire prior to data collection and recruitment. All protocols were executed in accordance with the Declaration of Helsinki (1964), except for registration. For all experimental studies (**Chapter 4-6**), ethical approval, participant information documents, and health screening documents are included with the **Appendix**.

PARTICIPANTS

Participants were recruited both from the University and wider community. Prior to testing, participants were provided with a written and verbal explanation regarding their participation in the study(s) along with the associated risks and benefits of taking part. Participants were required to provide informed written consent before commencing with any study. Participants were informed that they would be free to withdraw from an experiment at any time and without consequence. Participants were assured that collected data would be anonymised prior to storage, and that it may be published in academic journals and presented elsewhere (e.g., at scientific conferences). During exercise testing and training phases, participants were instructed to arrive at the laboratory rested and hydrated, having avoided strenuous activity, and abstaining from alcohol consumption in the 24 h prior to any experiment. Participants were asked to maintain a consistent caffeine intake prior to each laboratory visit. Where possible, every effort was made to conduct exercise testing and training at similar times of day to avoid diurnal differences in performance.

HEALTH AND SAFETY

All experimental protocols adhered to the University of Hertfordshire Sport, Health, and Exercise subject group Protocols of Safe Working and the University of Hertfordshire School

of Life and Medical Sciences health and safety policies. All work surfaces were disinfected before and after each participant was tested using 5% Milton solution (Milton, Newmarket, UK). Any non-disposable equipment contaminated with biological substances was disinfected using 5% Milton solution. Contaminated sharp consumables were disposed of in a sharps bin in accordance with the Human Tissue Act 2004. Similarly, all soft materials (e.g., tissues) contaminated with biological substances were disposed of in a biological waste bin. Contents of these bins were incinerated on a regular basis. Respiratory equipment was disinfected in line with manufacturer's instructions. All testing equipment used in experimental procedures were serviced and maintained in accordance with manufacturer's instructions.

DESCRIPTIVE DATA

Participants age, date of birth, height and body mass were recorded prior to testing for all corresponding experiments. Height was recorded to the nearest 0.1 cm during inspiration at the point where the headboard compresses the hair (Holtain Limited, United Kingdom). Body mass was recorded to the nearest 0.1 kg barefoot and in minimal clothing (Seca Electrical Column Digital Scales 780, Germany).

CYCLE ERGOMETRY

All experimental chapters included exercise tests and training sessions performed on an electrically braked cycle ergometer (Lode Excalibur Sport and Lode Corival, Groningen, Nederlands). On both cycle ergometers, external power output was controlled independent of pedal cadence by instantaneously adjusting the flywheel resistance via electrical braking. The Lode Excalibur Sport ergometer was used exclusively for all exercise testing sessions in **Chapter 4** and **Chapter 5**, and for the majority of exercise training sessions in **Chapter 5**. The Lode Corival ergometer was used for exercise training sessions only in situations where the Lode Excalibur Sport was out of use (**Chapter 5**).

TASK FAILURE

In all experimental chapters, 'task failure' was defined as the point at which exercise could no longer be sustained following maximal exertion. Specifically, the point of task failure was considered to occur when a participant was no longer able to maintain the required work rate despite strong verbal encouragement and pedal cadence dropped by more than 10 rpm for 5 consecutive seconds without recovery.

MEASUREMENT OF PULMONARY GAS EXCHANGE

Gas exchange data were measured continuously breath-by-breath using an online gas analyser (MetaLyzer 3B, Cortex Biophysik, Leipzig, Germany). Participants wore a face mask with low dead space (125 mL) and breathed through a low resistance (<0.1 $kPa \cdot L^{-1}$ at 20 $L \cdot s^{-1}$) impeller turbine with O_2 and CO_2 samples at 50 Hz. The gas analyser was calibrated prior to each exercise session with gases of known concentration and the turbine volume transducer was calibrated using a 3 L syringe (Hans Rudolph, Inc. Kansas City, MO). Barometric pressure was calibrated with values measured by a digital barometer (GPB 3300, Greisinger, Regenstauf, Germany). Rise time of the gas analyser and transit delay for O_2 and CO_2 were <100 ms and 800-1200 ms, respectively, allowing for breath-by-breath calculation. Measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ were recorded breath-by-breath and exported as 10-s moving averages for subsequent analyses.

MEASUREMENT OF CAPILLARY BLOOD SAMPLING

To avoid cross-contamination, medical grade nitrile gloves were worn during sampling and analysis by the researcher. The skin of fingertip on the chosen hand was prepared for blood extraction with a 70% v/v isopropyl alcohol swab (STERETS, Mölnlycke Health Care, Gothenburg, Sweden). The lateral or medial aspect of the fingertip was then punctured using a disposable lancet (Safe-T-Pro Plus, Accu-Chek, Indianapolis, IN, USA). The first drop of blood was wiped away prior to the first collection of blood in the capillary tube (10 µL). The capillary tube was then placed into a sample cup filled with haemolysing solution. Samples were stored at room temperature for no more than 60 min before analysis using the blood

analyser (Biosen C-line, EKF Diagnostic, Barleben, Germany). The blood analyser was calibrated prior to use and then hourly using a standard solution ([La] corresponding to 12 mmol·L).

MAXIMAL RAMP EXERCISE TESTS

A maximal effort ramp exercise test (GXT) was used to determine maximum oxygen uptake ($\dot{V}O_{2max}$), maximum heart rate (HR_{max}), and the gas exchange threshold (GET). Participants performed a 3-min warm up at 25 W, after which, work rate was increased at a rate of 20 or 30 $W \cdot min^{-1}$ in a linear fashion until task failure. Participants cycled at a self-selected cadence between 60-100 rpm. To determine $\dot{V}O_{2max}$ and HR_{max} the highest mean $\dot{V}O_2$ and HR achieved during any 30 s period were taken. Participant's GET was estimated as the first disproportionate increase in carbon dioxide production ($\dot{V}CO_2$) from visual inspection of individual $\dot{V}CO_2$ vs. $\dot{V}O_2$ plots. GET was then confirmed by visual inspection of additional breath-by-breath plots using an online exercise threshold determination tool (Keir et al., 2022). GET was estimated by two independent assessors with any disagreements solved by a third assessor.

DETERMINATION OF THE POWER-DURATION RELATIONSHIP

The power-duration relationship was determined for each participant. To do so, a series of constant work rate exercise tests (CWR) were performed to task failure and were performed at work rates intended to elicit task failure between 2-15 min (work rate ~65-95% of maximum power output achieved in GXT). A maximum of two CWR were performed per testing day with an inter-trial recovery period of 45 min to 1 h. Participants completed a 3 min warm up at 25 W, after which, work rate was increased via a step increase to the test work rate. Participants cycled to task failure at a self-selected cadence between 60-100 rpm. Critical power (CP) and the curvature constant of the hyperbolic power-duration relationship (W′; work-prime) were estimated using three equations:

1) non-linear *power-time model*

$$T_{lim} = W' / (P - CP)$$

where, T_{lim} is time to task failure (s), P is power output (W), CP is the asymptote of the hyperbolic relationship, and W′ is the curvature constant;

2) linear *work-time model*

$$W = W' + CP \, x \, T_{lim}$$

using linear regression analysis where, W is work (kJ), the y-intercept represents W′, and the slope represents CP;

3) linear *1/time model*

$$P = CP + W' \, x \, {T_{lim}}^{-1}$$

where the y-intercept represents CP, and the slope represents W′. For each participant, the standard error of estimate (SEE) was determined for CP and W′ and the model producing the lowest combined SEE for each individual was used to estimate CP and W′ on an individual basis. If SEE was >5% and >15% for CP and W′, respectively, an additional CWR trial was conducted.

STATISTICAL METHODS

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, IBM Corp, Armonk, NY), JASP Team (Nederland), and/or R (R Foundation for Statistical Computing, Vienna, Austria). Specific information regarding the statistical tests implemented are presented in each experimental chapter.

CHAPTER 4 – CHANGES IN CARDIORESPIRATORY FITNESS FOLLOWING EXERCISE TRAINING PRESCRIBED RELATIVE TO TRADITIONAL INTENSITY ANCHORS AND TO PHYSIOLOGICAL THRESHOLDS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

INTRODUCTION

Cardiorespiratory fitness, measured as maximum oxygen uptake ($\dot{V}O_{2max}$), represents the upper limit of cardiopulmonary-muscle oxidative function (A. V. Hill & Lupton, 1923), quantifying the body's ability to transport and utilise oxygen (Poole & Jones, 2012). As such, $\dot{V}O_{2max}$ is recognised as a key determinant of endurance performance, with elite endurance athletes demonstrating some of the highest $\dot{V}O_{2max}$ values ever recorded (Bassett & Howley, 2000; Joyner & Coyle, 2008). Additionally, $\dot{V}O_{2max}$ is an important marker of cardiovascular health (Ezzatvar et al., 2021; Harber et al., 2017; R. Ross et al., 2016) and low levels of $\dot{V}O_{2max}$ are a strong risk factor for all-cause and disease-specific mortality (Harber et al., 2017). Despite being the only major risk factor not routinely assessed in clinical practice, growing epidemiological and clinical evidence suggests that $\dot{V}O_{2max}$ may be a stronger predictor of mortality than traditionally assessed risk factors such as smoking, type 2 diabetes mellitus, and obesity (R. Ross et al., 2016). Increasing $\dot{V}O_{2max}$ is thus a commonly sought-after phenotypic change across different populations. Evidence indicates that increasing $\dot{V}O_{2max}$ by one metabolic equivalent (MET; 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) can reduce mortality risk by ~10-30% (Harber et al., 2017; Laukkanen et al., 2022) and health care costs by ~5% (Bachmann et al., 2015; Myers et al., 2018). In turn, a value of one MET can be used as a minimum important difference (MID) when evaluating changes in $\dot{V}O_{2max}$ following a period of exercise training (Bonafiglia et al., 2019; R. Ross et al., 2016).

Changes in $\dot{V}O_{2max}$ can be explained by the Fick principle, where $\dot{V}O_{2max}$ is the product of maximum cardiac output and arteriovenous oxygen difference (Shapiro, 1972; Willis Hurst et al., 2000). Adaptations causing changes in cardiac output (i.e., the product of heart rate and stroke volume) represent 'central' adaptations whereby phenotypic modifications alter convective oxygen delivery, whereas adaptations causing changes in arteriovenous oxygen difference reflect 'peripheral' adaptations, comprised of changes in oxygen extraction and utilisation (Ekblom et al., 1968). The most effective means of increasing $\dot{V}O_{2max}$ is through endurance training, typically in the form of constant load continuous training and/or interval-based training, which are shown to increase $\dot{V}O_{2max}$ by ~5.5 and ~4.9 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively (Milanović et al., 2015). On the other hand, $\dot{V}O_{2max}$ is markedly reduced by periods of inactivity (e.g., bed rest) (Saltin, Blomqvist, Mitchell, Johnson, Wildenthal, & Chapman, 1968). Whilst both approaches of exercise training have been demonstrated to be efficacious at the group level (Milanović et al., 2015), the individual effect of exercise training on $\dot{V}O_{2max}$ appears to exhibit a heterogenous distribution (Bouchard et al., 1999; Williams et al., 2019), suggesting that some individuals do not attain some of the benefits of exercise.

Several biological and methodological factors underpin this apparent 'response variability' (**Chapter 2**), as well as measurement error and day-to-day biological variability (Bonafiglia et al., 2022). To tackle response variability, and specifically the number of individuals attaining a change in $\dot{V}O_{2max}$ surpassing a predefined threshold, interventions commonly adopt 'additive' approaches (for a review see (Adams et al., 2021)). For example, augmenting the exercise stimulus (i.e., increasing training volume, frequency, and/or intensity) often proves effective in increasing response rate as a result of greater group mean increases in $\dot{V}O_{2max}$ (Bonafiglia et al., 2021; Montero & Lundby, 2017; R. Ross et al., 2015; Sisson et al., 2009). Aiming to elicit superior changes in $\dot{V}O_{2max}$ and reduce response variability to the initial stimulus, an example of a 'subtractive' approach (Adams et al., 2021), may be achieved through changing the method used to prescribe exercise intensity (**Chapter 2**). However, the effect of using different means of exercise prescription to do so are unclear.

Exercise intensity is commonly prescribed relative to traditional (TRAD) intensity anchors (Table 1) (Milanović et al., 2015) whereby recommended percentages of such values are used to prescribe exercise in a given intensity domain. It is worth noting that whilst various nomenclature is used to describe the different intensity domains in performance and health settings (Coates et al., 2023), the three-domain classification (moderate, heavy, and severe intensity exercise) will be referred to in the present study. Notably, TRAD approaches are evidenced to elicit marked variation in acute physiological responses and exercise tolerance (Baldwin et al., 2000; Iannetta et al., 2021; Katch et al., 1978; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). As changes in $\dot{V}O_{2max}$ manifest in response to specific exercise-induced adaptive stimuli (Flück, 2006), when different stimuli are experienced by individuals over time, it is plausible that this may contribute to a portion of $\dot{V}O_{2max}$ response variability (Mann et al., 2013; Scharhag-Rosenberger et al., 2010).

Table 4.1. 'Traditional' anchors of exercise intensity.

Intensity Anchor	Abbreviation	Description
Maximum oxygen uptake	$\dot{V}O_{2max}$	Maximum oxygen uptake attained during maximal exercise despite increases in external workload
Oxygen uptake reserve	$\dot{V}O_2R$	Difference between maximum and resting oxygen uptake
Maximum heart rate	HR_{max}	Maximum heart rate reached during maximal exercise despite increases in external workload
Heart rate reserve	HRR	Difference between maximum and resting heart rate
Maximum work rate	WR_{max}	Maximum work rate achieved during an incremental exercise test

Instead, using physiological thresholds that demarcate the intensity domains as intensity anchors (**Table 4.2**) has shown to elicit more homogenous acute physiological (Baldwin et al., 2000; Lansley et al., 2011; McLellan & Skinner, 1981). It is of interest to explore whether this has a positive impact on longer term responses (i.e., training-induced changes in $\dot{V}O_{2max}$) regarding their magnitude and variability. If the magnitude of training-induced changes in $\dot{V}O_{2max}$ can be increased among a larger proportion of individuals, and the number of individuals experiencing negligible changes in their $\dot{V}O_{2max}$ is reduced, this could have profound implications for improving health outcomes and approaches to exercise prescription.

Table 4.2. Physiological thresholds delineating the boundary of the moderate and heavy intensity domain and the heavy and severe intensity domain.

Physiological threshold	Description
Boundary between the moderate and heavy intensity domain	
Lactate threshold (LT)	Blood lactate concentration rises above baseline levels
Gas exchange threshold (GET)	First breakpoint at which $\dot{V}CO_2$ increases disproportionately to $\dot{V}O_2$
Ventilatory threshold (VT)	First breakpoint at which $\dot{V}_E$ increases disproportionately to $\dot{V}O_2$
Boundary between the heavy and severe intensity domain	
Maximum lactate steady-state (MLSS)	Highest constant work rate that leads to a balance between lactate production and elimination
Respiratory compensation point (RCP)	Second breakpoint at which $\dot{V}_E$ increases disproportionately to $\dot{V}O_2$
Critical power (CP)	Asymptote of the power–duration relationship

CO_2: Carbon dioxide, $\dot{V}_E$: minute ventilation, $\dot{V}O_2$: oxygen uptake

Objectives

Examining differences between THR and TRAD exercise programmes (and using non-exercising control groups [CON] where applicable), we sought to: a) compare the mean change scores in $\dot{V}O_{2max}$ and the proportion of individuals expected to attain increases in $\dot{V}O_{2max}$ beyond a MID of one MET (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) between THR and TRAD; and b) test the hypothesis that $\dot{V}O_{2max}$ response variability is lower in THR compared to TRAD.

METHODS

Protocol and registration

This review was pre-registered on PROSPERO (id: CRD42021226644) and the present protocol has been conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis of Individual Participant Data guidelines (Stewart et al., 2015) (Supplementary file).

Eligibility criteria

Type of study

Randomised controlled and non-controlled training studies, written in English, and published before October 2023.

Type of participants

Healthy males and females, ≥18 years of age, BMI ≤30 $kg \cdot m^2$, and were not suffering from any acute or chronic disease(s).

Type of interventions

Training interventions had to meet the following criteria: a) exercise training lasted ≥3 weeks; b) consisted of either continuous training, interval training, or a combination of both, c) exercise was either walking, running or cycling; d) $\dot{V}O_{2max}$ was directly measured pre- and post-intervention via indirect calorimetry during an incremental test to task failure; and e) individuals were either allocated to traditionally prescribed exercise training (TRAD), whereby exercise intensity was prescribed relative to a physiological value, as outlined in **Table 4.1**; and/or to a physiological threshold (THR) as outlined in **Table 4.2**. The latter includes studies using the delta method (∆) whereby intensity is prescribed using a physiological threshold and physiological value (i.e., 50% ∆ = gas exchange threshold + [0.5 x (critical power-gas exchange threshold)]). Exercise groups involving additional interventional manipulations, such as nutritional supplementation and/or environmental manipulation were excluded. Two datasets were created from eligible studies, one containing 'controlled' studies, where studies included volume matched THR and TRAD exercise group and a non-exercising control group (CON); and 'non-controlled' studies, where data from any single THR and TRAD exercise group was included.

Identifying studies for systematic review - information sources and search strategy

Electronic databases PubMed and Scopus were searched initially in 2021 and updated in 2023 such that papers published before October 2023 were included. Databases were searched using the following terms: 'high-intensity interval training', 'continuous training', 'endurance training', 'maximum oxygen uptake', 'peak oxygen uptake', '$\dot{V}O_{2max}$', 'cardiorespiratory fitness', 'healthy adults'. Additional resources were sought via the scrutinisation of reference lists, review articles, and contact with research teams of relevant papers. The literature search and study selection process was carried out independently by two authors (SM and BH) using a systematic review software (Covidence, Veritas Health Innovation, Australia). A third reviewer (author DM) resolved any disagreements regarding study eligibility. The title and abstracts were extracted from the database searches and duplicates were removed automatically by the Covidence software. Papers that were not relevant based on the title were removed. Title and abstracts were screened to identify studies that appeared to meet the predefined eligibility criteria. Full texts of studies passing the title and abstract screening were then scrutinised to determine their eligibility for inclusion in the review.

Data collection processes

Corresponding authors of eligible studies were contacted via email or by other means of contact (e.g., ResearchGate, social media). Authors were provided with a brief summary of the aims of the present study and invited to share anonymised individual participant data (IPD). Anonymised IPD included age, sex, height (cm), pre- and post-intervention mass (kg), $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$ and $L \cdot min^{-1}$), and BMI for all individuals. Lead authors were contacted in the same manner if corresponding authors were unreachable. A follow-up email containing a deadline for response was sent to authors in the absence of a reply.

IPD integrity

Once IPD was received, data were checked for consistency with the published report, at the individual level for inconsistencies and missing data. Only individuals with a complete data set were included in the review and individual data not meeting the participant eligibility criteria were excluded. Any discrepancies between IPD and published reports were discussed with the study authors.

Risk of bias

Risk of bias was assessed in each individual study by two reviewers (SM and DMP). For randomised trials, the Cochrane risk-of-bias tool for randomised trials (RoB2) was used (J. A. C. Sterne et al., 2019). The ROBINS-I tool was used for assessing risk of bias in non-randomised and uncontrolled intervention studies (J. A. Sterne et al., 2016). An inter-reviewer reliability analysis using the Kappa statistic (k) was performed to determine consistency between reviewers (supplementary file).

Specification of outcomes and effect measures

All analyses were conducted using $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) change scores, calculated for each individual as the post-intervention value minus the baseline value. Measures of effect were based on group differences according to this absolute scale and percentage expected to exceed the MID.

Synthesis methods

Across all analyses, one-stage IPD meta-analysis models were developed. All models were conducted within a Bayesian framework with random intercepts to account for systematic variation across individual studies. Change scores relative to baseline were calculated for each participant on an absolute scale ($mL \cdot kg^{-1} \cdot min^{-1}$) and distributional models were used to estimate both the mean difference and standard deviation of the difference. A group term (TRAD vs. THR, or Exercise vs. Control) was added as a predictor for the mean and standard deviation, with a log link used for the latter. Posterior distributions were summarised by

reporting the median and 95% credible intervals (CrI) for the mean and 75% CrIs for the standard deviation. Separate Bayes factors were estimated comparing models with and without the group predictor for the mean and standard deviation. A Bayes factor greater than 1.0 provided evidence supporting a group difference, whereas values less than 1.0 provided evidence supporting no group difference. The overall strength of evidence in favour of the different models was evaluated according to a previously defined scale (Lee & Wagenmakers, 2014), with non-neutral descriptions ranging from anecdotal to extreme evidential strength (**Table 6.3**).

Table 6.3. Category of evidence for Bayes Factor interpretation**.**

Bayes Factor (BF)	Strength of Evidence
≥100	Extreme
30-100	Very strong
10-30	Strong
3-10	Moderate
1-3	Anecdotal
1	No evidence

To investigate the proportion of individuals exceeding the MID, we used the posterior samples from the distributional model to generate posterior predictions (n=10,000) and calculated the proportion that exceeded the threshold in each group. Default weakly informative priors were used including Student-t and half-t priors with 3 degrees of freedom. All analyses were performed using the R wrapper package brms interfaced with Stan to perform sampling (Bürkner, 2017) and the R package bridgesampling to calculate Bayes factors. Convergence of parameter estimates was obtained for all models with Gelman-Rubin R-hat values below 1.1 (Gelman et al., 2013).

RESULTS

Study selection and IPD obtained

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (**Figure 4.1**) depicts the flow of information through the different phases of the systematic review.

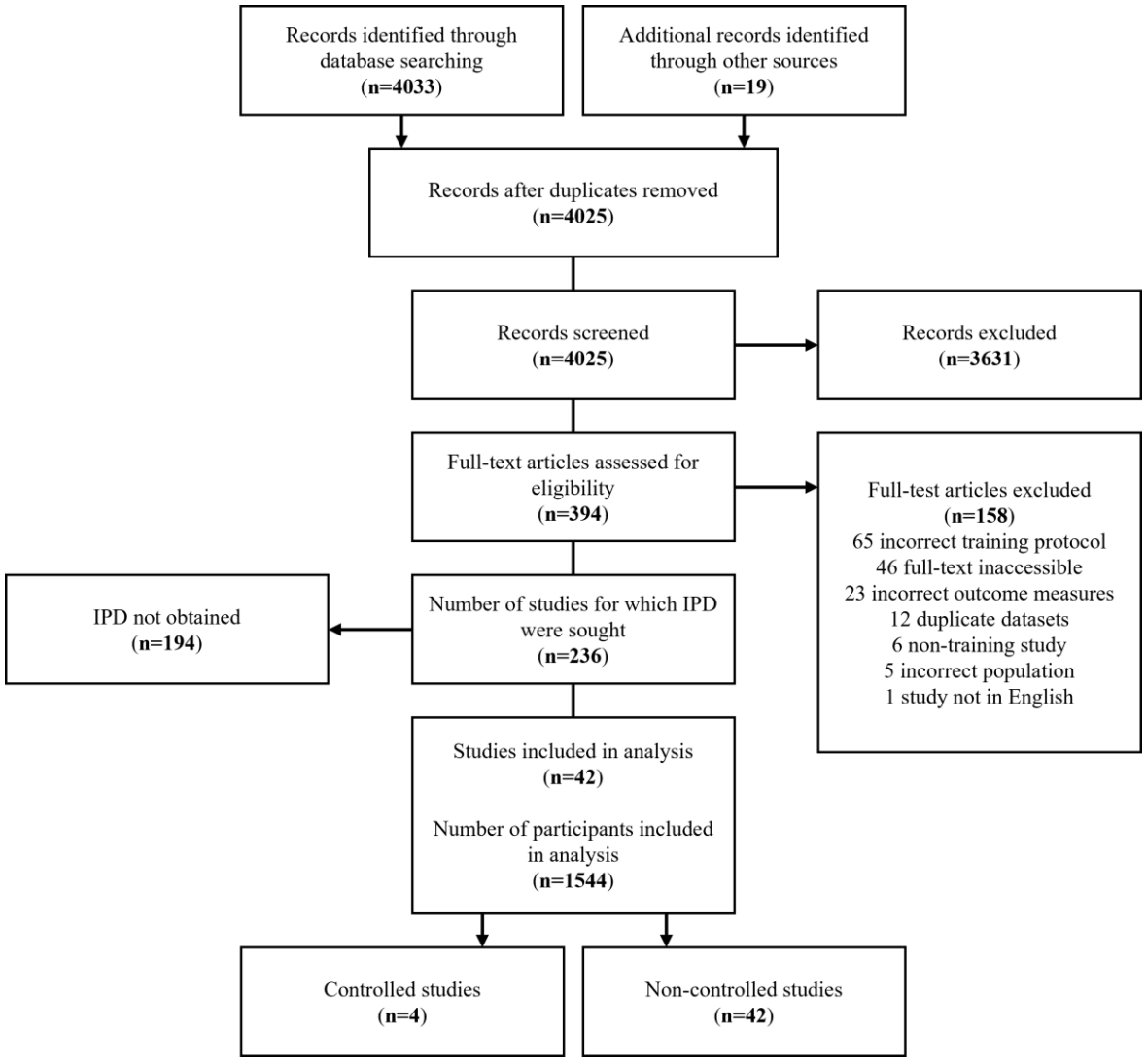

Figure 4.1. Flow diagram of the study identification and screening process.

IPD integrity and risk of bias within studies

There were no issues that needed to be raised following the checking of IPD. Risk of bias assessments for individual studies are included in the supplementary file. There was no need for any weighting adjustments prior to the subsequent analyses. Domain 1: low risk 87%, some

concerns 3%, high risk 10%; Domain 2: low risk 100%; Domain 3: low risk 100%; Domain 4: low risk 100%; Domain 5: low risk 10%, high risk 90%; Overall: low risk 10%, some concerns 80%, high risk 10% (Supplementary file). Of note, IPD from the HERITAGE study (Bouchard et al., 1999) was included in the current analyses. Due to the large amount of HERITAGE IPD analysed (n=562) compared to that of the other eligible studies combined (n=953), the analyses were run with and without its inclusion. There was, however, no difference between the primary results in either case and thus the results are reported including the HERITAGE IPD.

Study characteristics

Individual study characteristics are presented in **Table 4.4** and summary characteristics of THR and TRAD studies are presented in **Table 4.5**.

Table 4.4 Participant characteristics, sample size, training characteristics and $\dot{V}O_{2max}$ change scores for studies included in the present individual participant data meta-analysis.

									$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})							
									Pre		Post		% change		Absolute change (mL·kg^{-1}·min^{-1})	
Study	**Year**	**Participants (age)**	**Sex**	**n**	**Method**	**Type**	**Mode (sessions)**	**Protocol**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Arboleda et al.	(2019)	Sedentary (29±8)	M	18	TRAD	INT	Running (24)	15 x 30 s @ 90-95% HR_{max}	40.1	6.2	43.7	6.2	9.7	9.8	3.6	3.5
				20	TRAD	CT	Running (24)	40 min @ 65-75% HR_{max}	43.5	8.6	44.9	8.7	4.3	15.4	1.4	6.7
Astorino et al.	(2018)	Active (27±8)	M/F	14	THR	INT	Cycling (9)	8-10 x 1 min @ 130% VT	38.8	4.3	41.0	4.6	5.7	3.9	2.2	1.6
Astorino et al.	(2013)	Sedentary (24±7)	F	4	TRAD	INT	Cycling (33)	6-10 x 1 min @ 80-90% W_{max}	31.7	4.4	36.4	4.2	15.4	9.1	4.7	2.5
				8	TRAD	INT	Cycling (33)	6-10 x 1 min @ 60-80% W_{max}	30.6	4.2	37.1	3.4	22.1	8.1	6.5	1.6
Berger et al.	(2006)	Active (23±4)	M	8	TRAD	CT	Cycling (18-24)	30 min @ 60% VO_{2max}	33.7	3.8	39.8	6.0	18.0	7.7	6.1	3.0
				8	TRAD	INT	Cycling (18-24)	20 x 1 min @ 90% VO_{2max}	34.6	6.8	43.0	8.3	24.3	5.1	8.4	2.1
Bonafiglia et al.	(2016)	Active (20±1)	M/F	21	TRAD	CT	Cycling (12)	30 min @ 65% VO_{2max}	42.2	6.5	43.9	6.5	4.4	7.9	1.7	3.2
Bouchard et al.	(1999)	Sedentary (35±14)	M/F	562	TRAD	CT	Cycling (60)	30-50 min @ 55-75% VO_{2max}	33.1	8.6	38.7	9.1	18.0	9.9	5.6	2.9
Branch et al.	(1997), (1999)	Sedentary (32±5)	F	8	TRAD	CT	Running (40)	150-375 kcal/session @ 80% HR_{max}	36.2	4.9	38.8	7.5	6.8	8.8	2.6	3.8
				10	TRAD	CT	Cycling (40)	150-375 kcal/session @ 80% HR_{max}	29.2	7.9	35.5	7.0	24.6	13.7	6.3	2.6
				8	TRAD	CT	Cycling (40)	150-375 kcal/session @ 40% HR_{max}	29.8	4.6	34.1	6.6	16.5	25.3	4.3	7.9
Byrd et al.	(2019)	Sedentary (32±9)	M/F	11	THR	INT + CT	Cycling + Running (30)	CT: 30-50 min @ <VT1 to >VT2; INT: 8-12 x 60 s @ 100% $\dot{V}O_{2max}$	33.6	4.0	38.4	4.4	14.3	3.6	4.8	1.1
				11	TRAD	INT + CT	Cycling + Running (30)	CT: 30-50 min @ 40-65% HRR	30.4	6.2	33.0	7.2	8.1	3.3	2.5	1.2
Casaburi et al.	(1987)	Sedentary (23±1)	M/F	9	THR	CT	Cycling (40)	45 min @ 50-75% Δ	34.5	4.1	40.3	4.1	17.3	8.0	5.8	2.5
Dalleck et al.	(2008)	Sedentary (37±6)	F	13	TRAD	CT	Walking (30-40)	(~180 min) 250-1000 kcal/wk @ 50% $\dot{V}O_2R$	35.5	5.9	37.9	4.5	7.8	8.0	2.5	2.3
Dalleck et al.	(2016)	Sedentary (68±8)	M/F	10	THR	CT	Aerobic exercise (21)	25-50 min @ <VT1 to >VT2	25.9	3.8	29.7	4.9	14.7	7.8	3.8	2.2
				9	TRAD	CT	Aerobic exercise (21)	25-50 min @ 40-65% HRR	24.1	12.3	26.3	11.9	11.4	9.5	2.2	1.5
Daussin et al.	(2008)	Sedentary (46±8)	M/F	13	THR	CT	Cycling (24)	20-35 min rep 5 min (4 min @ LT, 1 min @ 90% P_{max})	29.1	5.9	31.9	6.4	9.8	8.7	2.8	2.5

									$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})							
									Pre		Post		% change		Absolute change (mL·kg^{-1}·min^{-1})	
Study	**Year**	**Participants (age)**	**Sex**	**n**	**Method**	**Type**	**Mode (sessions)**	**Protocol**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
				13	THR	INT	Cycling (24)	Work matched with INT	27.5	5.3	32.3	6.5	18.5	16.7	4.8	4.9
Fiorenza et al.	(2019)	Sedentary (57±8)	M	12	TRAD	INT	Cycling (18)	10-15 min of '10-20-30 training', 3 min rec between 5 min bouts @30%, 50%, 100% max intensity	36.6	8.4	39.4	4.8	7.8	7.8	2.8	2.7
Ghiarone et al.	(2019)	Active (26±5)	M	8	THR	INT + CT	Cycling (18)	Train twice daily (3d/wk) CT: 5 min @ LT1 plus 100 min @ 50% Δ (LT1 and LT2), INT: 10 x 2 min @ 20% Δ (LT2 and PPO)	36.0	4.3	39.3	5.4	9.0	7.0	3.3	2.5
				7	THR	INT + CT	Cycling (18)	Train once daily (6d/wk) CT: CT: 5 min @ LT1 plus 100 min @ 50% Δ (LT1 and LT2), INT: 10 x 2 min @ 20% Δ (LT2 and PPO)	37.9	7.9	40.2	6.6	8.6	21.9	2.3	5.8
Gormley et al.	(2008)	Active (22±3)	M/F	14	TRAD	CT	Cycling (22)	30-40 min @ 50-75% HRR	34.5	8.6	39.1	9.0	13.9	10.3	4.6	3.3
				12	TRAD	INT	Cycling (18)	Wk 1 and 2: 30-40 min @ 50-75% HRR, Wk 3-6: 5 x 5 min @ 95% HRR	36.5	5.8	43.0	7.6	17.7	10.2	6.5	3.8
				14	TRAD	CT	Cycling (23)	30-60 min @ 50% HRR	35.5	7.9	38.8	9.1	10.0	10.9	3.4	4.0
Granata et al.	(2016)	Active (21±2)	M	10	THR	INT	Cycling (52)	4-7 x 4 min @ 35-75% Δ (LT and WR_{peak}); 5-12 x 4 min @ 30-80% Δ; 8-20 x 2 min @ 50-80% Δ	45.1	7.6	52.2	7.8	16.2	6.6	7.1	2.8
Hov et al.	(2023)	Healthy (23±2)	M	10	TRAD	INT	Running (24)	4 x 4 min @ 90-95% HR_{max}	62.1	4.8	66.0	5.0	6.3	2.4	3.9	1.5
Jacques et al.	(2021)	Moderately trained (35±10)	M	15	THR	INT	Cycling (24)	6-14 x 2 min @ 40-70% Δ	52.3	9.8	56.5	10.0	8.8	12.6	4.2	6.2
Landen et al.	(2021)	Moderately trained (35±7)	F	18	THR	INT	Cycling (12)	6-14 x 2 min @ 40-70% Δ	44.5	9.0	45.9	8.1	3.9	5.2	1.5	2.1
Litleskare et al.	(2020)	Active (25±4)	M/F	12	TRAD	CT	Running (24)	30-60 min @ 70-80% HR_{peak}	47.9	5.9	49.7	6.2	3.9	5.6	1.8	2.6
Maturana et al.	(2021)	Sedentary (27±6)	M/F	21	THR	CT	Cycling (18)	60 min @ LTP1	30.4	4.3	32.7	4.2	7.9	8.6	2.3	2.6
				21	TRAD	INT	Cycling (18)	4 x 4 min @ 90% HR_{max}	31.9	4.1	37.2	4.1	17.0	7.9	5.3	2.1
Maunder et al.	(2021)	Active (32±7)	M	8	THR	INT + CT	Cycling (15)	4-6 x 8 min @ VT2; 90 min @ 95% VT1; 3 x 25 min @ 50% Δ (VT1 and VT2); 6-10 x 3 min	52.5	6.4	53.4	6.9	1.7	3.5	0.9	1.8

									$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})							
									Pre		Post		% change		Absolute change (mL·kg^{-1}·min^{-1})	
Study	**Year**	**Participants (age)**	**Sex**	**n**	**Method**	**Type**	**Mode (sessions)**	**Protocol**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
McNicol et al.	(2009)	Active (21±5)	M/F	14	THR	CT	Running (18)	20 min @ 0.8 km/h less than LTv + 0.1 km/h per session	44.0	5.5	47.6	6.5	8.7	12.2	3.6	5.1
				13	THR	CT	Running (18)	20 min @ 0.8 km/h less than LTv	44.0	6.9	45.3	7.0	3.0	2.4	1.3	1.0
Mendes et al.	(2013)	Untrained (23±2)	M	13	THR	CT	Cycling (18)	24-39 min @ MLSS	44.9	4.8	49.8	4.5	11.2	7.2	4.9	3.1
Myrkos et al.	(2023)	Young adults (21±3)	M/F	13	TRAD	INT	Running (14)	Running bouts @ 90% PTV	57.7	8.0	61.4	9.23.0	6.5	5.7	3.8	3.4
				11	THR	CT	Running (14)	-2.5% of CV	58.2	7.5	61.1	6.4	5.6	6.7	3.0	3.7
Nicolini et al.	(2019)	Sedentary (23±4)	M	15	TRAD	INT	Cycling (18)	5 x 1 min @ 105-135% WR_{peak}	35.5	4.8	40.0	5.1	12.9	7.0	4.5	2.2
Nio et al.	(2020)	Untrained (52±4)	F	25	TRAD	INT	Cycling (36)	4 x 4 min @ 90-95% HR_{max}	29.4	5.3	35.4	5.4	21.6	11.4	6.1	2.9
O'Leary et al.	(2017)	Untrained (26±5)	M/F	10	THR	CT	Cycling (18)	90% LT matched to work (KJ) done in INT	43.5	5.9	47.4	8.0	8.6	8.4	3.9	3.8
				8	THR	INT	Cycling (18)	6-8 x 5 min @ 50% Δ	44.8	4.2	48.8	5.4	8.8	7.3	4.0	3.1
Pothier et al.	(2021)	Untrained (69±5)	M/F	21	TRAD	INT + CT	Cycling (36)	INT: 20 x 15s @ 100-110% MAP, CT: 20 min @ 65-75% MAP	22.2	6.2	24.3	7.0	10.4	16.6	2.1	3.4
Preobrazenski et al.	(2019)	Active (21±2)	M	14	TRAD	CT	Cycling (15)	30 min @ 65% WR_{peak}	46.0	6.7	49.7	5.2	8.7	7.3	3.7	3.1
				14	THR	CT	Cycling (15)	30 min @ 'NEG' talk-test stage	45.8	5.9	51.2	6.1	12.2	7.1	5.4	3.0
Reuter et al.	(2023)	Untrained (46±8)	M/F	16	TRAD	CT	Running/walking (78)	50 min @ 55% HRR	34.5	3.8	35.3	4.0	2.6	9.1	0.8	3.1
				15	TRAD	CT + INT	Running/walking (78)	CT: 50 min @ 55% HRR, INT: 4 x 4 min @ 95% HR_{max}	33.9	5.3	37.3	4.9	10.7	8.0	3.4	2.7
Schaun et al.	(2018)	Healthy (23±4)	M	14	TRAD	INT	Running (48)	8 x 20 s @ 130% v$\dot{V}O_{2max}$	46.8	7.1	57.7	6.7	24.9	15.6	11.0	6.2
				14	THR	CT	Running (48)	30 min @ 90-95% HR at VT2	47.9	7.5	56.6	7.9	19.6	15.6	8.8	6.0
Schubert et al.	(2017)	Active (30±9)	M/F	11	TRAD	INT	Cycling (12)	6-8 x 90% PPO	31.4	9.7	33.1	9.8	6.1	5.2	1.8	1.7
Scharhag-Rosenberger et al.	(2012)	Untrained (41±6)	M/F	20	TRAD	CT	Running/walking (150)	45 min @ 60% HRR	37.8	5.3	43.1	7.1	14.2	11.7	5.3	4.2
Stensvold et al.	(2015)	Older adults (72±2)	M/F	77	TRAD	CT	Aerobic exercise (156)	50 min @ 70% HR_{peak}	31.1	5.9	32.6	6.1	5.5	10.7	1.5	3.4
			M/F	49	TRAD	INT	Aerobic exercise (156)	repetitions of 4 min intervals with 3 min recovery periods 85-95% HR_{peak}	31.8	6.9	35.7	6.7	13.7	14.6	3.9	4.3
Tarumi et al.	(2022)	Older adults (70±6)	M/F	28	TRAD	CT	Running/walking (125)	CT: 25-40 min @ 75-85% and 85-90% HR_{max}	22.5	4.0	25.1	4.1	15.0	28.4	2.6	5.5

									$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})							
									Pre		Post		% change		Absolute change (mL·kg^{-1}·min^{-1})	
Study	**Year**	**Participants (age)**	**Sex**	**n**	**Method**	**Type**	**Mode (sessions)**	**Protocol**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Tjønna et al.	(2013)	Inactive (42±3)	M	10	TRAD	INT	Running/walking (30)	1 x 4 min @ 90% HR_{max}	39.2	5.3	44.1	5.6	12.9	7.7	4.9	2.7
				12	TRAD	INT	Running/walking (30)	4 x 4 min @ 90% HR_{max}	44.8	5.3	51.0	4.6	14.4	8.9	6.2	3.6
Vanhatalo et al.	(2008)	Habitually active (29±6)	M/F	9	THR	INT	Cycling (12)	2 x p/wk 6 x 5 min at 105% EP + 1 x p/wk 10 x 2 min @ 50% WEP expenditure during the first 2 min period	50.7	5.4	56.0	6.0	10.5	5.3	5.3	2.7
Vollaard et al.	(2009)	Healthy (24±2)	M	23	TRAD	CT	Cycling (24)	45 min @70% $\dot{V}O_{2max}$	49.2	5.2	55.6	7.1	13.1	10.8	6.4	4.9
Weatherwax et al.	(2019)	Sedentary (46±11)	M/F	16	THR	CT	Aerobic exercise (33)	Energy Expenditure of 5.6-15.4 kcal/kg/wk @ HR <VT1 to >VT2	30.5	6.6	34.0	7.7	11.4	3.9	3.5	1.5
				13	TRAD	CT	Aerobic exercise (33)	Energy Expenditure of 5.6-15.4 kcal/kg/wk @ 40-65% HRR	25.2	4.7	26.5	4.2	6.1	7.7	1.4	1.9
Wolpern et al.	(2015)	Sedentary (33±10)	M/F	9	THR	CT	Running (31)	20-30 min @ HR <VT1 to >VT2	35.4	8.8	39.5	8.8	12.2	5.2	4.1	0.9
				11	TRAD	CT	Running (31)	20-30 min @ 40-65% HRR	35.1	5.5	36.4	5.7	4.0	5.4	1.4	1.8
Yan et al.	(2017)	Moderately trained (32±8)	M	66	THR	INT	Cycling (12)	6-14 x 2 min @ 40-70% Δ	49.2	8.0	50.5	7.7	3.2	9.4	1.3	4.3

THR: exercise prescribed relative to physiological thresholds, TRAD: exercise prescribed relative to a traditional intensity anchor, CT: continuous exercise, INT: interval exercise, HR_{max}: maximum heart rate, HR_{peak}: peak heart rate, HRR: heart rate reserve, $\dot{V}O_{2max}$: maximum oxygen uptake, $\dot{V}O_2R$: oxygen uptake reserve, VT: ventilatory threshold, WEP: work above end power during a 3 min all out test, PPO: peak power output, v$\dot{V}O_{2max}$: velocity at $\dot{V}O_{2max}$, WR_{peak}: peak work rate, MAP: maximum aerobic power, LT: lactate threshold, Δ: delta method, MLSS: maximum lactate steady state, LTv: velocity at LT, CV: critical velocity, PTV: peak treadmill velocity, LTP: lactate turn point, Pmax: maximum power, M: males, F: females.

Table 4.5. Summary characteristics of controlled and non-controlled THR and TRAD studies included in the present individual participant data meta-analysis.

	Study group		
Controlled Studies	**THR**	**TRAD**	**CON**
Studies (n)	4	4	4
Individuals (n)	46	44	49
Sex (M, F)	18, 28	16, 28	20, 29
Age (y)	43±17	46±17	44±14
Body mass (kg)	72±11	73±11	75±10
Baseline $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	31±7	29±5	29±6
Training duration (wks.)	13±1	13±1	
Training sessions (n)	29±5	29±5	
Continuous exercise	3	3	
Interval exercise	0	0	
Combination	1	1	
Non-controlled Studies	**THR**	**TRAD**	
Studies (n)	18	25	
Individuals (n)	354	1190	
Sex (M, F)	239, 115	565, 622	
Age (y)	31±12	38±18	
Body mass (kg)	75±13	71±13	
Baseline $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	42±10	34±9	
Training duration (wks.)	7±4	14±14	
Training sessions (n)	23±11	43±39	
Continuous exercise	13	19	
Interval exercise	8	16	
Combination	4	4	

$\dot{V}O_{2max}$: maximum oxygen uptake. Data are presented as means or mean ± standard deviation.

Result of syntheses

Changes in maximum oxygen uptake

Controlled studies

'Extreme' evidence (BF>100) was identified in support of a greater improvement in $\dot{V}O_{2max}$ for THR (4.1 [95%CrI: 3.1 to 5.0 $mL \cdot kg^{-1} \cdot min^{-1}$]) compared to TRAD (1.8 [95%CrI: 0.9 to 2.8 $mL \cdot kg^{-1} \cdot min^{-1}$]; **Figure 4.2**). Individuals were estimated to be approximately four times more likely to experience an increase in $\dot{V}O_{2max}$ greater than the MID in THR (64%) compared to TRAD (16%). There was 'anecdotal' evidence (BF=0.55) in support of no difference in variation of $\dot{V}O_{2max}$ change scores between THR (1.5 [75%CrI: 1.2 to 1.8 $mL \cdot kg^{-1} \cdot min^{-1}$]) and TRAD (1.7 [75%CrI: 1.4 to 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$]; **Figure 4.2**). When THR and TRAD were combined, 'strong' evidence (BF=12.4) was identified in support of a greater variation in $\dot{V}O_{2max}$ change scores in the training groups (1.9 [75%CrI: 1.7 to 2.2] $mL \cdot kg^{-1} \cdot min^{-1}$]) compared to CON (1.3 [75%CrI: 1.1 to 1.6] $mL \cdot kg^{-1} \cdot min^{-1}$]; **Figure 4.3**).

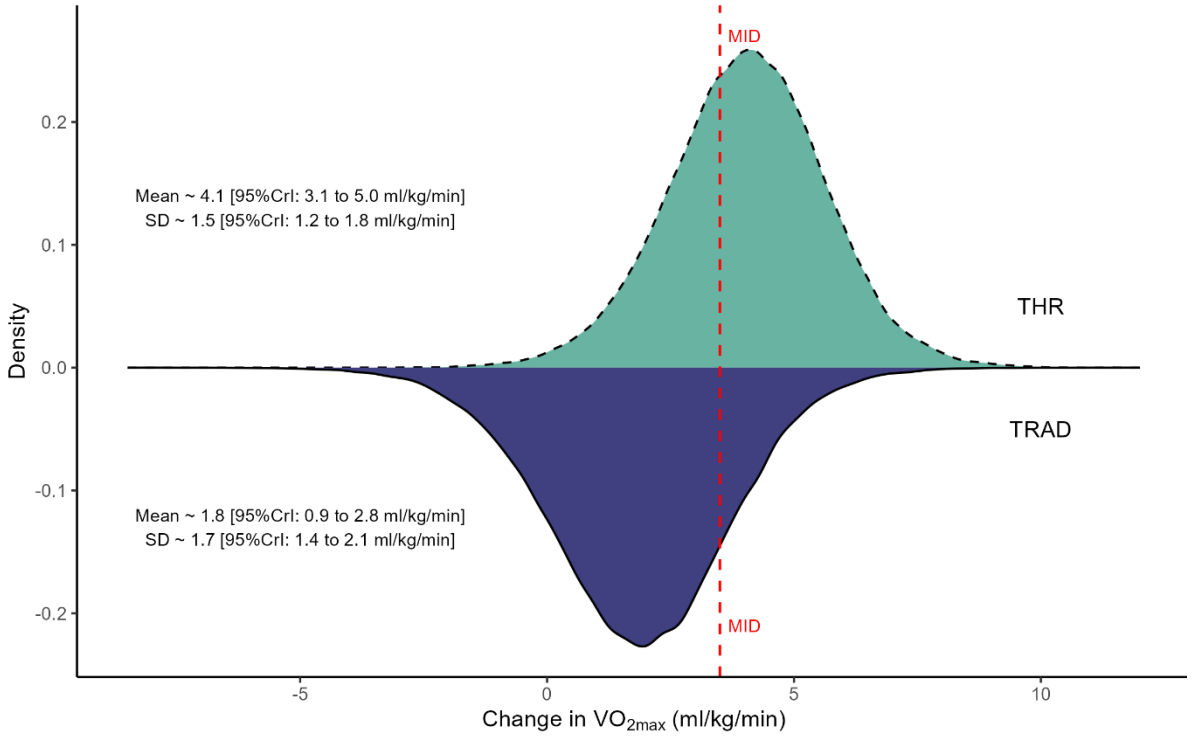

Figure 4.2. Modelled changes in $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) from controlled studies comparing exercise prescription using traditional intensity anchors or physiological thresholds. MID: minimum important difference, THR: exercise training prescribed relative to physiological thresholds, TRAD: exercise training prescribed relative to traditional intensity anchors, SD: standard deviation; CrI: credible interval.

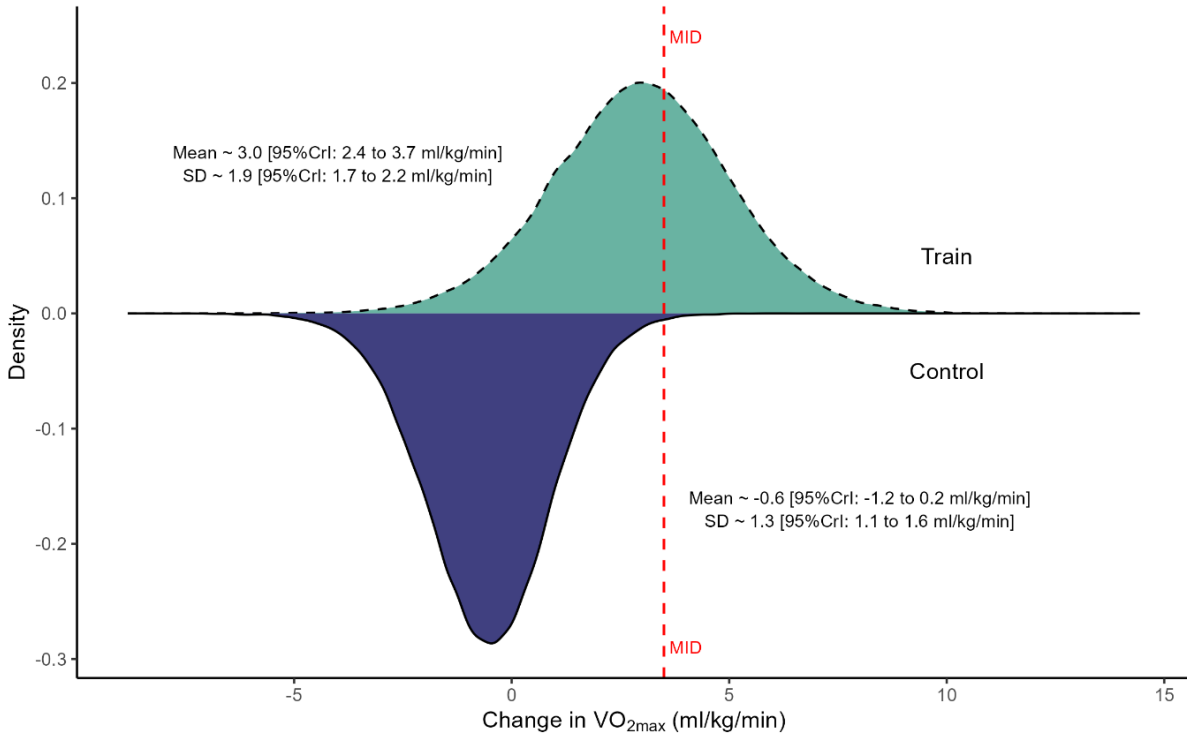

Figure 4.3. Modelled changes in $\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1}) from controlled studies comparing pooled data from all training groups and control. MID: minimum important difference Train: comprises data from groups where exercise training is prescribed using either traditional intensity anchors or relative to physiological thresholds, SD: standard deviation; CrI: credible interval.

Non-controlled studies

In general, similar findings to those obtained for controlled studies were observed in non-controlled studies. 'Very strong' evidence (BF=35.1) was identified in support of a greater improvement in $\dot{V}O_{2max}$ for THR (4.4 [95%CrI: 3.7 to 5.2 mL·kg^{-1}·min^{-1}] compared to TRAD (3.4 [95%CrI: 2.8 to 4.1 mL·kg^{-1}·min^{-1}]; **Figure 4.4**). Predictions using the fitted model estimated 60% of individuals in THR should be expected to increase $\dot{V}O_{2max}$ beyond the MID, with 47% expected in TRAD. 'Anecdotal' evidence (BF=0.41) was identified in support of no difference in variation of $\dot{V}O_{2max}$ change scores between THR (3.0 [75%CrI: 2.7 to 3.3 mL·kg^{-1}·min^{-1}]) and TRAD (3.2 [75%CrI: 2.9 to 3.5 mL·kg^{-1}·min^{-1}]; **Figure 4.4**).

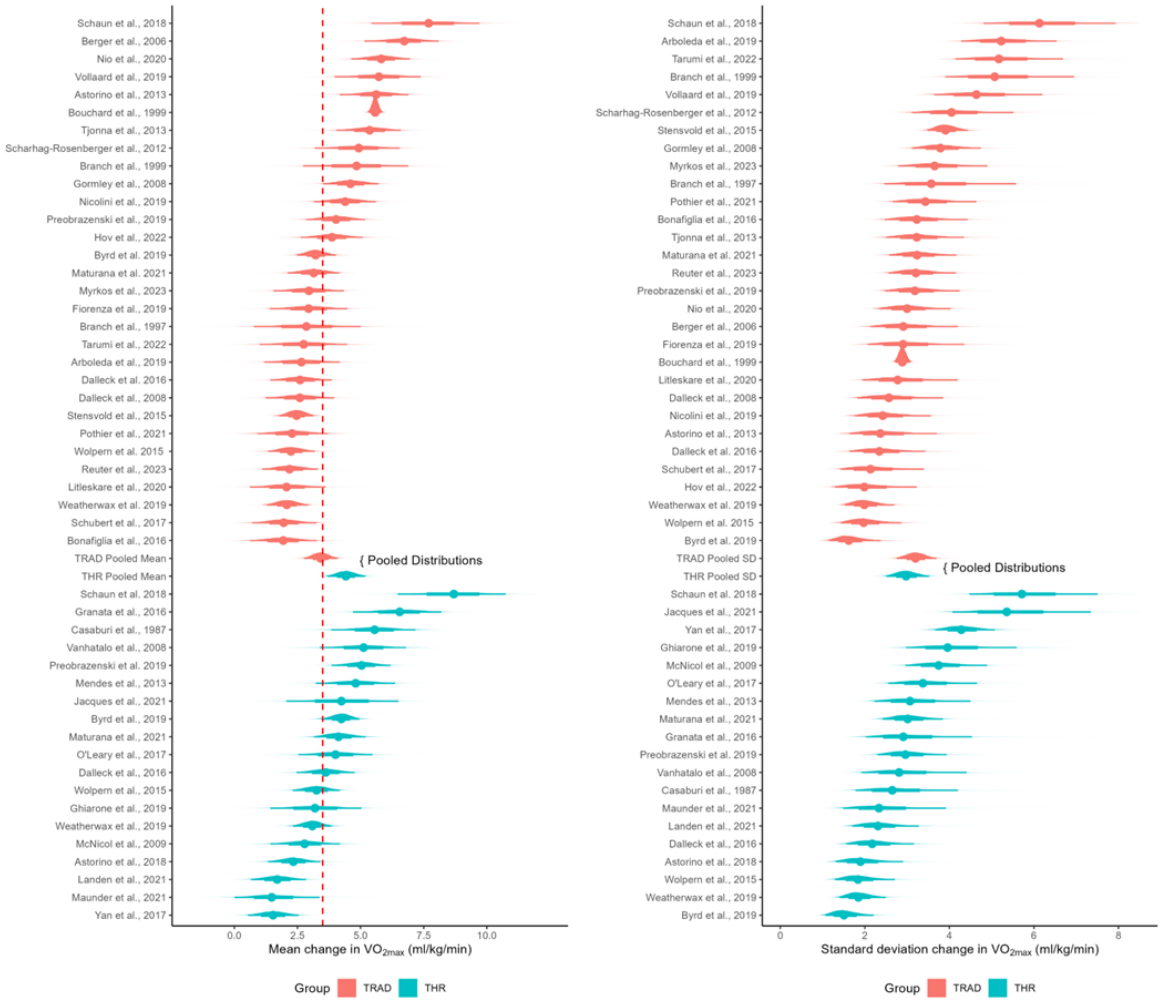

Figure 4.4. Forest plot of modelled mean (left) and standard deviation (right) change in $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) across non-controlled studies comprising exercise prescription using either traditional intensity anchors or physiological thresholds. Distributions represent "shrunken estimates" based on all relevant effect sizes, the random effects model fitted, and borrowing of information across studies to reduce uncertainty. Circles and connected intervals represent the median value and 95% credible intervals for the shrunken estimates. Pooled estimates across conditions are presented in the centre of the plot. Red line illustrates the minimum important difference threshold. THR: exercise training prescribed relative to physiological thresholds, TRAD: exercise training prescribed relative to traditional intensity anchors.

DISCUSSION

This is the first IPD meta-analysis to explore the magnitude and variation in $\dot{V}O_{2max}$ change scores elicited by training programmes using THR and TRAD approaches. The main findings were: 1) prescribing exercise intensity using THR approaches elicited superior mean changes in $\dot{V}O_{2max}$ and increased the likelihood of an individual increasing $\dot{V}O_{2max}$ beyond the MID; and 2) there appeared to be no difference in response variability between THR and TRAD.

Mean changes in $\dot{V}O_{2max}$

Superior increases in $\dot{V}O_{2max}$ were observed in THR compared to TRAD in both the controlled and non-controlled analyses. In the controlled studies, it was estimated that individuals were approximately four times as likely to experience an increase in $\dot{V}O_{2max}$ beyond the MID. This estimate was based on the statistical model indicating 64% of participants undergoing THR would experience an increase of ≥3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ compared with 16% of participants undergoing TRAD. In the non-controlled studies, greater variability was observed across the larger data set, however, it was estimated that on average, 60% and 47% of individuals would experience changes beyond the MID in THR and TRAD, respectively.

Regarding the notion of increasing 'response rates', herein defined as the proportion of individuals improving a given parameter beyond a predefined threshold, the present findings agree with previous literature whereby increased $\dot{V}O_{2max}$ response rates are typically explained by greater mean change scores as opposed to reductions in inter-individual variability (Bonafiglia et al., 2021). In turn, using THR approaches represents a viable approach in increasing response rates, and thus, increasing the likelihood of individuals attaining the health- and performance-related benefits of exercise training. Importantly, instead of requiring increases in training dose following TRAD (i.e., by increasing training intensity, frequency, and/or duration), using THR approaches appears to be an effective method to increase the proportion of individuals attaining increases in $\dot{V}O_{2max}$ beyond a predefined threshold in response to the initial exercise stimulus.

Variability in $\dot{V}O_{2max}$ change scores

An interesting finding of the current analysis was that greater variability in $\dot{V}O_{2max}$ change scores were observed in exercising groups compared with the non-exercising control group (**Figure 4.3**). Whilst the magnitude of this evidence was small, this provides evidence of inter-individual differences in $\dot{V}O_{2max}$ trainability (Bacon et al., 2013; Bouchard et al., 2011; Skinner et al., 2001; Williams et al., 2019). This warrants further investigation as currently, differences in inter-individual variability are often found to be attributable to measurement error and biological variability as opposed to differences in trainability (Atkinson & Batterham, 2015; Bonafiglia et al., 2022; Islam & Gurd, 2020).

However, contrary to our hypothesis, weak evidence was obtained in support of no difference in the variability of $\dot{V}O_{2max}$ change scores between THR and TRAD in both analyses. It has been shown that using THR approaches better normalises exercise intensity among individuals compared to when using TRAD anchors, reducing the variability in exercise tolerance and eliciting more homogenous acute physiological responses (Baldwin et al., 2000; Lansley et al., 2011; McLellan & Skinner, 1981). Based on the acute data presented in these studies, it was hypothesised that repeated performance of THR would manifest in a more consistent chronic stimulus across participants, resulting in reduced variation in change scores. Previous studies have reported increased $\dot{V}O_{2max}$ response rates following exercise training prescribed using THR compared to TRAD (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015), however, in such studies it was unclear whether the increased response rates were the product of a reduction in response variability or simply increased group mean changes in $\dot{V}O_{2max}$, or both. Based on the present findings and a lack of evidence supporting a difference in the variability in $\dot{V}O_{2max}$ change scores following THR, it appears that increased response rates are primarily explained by greater mean $\dot{V}O_{2max}$ change scores.

Typically, THR studies implemented continuous training (Casaburi et al., 1987; Dalleck et al., 2016; Maturana et al., 2021; McNicol et al., 2009; Mendes et al., 2013; Myrkos et al., 2023;

O'Leary et al., 2017; Preobrazenski et al., 2019; Schaun et al., 2018; Weatherwax et al., 2019; Wolpern et al., 2015). It is plausible that the prescribed intensities were low enough such that acute metabolic responses to THR and TRAD exercise were not markedly different, despite what may have been large differences in external work rate among individuals. Notably, when intensities approach or exceed the boundary between the heavy- and severe-intensity domain, marked differences in exercise durations and responses can be observed despite only minimal differences in external work rate (R. de Almeida. Azevedo et al., 2021; Jones et al., 2019; Nixon et al., 2021). Using physiological thresholds to prescribe and control exercise around this transition may be where such approaches hold their value. Furthermore, the activation of signalling pathways associated with key physiological changes promoting increases in $\dot{V}O_{2max}$ (e.g., mitochondrial biogenesis) are shown to increase at intensities within the severe intensity domain compared to the moderate and heavy intensity domains (Jamnick, 2019). Thus, having the ability to prescribe exercise accurately both above and below the boundary between the heavy and severe intensity domain, as is shown when using THR approached, might have beneficial implications on the manifestation of subsequent adaptation.

Various approaches are used to determine and apply physiological thresholds for training purposes (Jamnick et al., 2020; Poole et al., 2020). Whilst they all aim to approximate the transition between the moderate and heavy intensity domain or the heavy and severe intensity domain, they are not identical (Caen et al., 2018). Critical power is often considered the most accurate representation of the latter boundary (Jones et al., 2019) and as aforementioned is shown to better control exercise intensity than when using TRAD approaches. This is likely explained by the fact that using TRAD approaches do not account for the relative positioning of an individual's critical power relative to a maximum physiological value, such as $\dot{V}O_{2max}$ or HR_{max}. Using critical power as a tool for exercise prescription, however, appears to be limited in exercise-related research with only one study in the present dataset (Vanhatalo et al., 2008) using the concept for training purposes. An advantage of using critical power is that a given work rate can be used to define the exercise session(s), negating the need to adjust exercise

intensity to match a given heart rate or $\dot{V}O_2$ response. In the HERITAGE study, the fluctuation in the training work rate was the third most impactful factor (6%) on $\dot{V}O_{2max}$ response variability, despite overall adherence being greater than 95% (Sarzynski et al., 2017). It would thus be interesting to investigate whether a reduction in response variability is observed to a higher degree were critical power used as an intensity anchor, particularly when comparing studies prescribing heavy- and/or severe-intensity exercise using a traditional intensity anchor, as this is where we may expect to see a more profound difference in response variability.

It is worth noting that the relative intensity of exercise is consistently shown to influence the magnitude of training-induced adaptations (Collins et al., 2022; Daussin et al., 2008; Gormley et al., 2008; Inglis et al., 2024; MacInnis et al., 2017; McNicol et al., 2009; Milanović et al., 2015) and that similar adaptations can be observed following a small volume of exercise performed at very high intensities and a large volume of exercise performed at lower intensities (Burgomaster et al., 2008; Gibala et al., 2006; Gillen & Gibala, 2014; Scribbans et al., 2014; Shepherd et al., 2013). In a recent study by Inglis et al. (Inglis et al., 2024), eighty-four healthy participants performed moderate, heavy, severe, or extreme intensity exercise training where exercise intensity was prescribed using a 'domain-based' approach (i.e., THR) using the LT and the maximum metabolic steady state (based on blood lactate and $\dot{V}O_2$ responses) to determine the boundaries between the moderate-heavy and heavy-severe intensity domains, respectively. Interestingly, all exercise groups bar the moderate intensity exercise group increased $\dot{V}O_{2max}$, the power output at the LT, and the power output at the maximum metabolic steady state. Such results further support the notion that that exercise intensity is a key determinant of training-induced changes in training-induced adaptations. All in all, exercise intensity demonstrates a clear influence on the magnitude of subsequent changes in markers such as $\dot{V}O_{2max}$.

Such findings incite the argument that the method used to prescribe exercise intensity is in fact irrelevant, and that irrespective of whether a THR or TRAD approach is used, whichever approach elicits the highest relative exercise intensity will likely induce the largest increases

in $\dot{V}O_{2max}$ thereafter. On this, it is important to consider the findings of Collins et al. (Collins et al., 2022) who conducted a training intervention comprised of CT prescribed at 44% of the maximum power output achieved in a GXT (P_{GXT}) and INT prescribed at 80% P_{GXT}. Of note, there were instances where exercise intensity, when expressed relative to critical power, was higher in the CT group compared to the INT group, and as a result, these individuals experienced superior changes in critical power post-training. At first glance, this contradicts the argument that high intensity INT is superior to lower intensity CT (Collins et al., 2022; Daussin et al., 2008; Gormley et al., 2008; Inglis et al., 2024; MacInnis et al., 2017; McNicol et al., 2009; Milanović et al., 2015); however, it instead admirably supports the notion that when prescribing exercise intensity, whether that be for CT or INT, anchoring intensity relative to a maximum physiological value such as $\dot{V}O_{2max}$ is not appropriate (Hofmann & Tschakert, 2011; Mann et al., 2013; Scharhag-Rosenberger et al., 2010). Overall, the authors concluded that the higher the training intensity is when expressed relative to critical power, instead of relative to $\dot{V}O_{2max}$, the greater the training-induced changes thereafter (Collins et al., 2022). Therefore, whilst the argument may be presented that the method used to prescribe exercise intensity is inconsequential so long as high intensity exercise is prescribed, a THR based approach should be used to ensure that exercise intensity is in fact 'high' for a given individual based on their unique intensity domains and not just *intended* to be 'high' based on a generalised approach to exercise intensity prescription. Additionally, in the instance that an individual has not achieved a change in $\dot{V}O_{2max}$, for example, above a given 'response' threshold, the possibility exists that the intensity elicited when using a TRAD based approach was simply too low when expressed relative to critical power (Collins et al., 2022; Lundby et al., 2017). Using critical power, or an alternative threshold, would negate this issue of heterogeneity in the prescribed exercise intensity; however, further studies utilising critical power as an intensity anchor are warranted to confirm this notion (Collins et al., 2022).

Limitations

A limitation of the present study was the limited amount of IPD obtained from those meeting the inclusion criteria. Whilst 236 studies met the predefined criteria (**Figure 4.1**), the response rate of IPD obtained was 18% (N=42). Additionally, THR IPD (n=354) was limited compared to that of TRAD IPD (n=1190). Exercise training programmes are still routinely prescribed at intensities anchored relative to traditional parameters (i.e., $\dot{V}O_{2max}$ and HR_{max}) (Bacon et al., 2013; Milanović et al., 2015; Scribbans et al., 2016; Wen et al., 2019; Williams et al., 2019). Understandably, using HR-based parameters can negate the need for laboratory or field testing, making this an attractive approach, albeit not the most accurate. However, the continued use of $\dot{V}O_{2max}$ as an intensity anchor is surprising given its known inaccuracy in controlling exercise intensity among individuals (Anselmi et al., 2021; Iannetta et al., 2020; Lansley et al., 2011; McLellan & Skinner, 1981; Scharhag-Rosenberger et al., 2010). Moreover, if measuring $\dot{V}O_{2max}$, data used to determine given physiological thresholds (e.g., gas exchange threshold) is readily available. Alternatively, self-assessed threshold tools such as rating of perceived exertion (RPE) can be used as surrogates for physiological thresholds and provide an easily accessible means of prescribing and controlling exercise intensity based off a threshold-based approach (Bok et al., 2022; Eston et al., 1987; Lehtonen et al., 2022). For example, using the 6-20 Borg scale, moderate, heavy, and severe intensity exercise can be prescribed at approximately ≤13, 14-16, and ≥17, respectively (Lehtonen et al., 2022). Lehtonen et al. (Lehtonen et al., 2022) also note that pairing RPE with external work (e.g., running pace or power output) and internal physiological response (e.g., heart rate) would add a further element of sophistication to the prescription and monitoring of exercise training. There is also evidence demonstrating that critical power and the running equivalent critical speed, can be derived from habitual training data and/or a series of time trials (B. Hunter et al., 2023; Karsten et al., 2013; Smyth & Muniz-Pumares, 2020). This allows for a more accessible means of critical speed and/or critical power determination, negating the need for laboratory-based testing (B. Hunter et al., 2023). The results presented herein will hopefully

encourage greater consideration of using THR approaches, where possible, when designing future exercise research studies.

Compared to the controlled dataset, the non-controlled dataset contained IPD from studies with marked differences in study characteristics. For example, studies adopted various training doses, populations, modes of exercise and training types (**Table 4.4** and **Table 4.5**). Effects of these differences were easily observed when comparing the range in mean $\dot{V}O_{2max}$ improvements estimated across the different studies (Figure 4). Despite differences in study characteristics, overall findings from both analyses were consistent. If enough data were available, stricter eligibility criteria could have been used such that a more homogenous dataset could have been analysed. This would have allowed a more robust comparison between THR and TRAD studies regarding the magnitude and variability in $\dot{V}O_{2max}$ change scores, as was done in the controlled study analysis. However, more THR studies are needed for this to occur. Additionally, information regarding adherence to training at the individual level in each independent study was not sought. Thus, conclusions concerning the impact of training adherence on subsequent $\dot{V}O_{2max}$ change scores cannot be elucidated.

CONCLUSION

The current IPD meta-analysis found no difference in $\dot{V}O_{2max}$ response variability between training programmes utilising THR and TRAD approaches. However, using THR approaches appears to be a more effective means of increasing the likelihood of an individual attaining meaningful increases in $\dot{V}O_{2max}$, and thus, increased response rates may be more commonly observed using such approaches. The current analysis also provides some evidence supporting the existence of inter-individual differences in $\dot{V}O_{2max}$ trainability based on greater variation in change scores between exercise and control groups. Future primary research should be conducted with adequate power to investigate the scope of inter-individual differences in $\dot{V}O_{2max}$ trainability, and if meaningful, the causative factors.

CHAPTER 5 – VARIABILITY IN EXERCISE TOLERANCE AND PHYSIOLOGICAL RESPONSES TO EXERCISE PRESCRIBED RELATIVE TO PHYSIOLOGICAL THRESHOLDS AND TO MAXIMUM OXYGEN UPTAKE

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INTRODUCTION

Cardiorespiratory fitness, measured as maximum oxygen uptake ($\dot{V}O_{2max}$), is an important marker of performance (Bassett & Howley, 2000) and cardiovascular health (Harber et al., 2017). The most effective means of increasing $\dot{V}O_{2max}$ is via endurance training (ET), encompassing high intensity interval training and/or continuous exercise (Milanović et al., 2015). However, the effect of ET on $\dot{V}O_{2max}$ appears to be largely heterogenous among individuals (Bouchard et al., 1999; Williams et al., 2019).

Many factors may contribute to $\dot{V}O_{2max}$ response variability. Some relate to *unmodifiable* factors, such as age and genetics, and some to *modifiable* factors, such as training characteristics, whilst others relate to measurement error and biological variability (**Chapter 2**) (Bonafiglia et al., 2022). A modifiable factor of interest is *how* exercise intensity is prescribed, which, when manipulated, may reduce response variability by creating a more homogenous exercise and training stimulus among individuals (**Chapter 2**). Improving exercise intensity prescription reflects a subtractive approach that may be a means of reducing response variability without having to exhaust additive approaches where additional stimuli are needed (Adams et al., 2021), for example by increasing training dose (Bonafiglia et al., 2021).

Exercise intensity is prescribed along a continuum of intensity domains partitioned into moderate, heavy (vigorous), and severe (near-maximal to maximal), each of which are associated with domain-specific metabolic and cardiopulmonary responses (Black et al., 2017; Carter et al., 2002). Notably, these domains are delineated by physiological thresholds, whereby the transition between the moderate and heavy domain and the heavy and severe domain can be determined by the gas exchange threshold (GET) and critical power (CP), respectively (Poole et al., 2020; Wasserman et al., 1973). To target each intensity domain and the associated exercise stimuli, intensity is commonly prescribed as a fixed %$\dot{V}O_{2max}$ (Milanović et al., 2015; Williams et al., 2019). However, among individuals, this approach elicits marked variations in the acute physiological responses to exercise and time-to-task failure despite undertaking exercise at the 'same' relative intensity (Baldwin et al., 2000; Iannetta et al., 2020; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010).

Alternatively, using physiological thresholds to prescribe exercise may improve intensity normalisation among individuals as they consider the size and positioning of an individual's intensity domains relative to $\dot{V}O_{2max}$. Compared to exercise prescribed relative to $\dot{V}O_{2max}$, more homogenous physiological responses have been observed when exercise is prescribed relative to physiological thresholds such as GET (Lansley et al., 2011), lactate threshold (Baldwin et al., 2000), and the onset(McLellan & Jacobs, 1991)ation (McLellan & Jacobs, 1991). As it has recently been argued that CP is the most accurate delineator of the transition between the heavy and severe intensity domains (Jones et al., 2019), using CP as an anchor of exercise intensity might improve intensity normalisation among individuals when exercising at higher intensities (Collins et al., 2022). However, exploring the variability in exercise tolerance and acute physiological responses to exercise prescribed relative to CP compared to traditional intensity anchors is yet to be investigated. Nor so has the magnitude of variability been explored in relation to interval-based exercise. Additionally, it is of interest to determine the variability in how exhaustive interval bouts are among individuals. This can be achieved

by modelling the depletion of an individual's finite work capacity (W′) that exists at intens(Skiba & Clarke, 2021)al power (Skiba & Clarke, 2021)2021).

The purpose of this study was, therefore, to compare the variability in acute physiological responses to moderate intensity continuous exercise, heavy intensity continuous exercise, and high intensity interval exercise prescribed relative to $\dot{V}O_{2max}$ (TRAD), and to GET and CP (THR). We hypothesised that the magnitude of variability in the acute physiological responses to exercise would be lower among individuals when exercise is prescribed using THR compared to TRAD approaches.

METHODS

Ethical approval

The study was approved by the University of Hertfordshire Health, Science, Engineering and Technology Ethics Committee and Delegated Authority (Protocol: LMS/PGR/UH/04708) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Participants

Ten healthy, recreationally active individuals volunteered to participate in the study (**Table 5.1**). Participants were 18+ years old, non-smokers, non-obese (BMI <30 $kg \cdot m^2$), and free from any disease and musculoskeletal injuries.

Table 5.1. Participant characteristics.

Sex	Males (n = 7)	Females (n = 3)	Total (n = 10)
Age (y)	22 ± 4	26 ± 9	23 ± 6
Height (cm)	180 ± 8	168 ± 5	176 ± 9
Mass (kg)	84 ± 13	63 ± 8	78 ± 15
BMI ($kg \cdot m^2$)	26 ± 4	22 ± 3	25 ± 4
$\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	37 ± 5	40 ± 3	38 ± 4
$\dot{V}O_{2max}$ ($L \cdot min^{-1}$)	3.11 ± 0.35	2.52 ± 0.12	2.93 ± 0.41

Data are reported means ± SD. BMI, body mass index; $\dot{V}O_{2max}$, maximum oxygen uptake.

Experimental design

This study implemented a randomised cross-over design. Participants visited the laboratory six times (**Figure 5.1**) undergoing a block of exercise testing (visits 1-3) followed by two batteries of exercise bouts where the intensity was prescribed using both TRAD and THR approaches (visits 4-6). Participants were randomly allocated into two groups. Group 1 performed THR exercise first followed by TRAD exercise. Group 2 performed TRAD exercise first followed by THR exercise. Participants were blinded to the experimental conditions being undertaken. Participants were asked to arrive at the laboratory fully rested, and all sessions were performed at similar times of day and separated by a minimum of 24 h. All exercise tests and exercise bouts were performed on an electromagnetically braked cycle ergometer (Lode Excalibur Sport V2, Groningen, Netherlands).

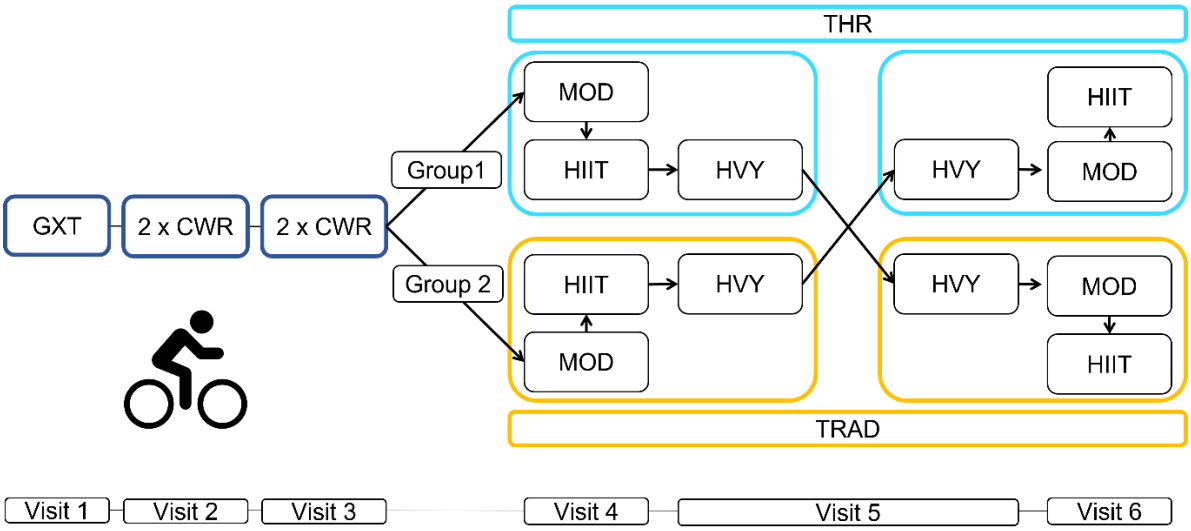

Figure 5.1. Experimental study protocol. CWR, constant work rate tests; GXT, graded maximal ramp exercise test; HIIT, high intensity interval training; HVY, heavy intensity continuous exercise; MOD, moderate intensity continuous exercise; THR, threshold-based exercise bouts; TRAD, traditionally prescribed exercise bouts.

Exercise testing

Maximal ramp exercise test (GXT). On visit one, participants performed a maximal GXT to determine GET, $\dot{V}O_{2max}$ and maximum heart rate (HR_{max}). Participants completed a standardised warm-up consisting of 3 min unloaded cycling at a self-selected cadence (70-90 rpm). Starting at 0 W, work rate increased by 30 W every minute until task failure. Task failure was defined as a decrease in cadence >10 rpm below self-selected test cadence for >5 s. Breath-by-breath pulmonary gas exchange and heart rate (HR) data were collected continuously throughout the test and averaged over 10 s periods. $\dot{V}O_{2max}$ was recorded as the highest mean $\dot{V}O_2$ during a 30 s period and GET as the first disproportionate increase in carbon dioxide production ($\dot{V}CO_2$) from visual inspection of individual $\dot{V}CO_2$ vs. $\dot{V}O_2$ (Keir et al., 2022). GET was then confirmed by visual inspection of additional breath-by-breath plots using an online exercise thresholds tool (Keir et al., 2022), and agreement with another researcher (D.M.) was then sought. To verify the attainment of $\dot{V}O_{2max}$, a verification bout

(VER), intended to last between 3-6 min, was performed following 20 min recovery post GXT (Nolan et al., 2014). Work rate was set at 85% of the maximum power output achieved in the GXT and was performed to task failure (Poole & Jones, 2017). The attainment of $\dot{V}O_{2max}$ was assumed if the difference between GXT and VER $\dot{V}O_{2max}$ was ≤5% and the average value of the two tests was taken forward as $\dot{V}O_{2max}$.

Constant work rate tests (CWR). On visits two and three, participants performed two CWR per day with an intertrial recovery time of 1 h in order to estimate CP and W′ (B. Hunter et al., 2021). Each CWR was intended to elicit task failure between 2- and 15-min. Participants completed a 3-min warm up, cycling at a low work rate of 25 W and self-selected cadence (70-90 rpm). Work rate was then suddenly increased to the target work rate and participants cycled to task failure at their self-selected cadence. Attainment of $\dot{V}O_{2max}$ during CWR was again confirmed if $\dot{V}O_{2max}$ was ≤5% of determined $\dot{V}O_{2max}$. Calculation of CP and W′ were determined in accordance with General Methods (**Chapter 2**).

Exercise bouts

Intra-visit exercise bouts were all separated by a 1-h recovery period. The intensity for exercise bouts were chosen to correspond to moderate (MOD), heavy (HVY), and severe intensity exercise (which was in the form of high intensity interval training; HIIT) (**Table 5.2**). MOD_{TRAD} and HVY_{TRAD} were prescribed as the midpoint between the ranges of $\dot{V}O_{2max}$ intended to elicit moderate (46-63%) and heavy (64-90%) intensity exercise, respectively (American College of Sports Medicine, 2017). The HIIT protocols implemented a 1:1 work:rest ratio, with active recovery at 20 W. HIIT exercise bouts were designed based on the findings of Wen et al. (2019) whereby long intervals (≥2 min) and high volumes (≥15 min) at 80-90% $\dot{V}O_{2max}$ are recommended to maximise training effects on $\dot{V}O_{2max}$. The power output for both $HIIT_{THR}$ and $HIIT_{TRAD}$ was intended to correspond to severe intensity exercise, when following the ACSM guidelines on severe intensity exercise, intensities of ≥91% $\dot{V}O_{2max}$ are proposed. However, following pilot testing this was not suitable when trying to complete ≥2 min intervals. Therefore, the intensity for $HIIT_{TRAD}$ was reduced to 85% $\dot{V}O_{2max}$ (‘*heavy’* intensity exercise according to

the ACSM guidelines (American College of Sports Medicine, 2017)). The work rate in TRAD sessions was extrapolated from the $\dot{V}O_2$-intensity relationship derived from the GXT, with the first minute of test $\dot{V}O_2$ data being removed from the calculation (Keir et al., 2022).

Table 5.2. Prescribed exercise bouts.

	THR	TRAD
MOD	30 min @ 90% GET	30 min @ 55% $\dot{V}O_{2max}$
HVY	20 min @ 50% Δ (GET + [0.5 × (CP – GET)])	20 min @ 75% $\dot{V}O_{2max}$
HIIT	5 × 3 min (1:1 work:rest ratio) @ 110% CP	5 × 3 min (1:1 work:rest ratio) @ 85% $\dot{V}O_{2max}$

THR, exercise prescribed relative to physiological thresholds; TRAD, exercise prescribed relative to $\dot{V}O_{2max}$; GET, gas exchange threshold; CP, critical power; $\dot{V}O_{2max}$, maximum oxygen uptake; MOD, moderate intensity continuous exercise; HVY, heavy intensity continuous exercise; HIIT, high-intensity interval training; 50% Δ, power at GET + 50% difference between GET and CP.

Util(Skiba & Clarke, 2021)$_{NT}$ model (Skiba & Clarke, 2021) was used to determine how much of the work capacity above CP (W′) was depleted during the HIIT exercise bouts. W′$_{BAL\text{-}INT}$ was calculated to the end of the final HIIT bout or at task failure, whichever was sooner. W′$_{BAL\text{-}INT}$ was calculated as:

$$W'_{BAL-INT}(t) = W'_0 - \int_0^t \left[e^{\left(-\frac{t-u}{\tau_{W'}}\right)} \right] W'_{EXP}(u)\, du$$

where W′$_{EXP}$ (u) was calculated as follows:

$$W'_{EXP}(u) = \begin{cases} 0, & P(u) \leq CP \\ \int (P(u) - CP) du, & P(u) > CP \end{cases}$$

and:

$$\tau_{W'} = 546 \cdot e^{(-0.01 \cdot Dcp)} + 316$$

where D_{CP} is the difference between CP and the power output (P) during the recovery period.

Measurements

During all exercise tests and exercise bouts, gas exchange data were measured continuously breath-by-breath using an online gas analyser (MetaLyzer 3B, Cortex Biophysik, Leipzig, Germany). Participants wore a face mask with low dead space (125 mL) and breathed through a low resistance (<0.1 kPa·L^{-1} at 20 L·s^{-1}) impeller turbine with O_2 and CO_2 samples at 50 Hz. The gas analyser was calibrated prior to each exercise session with gases of known concentration and the turbine volume transducer was calibrated using a 3 L syringe (Hans Rudolph, Inc. Kansas City, MO). Rise time of the gas analyser and transit delay for O_2 and CO_2 were <100 ms and 800-1200 ms, respectively, allowing for breath-by-breath calculation. Measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ were recorded breath-by-breath and exported as 10-s moving averages for subsequent analyses. Heart rate was measured telemetrically throughout the exercise session and exported as 10-s moving averages for subsequent analyses (Polar H10, Polar Electro, Kempele, Switzerland). During the exercise bouts, capillary blood samples (10 uL) were taken from the fingertip and analysed (Biosen C-Line, EKF Diagnostics, Cardiff, UK) to determine blood lactate concentration (BLa). For MOD and HVY, blood samples were taken at rest, during the last 30 s of the warm-up, and then every five minutes for the remainder of the exercise bout or at task failure. During HIIT, blood samples were taken at rest and at the start of each recovery period or until task failure.

Statistical analyses

To evaluate the magnitude of acute physiological response variability, the standard deviation (SD) and mean responses were first calculated for THR and TRAD during MOD, HVY and HIIT exercise bouts. The SD were then compared between THR and TRAD sessions using the *F* distribution. Where data for an individual was missing (i.e., at time points after a

premature cessation of exercise) a sensitivity analyses was conducted to determine the effect of different assumptions about the missing values on the mean to avoid missing data biasing conclusions based on observed data. Taking into consideration the sample size of the current study (n=10), interpretation of the comparison between variances will consider both the *P* value and the magnitude of the *F* ratio as an indicator of the magnitude of difference. As the *F* test is being used with n=10, the *F* statistic will be treated as an effect size estimator, and any ratio <0.33 will be considered of sufficient magnitude to indicate a difference that could potentially be significant with a larger sample (Chen & Chen, 2010)2010). This approach helps protect against accepting the null hypothesis when there is a lack of power to truly evaluate the difference. Chi square tests were used to compare the proportion of individuals completing THR and TRAD sessions. Differences in group means were compared using a *t* test. Significance was accepted when $P < 0.05$. Statistical analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria) and JASP (Nederlands).

RESULTS

Exercise tests

In the GXT and the verification test, the highest $\dot{V}O_2$ recorded over a 30 s period was 38 ± 4 $mL \cdot kg^{-1} \cdot min^{-1}$ (2.95 ± 0.43 $L \cdot min^{-1}$) and 38 ± 4 $mL \cdot kg^{-1} \cdot min^{-1}$ (2.91 ± 0.39 $L \cdot min^{-1}$), respectively, with a difference of 1 ± 3% (range: -2 to 5 $mL \cdot kg^{-1} \cdot min^{-1}$). Therefore, $\dot{V}O_{2max}$ was calculated as the average of values attained in the GXT and verification test. Peak power output in GXT was 292 ± 33 W. Power output at GET was 113 ± 17 W and occurred at 52 ± 4% $\dot{V}O_{2max}$.

Power output at CP was 172 ± 27 W and occurred at 69 ± 6% $\dot{V}O_{2max}$. GET occurred at 67 ± 12% CP. The highest $\dot{V}O_2$ attained in all CWR trials was 39 ± 5 $mL \cdot kg^{-1} \cdot min^{-1}$ (3.02 ± 0.44 $L \cdot min^{-1}$) which was not different to VO2max ($P = 0.954$). For individuals where linear work-time CP model was used (n = 9), fits were $R^2 = 0.99$. The linear $1 \cdot Time^{-1}$ model was used for the

remaining individual (n = 1) where the fit was $R^2 = 0.99$. Shortest time to exhaustion CWR trials were 196 ± 36 s and longest were 796 ± 167 s.

Exercise bouts

Summary data for each exercise bout is presented in **Table 5.3**. Whilst all exercise bouts were completed to their entirety in MOD_{THR}, MOD_{TRAD}, HVY_{THR}, and $HIIT_{THR}$, the duration of the HVY_{TRAD} and $HIIT_{TRAD}$ completed ranged between 387-1200 s and 310-1800 s, respectively. There was no difference in work rate variance expressed as a percentage of CP between MOD_{THR} and MOD_{TRAD}; however, the variability was lower in HVY_{THR} compared to HVY_{TRAD} and in $HIIT_{THR}$ compared to $HIIT_{TRAD}$. Expressed as a percentage of CP, intensities ranged between 45-79% and 57-85% in MOD_{THR} and MOD_{TRAD}, respectively, 75-94% and 96-132% in HVY_{THR} and HVY_{TRAD}, respectively, and 110% and 115-156% in $HIIT_{THR}$ and $HIIT_{TRAD}$, respectively.

Physiological data from all exercise bouts are presented in **Table 5.4**. There was no difference in the variability of peak or average $\dot{V}O_2$, HR, or BLa between MOD_{THR} and MOD_{TRAD}, or between HVY_{THR} and HVY_{TRAD}. There was no difference in the variability of peak or average $\dot{V}O_2$ or HR between $HIIT_{THR}$ and $HIIT_{TRAD}$. The variability in peak and average BLa was lower in $HIIT_{THR}$ compared to $HIIT_{TRAD}$. W′ depleted in the first 3-min interval during the HIIT exercise was greater ($P < 0.001$) in $HIIT_{TRAD}$ (49 ± 7%, 39-58%) compared to $HIIT_{THR}$ (17 ± 7%, 10-30%), and W′ depleted at the end-point of exercise was greater ($P < 0.001$) in $HIIT_{TRAD}$ (73 ± 22%, 44-99%) compared to $HIIT_{THR}$ (30 ± 12%, 17-53%). The variability in W′ depleted at the end of HIIT was lower in $HIIT_{THR}$ compared to $HIIT_{TRAD}$ ($F = 0.305$).

Table 5.3. Summary of group data from exercise bouts.

Exercise bout	Work rate (W)	Work rate (%CP)	F ratio	Individuals completing exercise bout (%)	P value	Percentage of exercise bout completed (%)
MOD_{THR}	102 ± 15	60 ± 11	1.412	100		100
MOD_{TRAD}	124 ± 14	73 ± 9		100		100
HVY_{THR}	143 ± 18	83 ± 6 †	0.234	100 *	< 0.001	100
HVY_{TRAD}	193 ± 19	113 ± 13		30		32 - 100
$HIIT_{THR}$	190 ± 30	110 ± 0 †	< 0.001	100 *	< 0.001	100
$HIIT_{TRAD}$	228 ± 23	134 ± 15		20		17 - 100

MOD: moderate intensity exercise bout, HVY: heavy intensity exercise bout, HIIT: high intensity interval training, THR: threshold-based exercise intensity prescription, TRAD: traditionally prescribed exercise intensity. * Indicates a significant difference between THR and TRAD ($P < 0.05$). † Indicates that the variance is significantly lower in THR group compared to TRAD ($F < 0.33$). n = 10.

Table 5.4. Summary of group peak physiological data from exercise bouts.

Exercise bout	$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	F ratio	$\dot{V}O_{2peak}$ ($\%\dot{V}O_{2max}$)	F ratio	HR_{peak} ($b \cdot min^{-1}$)	F ratio	HR_{peak} ($\%HR_{max}$)	F ratio	BLa_{peak} (mmol·L)	F ratio
MOD_{THR}	1.77 ± 0.31	0.900	61 ± 9	1.648	140 ± 12	1.085	75 ± 7	1.976	2.95 ± 1.35	0.973
MOD_{TRAD}	2.02 ± 0.32		69 ± 7		149 ± 11		80 ± 5		3.82 ± 1.37	
HVY_{THR}	2.27 ± 0.37	0.947	78 ± 7	1.777	160 ± 11	0.701	85 ± 5	0.979	4.68 ± 1.48	0.361
HVY_{TRAD}	2.80 ± 0.38		96 ± 6		182 ± 13		97 ± 5		9.48 ± 2.46	
$HIIT_{THR}$	2.73 ± 0.37	0.825	93 ± 5	1.116	176 ± 11	1.190	94 ± 6	1.395	7.45 ± 1.70 †	0.274
$HIIT_{TRAD}$	2.93 ± 0.41		100 ± 5		184 ± 12		98 ± 5		10.91 ± 3.23	

MOD: moderate intensity exercise bout, HVY: heavy intensity exercise bout, HIIT: high intensity interval training, THR: threshold-based exercise intensity prescription, TRAD: traditionally prescribed exercise intensity. $\dot{V}O_{2max}$: maximum oxygen uptake, $\dot{V}O_{2peak}$: peak oxygen uptake, HR_{max}: maximum heart rate, HR_{peak}: peak heart rate, BLa_{peak}: peak blood lactate. † Indicates that the variance is significantly lower in THR group compared to TRAD ($F < 0.33$). n = 10.

Table 5.5. Summary of group mean physiological data from exercise bouts.

Exercise bout	$\dot{V}O_{2avg}$ (L·min^{-1})	F ratio	$\dot{V}O_{2avg}$ (%$\dot{V}O_{2max}$)	F ratio	HR_{avg} (b·min^{-1})	F ratio	HR_{avg} (%HR_{max})	F ratio	BLa_{avg} (mmol·L)	F ratio
MOD_{THR}	1.67 ± 0.28	0.708	58 ± 8	1.513	134 ± 13	1.51	71 ± 7	2.351	2.43 ± 1.20	0.874
MOD_{TRAD}	1.91 ± 0.33		65 ± 6		143 ± 11		76 ± 5		3.31 ± 1.28	
HVY_{THR}	2.20 ± 0.34	0.828	75 ± 6	1.049	154 ± 10	0.657	82 ± 5	1.136	4.12 ± 1.30	0.403
HVY_{TRAD}	2.71 ± 0.37		93 ± 6		175 ± 12		94 ± 5		8.06 ± 2.85	
$HIIT_{THR}$	2.61 ± 0.32	0.703	89 ± 5	0.889	171 ± 12	1.031	91 ± 6	1.925	6.50 ± 1.30 †	0.318
$HIIT_{TRAD}$	2.85 ± 0.38		97 ± 5		179 ± 12		96 ± 6		9.09 ± 2.31	

MOD: moderate intensity exercise bout, HVY: heavy intensity exercise bout, HIIT: high intensity interval training, THR: threshold-based exercise intensity prescription, TRAD: traditionally prescribed exercise intensity. $\dot{V}O_{2max}$: maximum oxygen uptake, $\dot{V}O_{2avg}$: average oxygen uptake, HR_{max}: maximum heart rate, HR_{avg}: average heart rate, BLa_{avg}: average blood lactate. † Indicates that the variance is significantly lower in THR group compared to TRAD ($F < 0.33$). n = 10.

DISCUSSION

This study is the first to explore the variability in exercise tolerance and acute physiological responses to moderate, heavy, and severe intensity exercise prescribed relative to GET and CP and to $\dot{V}O_{2max}$. When prescribing severe intensity exercise relative to $\dot{V}O_{2max}$, the magnitude of variability in exercise tolerance and metabolic responses was greater than when exercise was prescribed relative to CP. This study demonstrates that using CP to prescribe exercise intensity creates a more homogenous exercise stimulus among individuals.

All individuals completed MOD_{THR} and MOD_{TRAD} to their entirety, and the majority displayed physiological response profiles consistent with moderate intensity exercise whereby early physiological steady state is attained (**Figure 5.2**). Accordingly, in the present study, one individual experienced a >1 $mmol \cdot L^{-1}$ increase in BLa from 600 s to 1800 s during MOD_{THR}. This supports the findings of McLellan and J(1991) and Baldwin et al. (2000) who observed no differences in BLa response variability among trained and untrained individuals when exercise was prescribed below the onset of blood lactate accumulation and the lactate threshold, respectively. When exercising at 55% $\dot{V}O_{2max}$, only four individuals' work rates were below GET, however the intensity was low enough such that 30 min of exercise could be completed and only one individual experienced an increase in BLa >1 $mmol \cdot L^{-1}$ from 600 s to 1800 s. In the present study, work rates corresponding to 55% $\dot{V}O_{2max}$ and 90% GET were both successful in prescribing continuous exercise that could be tolerated for 30 min. If intensity control is a primary focus, then using GET to prescribe moderate intensity exercise may be more beneficial. Online tools are available to help determine individual's thresholds from GXT's and should facilitate a switch from using fixed $\%\dot{V}O_{2max}$ to inform exercise prescription (Keir et al., 2022).

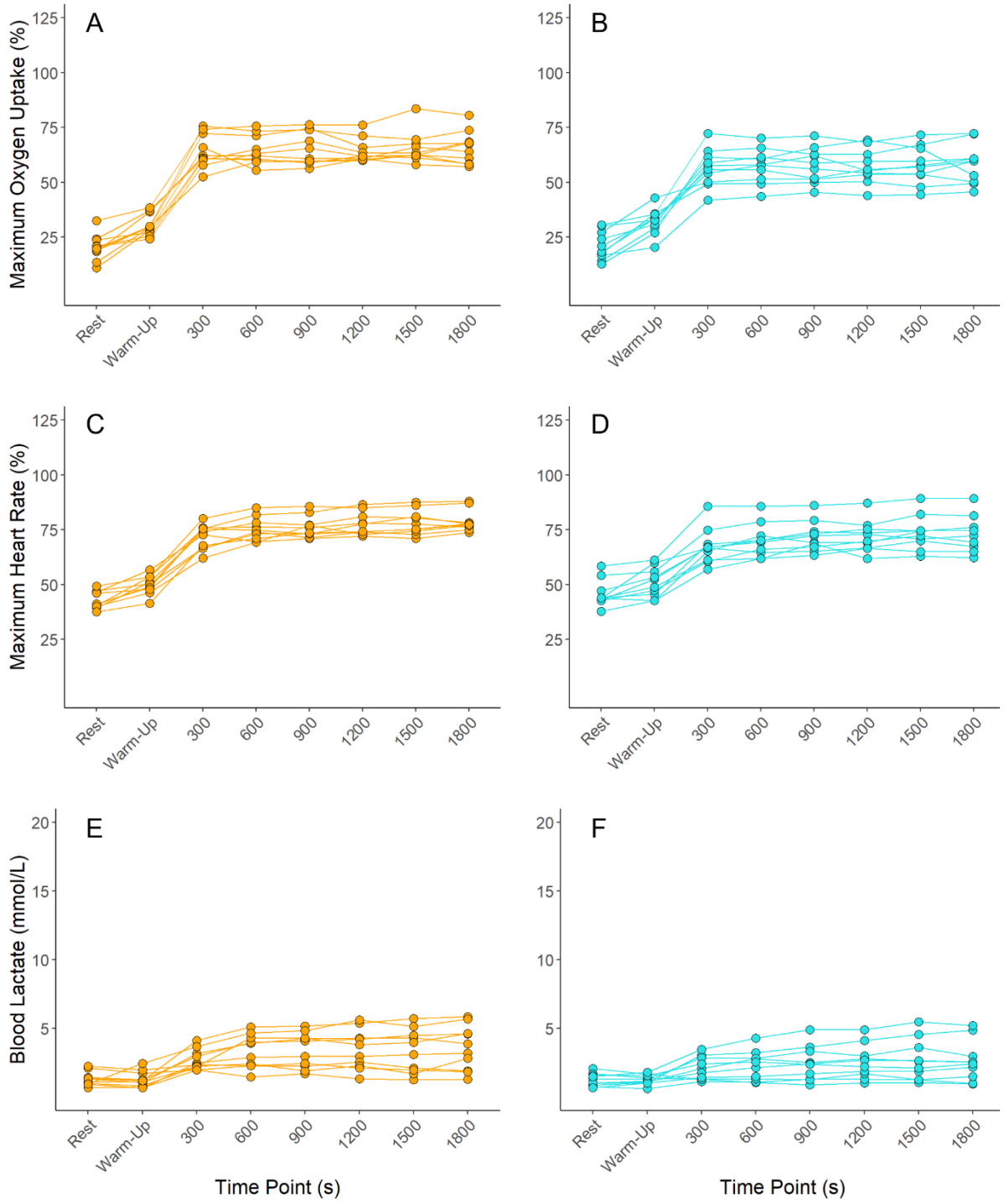

Figure 5.2. Individual (orange: MOD_{TRAD}, blue: MOD_{THR}) responses in oxygen uptake expressed relative to maximum oxygen uptake (A, B), heart rate expressed relative to maximum heart rate (C, D), and absolute blood lactate levels (E, F).

Completion rates for HVY_{THR} and HVY_{TRAD} were 100% and 30%, respectively. In the three individuals who completed HVY_{TRAD}, the work rates associated with 75% $\dot{V}O_{2max}$ were below

or at CP (96-100% CP). For these individuals, the intensity elicited was primarily consistent with heavy intensity exercise whereby exercise can be continued for extended periods of time with physiological perturbations reaching a delayed steady-state (Poole et al., 2016). In the seven individuals who were not able to complete HVY_{TRAD}, work rates were all above CP (101-132% CP). Exercising above CP elicits non-steady state exercise and continuation in this domain leads to the eventual attainment of $\dot{V}O_{2max}$ and, ultimately, exhaustion (Poole et al., 2016). Accordingly, in those who were not able to complete HVY_{TRAD} and were exercising >CP, end $\dot{V}O_2$ and HR values reached ~95% $\dot{V}O_{2max}$ and ~97% HR_{max}. In comparison, all individuals were able to complete HVY_{THR} and were all exercising <CP. Accordingly, end $\dot{V}O_2$ and HR values in HVY_{THR} were ~76% $\dot{V}O_{2max}$ and ~85% HR_{max}, respectively. This highlights the disparity between the prescribed work rates and the actual work rates elicited through TRAD compared to THR prescription methods. Furthermore, compared to HVY_{THR} where only one individual saw an increase of BLa >1 $mmol \cdot L^{-1}$ from 600 s to 1200 s, four individuals saw an increase >1 $mmol \cdot L^{-1}$ from 600 s to 1200 s in HVY_{TRAD} (**Figure 5.3**). Exercising at 50% Δ, thus, better normalised exercise intensity among individuals, controlling exercise intensity in the heavy intensity domain. This approach also elicited 46% less variability in work rates (*F = 0.234*). Overall, these findings are consistent with those of Lansley et al. (2011), whereby four individuals (44%) could not complete 20 min of exercise at 70% $\dot{V}O_{2max,}$ all reaching $\dot{V}O_{2max}$ and volitional exhaustion before 20 min had elapsed. Similarly, Scharhag-Rosenberger et al. (2010) noted two (10%) and seventeen (81%) individuals were not able to complete 60 min continuous exercise at 60% and 75% $\dot{V}O_{2max}$, respectively. It is thus clear that using a fixed $\%\dot{V}O_{2max}$ does not control exercise intensity effectively among individuals.

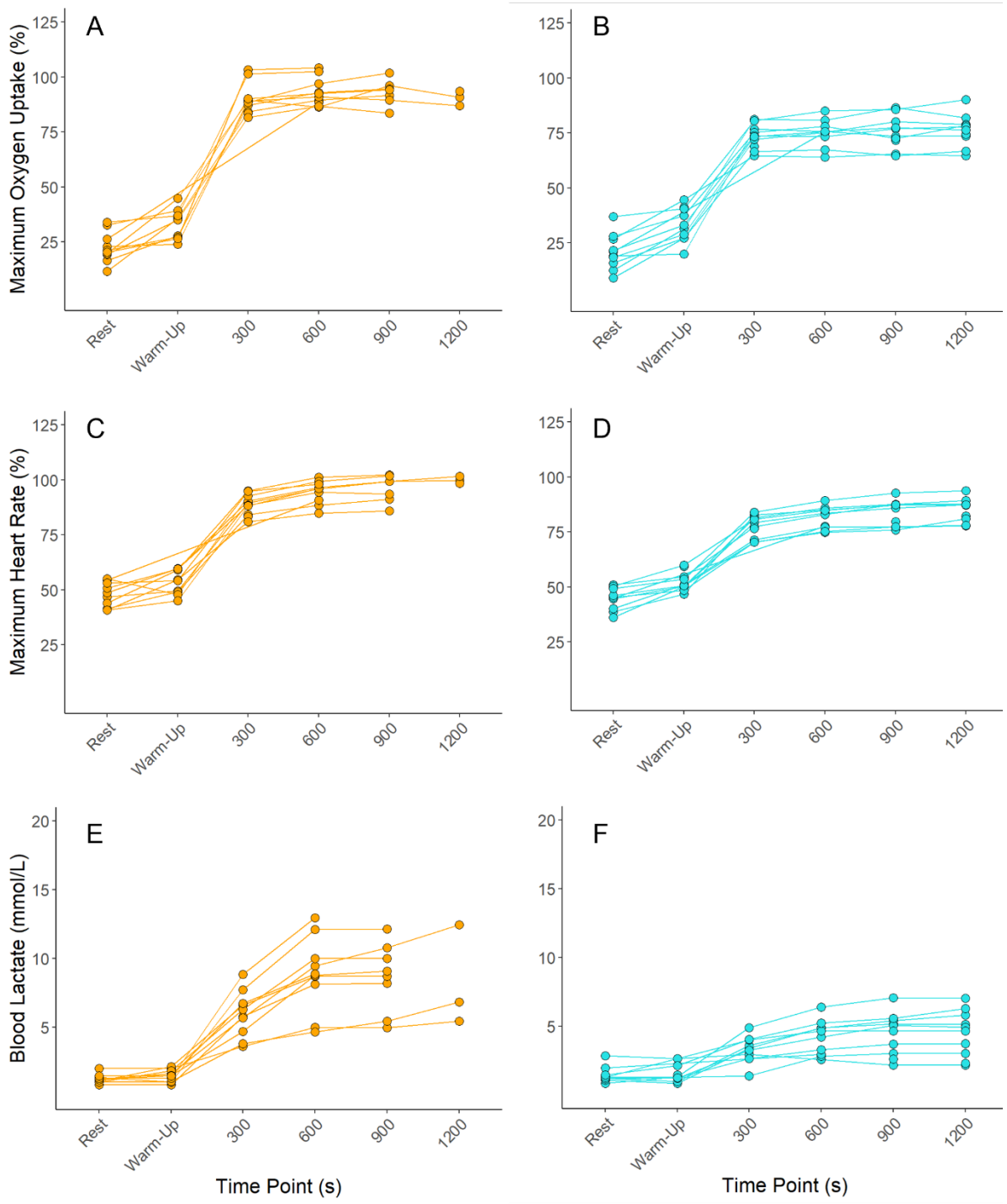

Figure 5.3. Individual (orange: HVY_{TRAD}, blue: HVY_{THR}) responses in oxygen uptake expressed relative to maximum oxygen uptake (A, B), heart rate expressed relative to maximum heart rate (C, D), and absolute blood lactate levels (E, F).

Notably, the physiological thresholds which delineate the intensity domains occur at different percentages of $\dot{V}O_{2max}$ among individuals (L. F. Azevedo et al., 2011; Hansen et al., 2019; Pymer et al., 2020). Thus, by using physiological thresholds to inform intensity prescription, the size and positioning of an individuals' intensity domains are considered (**Figure 5.4**). In the present study, 70% of those exercising at 75% $\dot{V}O_{2max}$, which is commonly, but erroneously assumed to elicit heavy intensity exercise at the individual level, resulted in exercise undertaken above CP, and elicited severe intensity responses to exercise. This corroborates the work of Collins et al. (2022) whereby exercise prescribed at 40% and 80% of GXT maximum power output elicited work rates of 60-72% and 109-148% CP, respectively. Combined with the present findings, this further advocates the use of CP as a primary anchor of exercise intensity. Due to the variability in work rates expressed relative to CP when intensity is prescribed using a fixed %$\dot{V}O_{2max}$, future work should determine whether the greater heterogeneity in the exercise stimulus contributes to the commonly observed $\dot{V}O_{2max}$ response variability following a period of traditionally prescribed training.

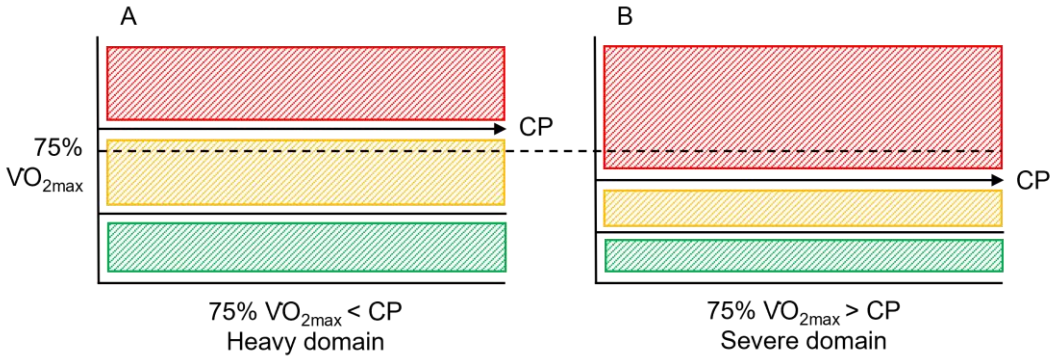

Figure 5.4. Intensity domain distribution from two representative individuals from the present study. For Individual A, critical power (CP) occurs at a higher percentage of maximum oxygen uptake ($\dot{V}O_{2max}$) compared to person B. When prescribed exercise at 75% $\dot{V}O_{2max}$, for person A this elicited heavy intensity exercise but severe intensity exercise for person B. If exercise is prescribed relative to CP, this considers the positioning of CP relative to the individual's $\dot{V}O_{2max}$.

Unlike Lansley et al. (2011), who observed lower inter-individual variability in the acute cardiopulmonary responses to exercise at 40% Δ (where Δ was determined as GET + [0.4 × ($\dot{V}O_{2max}$ – GET)]) compared to 70% $\dot{V}O_{2max}$, no such differences were observed in the present study between HVY_{THR} and HVY_{TRAD} sessions (**Figure 5.3**). Based on the marked differences in exercise tolerance in HVY_{TRAD} and HVY_{THR} it is surprising that no additional differences in metabolic or cardiopulmonary response variability were observed.

Completion rates for $HIIT_{THR}$ and $HIIT_{TRAD}$ were 100% and 20%, respectively. In $HIIT_{TRAD}$, two subjects completed all five intervals, four completed four intervals, three completed three intervals, and one individual completed one interval (**Figure 5.5**). This demonstrates the large variability in the exercise stimulus elicited when exercising at a work rate corresponding with 85% $\dot{V}O_{2max}$ compared to that of 110% CP. Compared to all individuals exercising at 110% CP in $HIIT_{THR}$, work rates ranged between 115-156% CP in $HIIT_{TRAD}$, explaining the variability in time to task failure demonstrated in **Figure 5.5**. This is noteworthy given recent findings by Collins et al. (2022) whereby changes in endurance performance were influenced strongly by the intensity of the exercise programme when expressed relative to CP. The variability in peak and average BLa responses to $HIIT_{THR}$ were 53% (*F = 0.274*) and 56% (*F = 0.318*) lower than those in $HIIT_{TRAD}$, respectively (**Table 5.4; Figure 5.6**). Observing no differences in HR and $\dot{V}O_2$ response variability between HIIT sessions may be explained by a ceiling effect whereby the physiological parameters approach their maximum values and thus room for variance begins to diminish. The observation of reductions in individuals $\dot{V}O_2$ from the last completed bout to that eliciting task failure (**Figure 5.5**) is likely explained by the shorter exercise time and thus a shortened amount of time in which $\dot{V}O_2$ can rise.

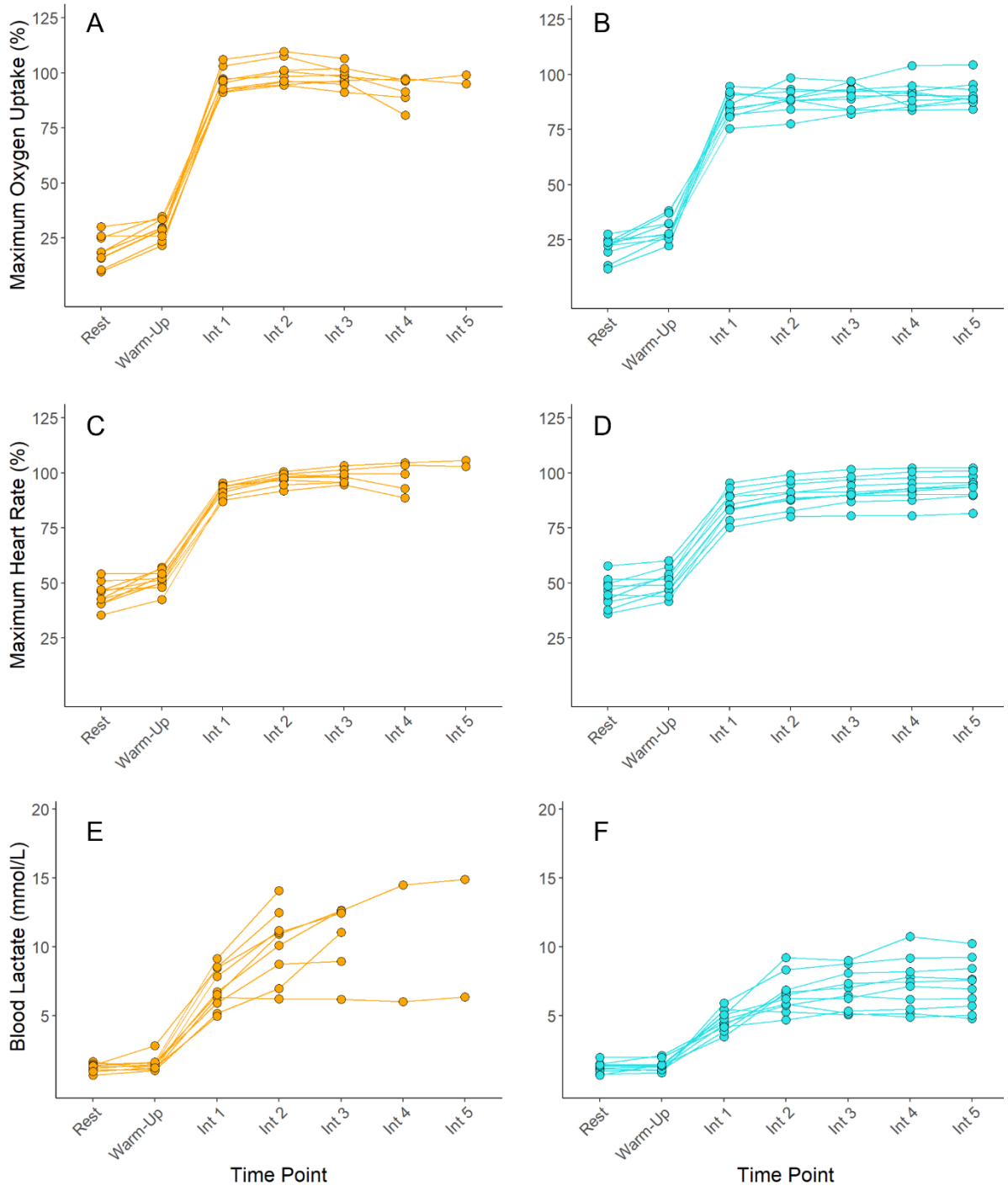

Figure 5.5. Individual (orange: $HIIT_{TRAD}$, blue: $HIIT_{THR}$) responses in oxygen uptake expressed relative to maximum oxygen uptake (A, B), heart rate expressed relative to maximum heart rate (C, D), absolute blood lactate levels (E, F). Int: severe intensity interval bout.

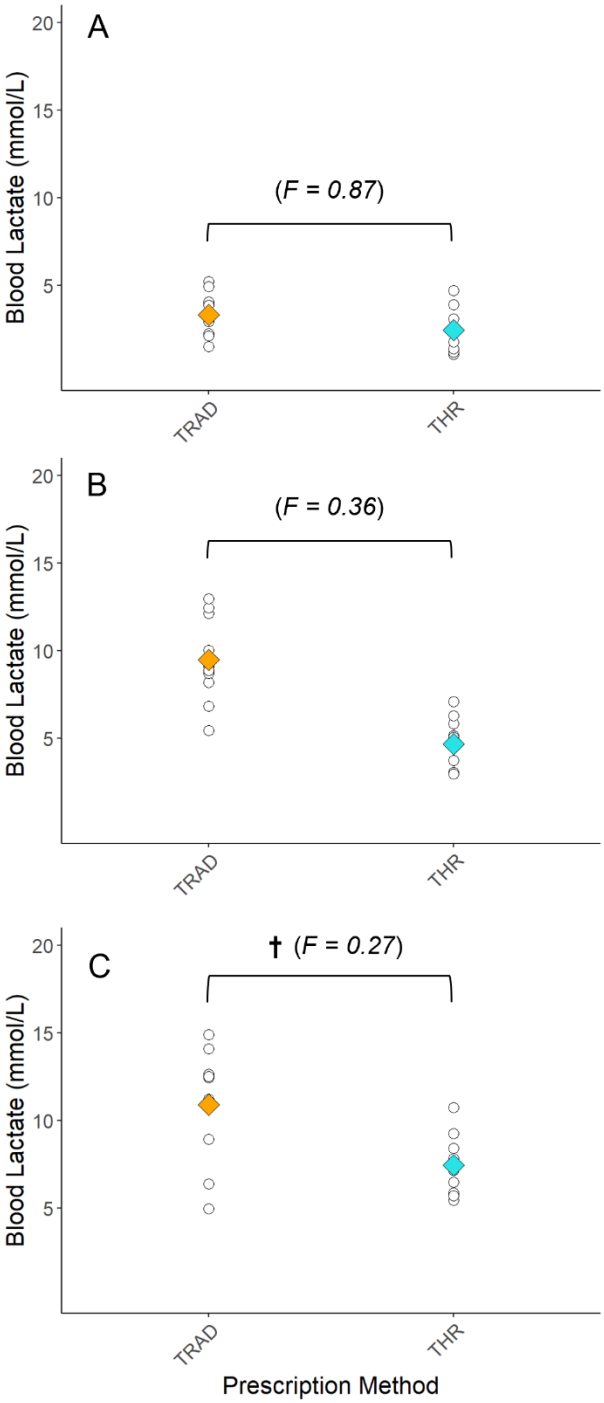

Figure 5.6. Individual (white circles) and mean (diamonds, orange: TRAD, blue: THR) values for average blood lactate during MOD (A) and peak blood lactate values during HVY (B) and HIIT (C). † Indicates lower variability in THR vs. TRAD exercise (*F <0.33*). n = 10.

In the present study, the $W'_{BAL\text{-}INT}$ model was used retrospectively (**Figure 5.7**). However, this model can be used to design and prescribe HIIT sessions (Galán-Rioja et al., 2022), for

example, designing and prescribing sessions for each individual that targets a given W′ depletion at the end of bout 1 or at the end of the final bout. Despite not doing so in the present study, 5 × 3 min at 110% CP was effective in creating a more homogenous exercise stimulus to that of $HIIT_{TRAD}$. For example, W′ depleted at the end of $HIIT_{THR}$ was 30 ± 12% compared to 73 ± 22% in $HIIT_{TRAD}$, a lower variability of 55% (*F = 0.305*). This helps explain the greater variability observed in exercise tolerance following $HIIT_{TRAD}$ and further highlights the disadvantages of using fixed $\%\dot{V}O_{2max}$ to prescribe exercise. It is of interest to determine whether using the $W'_{BAL\text{-}INT}$ model to design and prescribe $HIIT_{THR}$ further amplifies the reduction in response variability to HIIT sessions and enables the prescription of more challenging but achievable interval sessions.

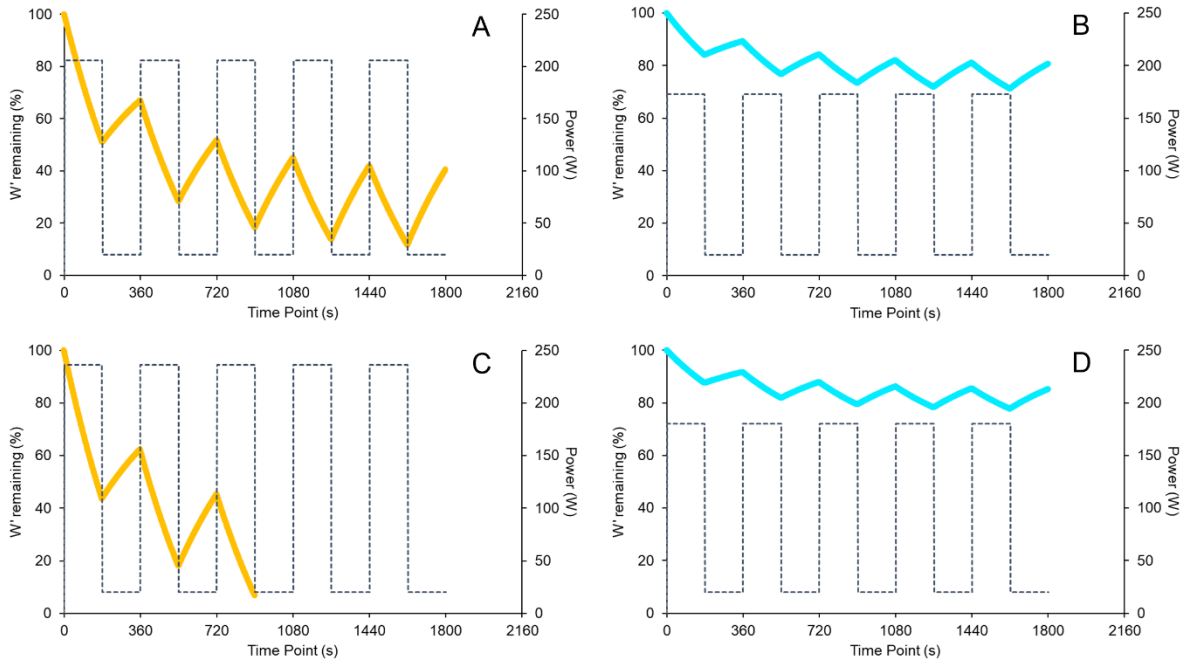

Figure 5.7. W′ balance during $HIIT_{TRAD}$ (orange) and $HIIT_{THR}$ (blue) for an individual who completed both $HIIT_{TRAD}$ and $HIIT_{THR}$ (A, B) and for an individual who completed $HIIT_{THR}$ but not $HIIT_{TRAD}$ (C, D).

Whilst the addition of CP determination can be time costly and requires the means of determining power output, the marked benefit it has on exercise intensity control is arguably

justified. Alternatively, the three-minute all-out test has been established as a time efficient alternative to the traditional means of determining CP, however, this requires large amounts of motivation, and a familiarisation session is recommended in order to obtain reliable data thereafter (Vanhatalo et al., 2007). Alternatively, determining critical speed, the running analogous of CP, is somewhat easier as this can be determined from training data (i.e., performance or training bests for a given distance) which does not require laboratory equipment beyond a stopwatch (Smyth & Muniz-Pumares, 2020b). Recent studies are exploring the use of self-assessed threshold tools such as rate of perceived exertion and the 'Talk Test' to estimate individuals' physiological thresholds (Lehtonen et al., 2022; Preobrazenski et al., 2019). This is an interesting avenue aiming to encourage the role out of individualised, population-wide approaches of exercise prescription that do not require access to laboratory facilities (Lehtonen et al., 2022). Additionally, the benefit of using such approaches is also being realised for use in various clinical populations (Anselmi et al., 2021b).

Finally, whilst it is recommended that practitioners prescribe exercise interventions known to elicit the largest mean changes in $\dot{V}O_{2max}$ in order to maximise the number of individuals experiencing clinically important cardiorespiratory changes (Bonafiglia et al., 2022), using physiological thresholds to anchor exercise intensity may have a similar effect, without having to exhaust training volume whereby a more appropriate exercise stimulus is created from the beginning.

CONCLUSION

Overall, prescribing exercise relative to $\dot{V}O_{2max}$ consistently overestimated the boundary between the heavy and severe intensity domains in the present study, in turn, causing greater heterogeneity in exercise tolerance and metabolic responses to exercise. More routine testing of individuals' CP is thus encouraged such that CP can be used to inform and prescribe exercise more appropriately. Future research exploring the feasibility and manipulation of CP determination across different populations is recommended.

PERSPECTIVE

Due to the widespread usage of traditional intensity anchors (e.g., %$\dot{V}O_{2max}$) in training programs and exercise research studies, it is plausible that this contributes to a heterogeneous training stimulus and thus, at least in part, the variability in physiological outcomes. This may have large implications on longer term training adaptations, and the variability of these adaptations among individuals. Future research determining whether this is the case is encouraged. If improving exercise intensity control by use of physiological thresholds does reduce the variability in subsequent exercise-induced adaptations among individuals, this could have marked benefits on improving exercise interventions and increasing the number of individuals attaining the desired exercise-induced adaptations targeting both health- and performance- related outcomes.

CHAPTER 6 – INDIVIDUAL AND GROUP CHANGES IN PHYSIOLOGICAL PARAMETERS FOLLOWING EXERCISE TRAINING PRESCRIBED RELATIVE TO CRITICAL POWER AND TO MAXIMUM OXYGEN UPTAKE: A FEASABILITY STUDY

INTRODUCTION

Exercise training is the most effective means of increasing maximum oxygen uptake ($\dot{V}O_{2max}$), an important marker of cardiorespiratory fitness and total body health (R. Ross et al., 2016). However, whilst effective at the group level, the effect of exercise training on changes in $\dot{V}O_{2max}$ appears to be heterogenous among individuals (Bouchard et al., 1999; Williams et al., 2019). Whilst various factors may affect this observed 'response variability' (Atkinson et al., 2019; Mann et al., 2014), the influence that the method used to prescribe exercise intensity has on response variability is unclear (**Chapter 2**).

Notably, exercise intensity is most commonly prescribed relative to a maximum physiological value such as $\dot{V}O_{2max}$ in both healthy populations (Milanović et al., 2015) and in those presenting with a disease/disorder (e.g., diabetes or obesity) (Bonafiglia et al., 2022). However, such approaches are consistently shown to elicit marked variability among individuals regarding exercise tolerance and physiological responses to acute bouts of exercise (**Chapter 5**) (Baldwin et al., 2000; Iannetta et al., 2021; Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). In turn, it is speculated that this acute heterogeneity may manifest over time as chronic heterogeneity in training-induced adaptations (**Chapter 2**) (Jamnick et al., 2020; Mann et al., 2013; Scharhag-Rosenberger et al., 2010).

Alternatively, exercise intensity can be prescribed relative to physiological thresholds (Jamnick et al., 2020). Physiological thresholds signify boundaries that represent the transition from the moderate and heavy intensity domains (threshold one) and the heavy and severe intensity domains (threshold two). Exercising in each of these domains is associated with distinct,

domain-specific physiological responses and homeostatic perturbations (Black et al., 2017; Carter et al., 2002). Notably, these boundaries occur at different percentages of $\dot{V}O_{2max}$ among individuals and thus, when using $\dot{V}O_{2max}$ to 'normalise' exercise intensity, these metabolic differences are neglected (Iannetta et al., 2020). As such, prescribing exercise in accordance with the current exercise guidelines (i.e., 150 min·wk^{-1} of moderate intensity exercise or 75 min·wk^{-1} of vigorous [heavy/severe] intensity exercise) using a fixed %$\dot{V}O_{2max}$ to characterise moderate and/or vigorous exercise will inevitably prescribe exercise sessions ranging across the intensity domains (**Chapter 5**, **Figure 5.7**). Therefore, utilising physiological thresholds allows for a more appropriate normalisation of exercise intensity among individuals, all of whom present with different sized intensity domains. A more homogenous exercise stimulus can thus be generated and the variability in exercise tolerance and physiological responses to the same training sessions can be reduced (**Chapter 5**) (Baldwin et al., 2000; Lansley et al., 2011; McLellan & Jacobs, 1991).

Critical power (CP), which demarcates the boundary between the heavy and severe intensity domains, estimates threshold two. Exercising below CP allows for the maintenance of a physiological steady state (i.e., metabolic stability and stabilised $\dot{V}O_2$ kinetics) (Craig et al., 2018; Jones et al., 2019). On the other hand, exercising above CP does not allow for a physiological steady state, instead, continuing to exercise above CP will result in inexorable increases in fatiguing metabolites (i.e., inorganic phosphates), blood lactate, and $\dot{V}O_{2max}$ will inevitably be reached resulting in task failure thereafter (Craig et al., 2018; Jones et al., 2019). Notably, exercise above CP is associated with discrete acute responses to exercise, and the amount of work done above CP can be accurately predicted. This thus lends itself to being a unique tool for exercise and training prescription. Despite this, its use as a tool for training purposes appears to be limited in the literature (**Chapter 2**). Training studies utilising the running derivative of CP, critical speed, have demonstrated its efficacy in prescribing interval training whereby significant increases in both critical speed and $\dot{V}O_{2max}$ were observed (Clark et al., 2013; Pettitt, 2016; Pettitt et al., 2015; Thomas et al., 2020). More recently, it has been

shown that using CP as an anchor for exercise intensity is more effective in creating a uniform exercise stimulus (**Chapter 5**) and may thus improve intensity normalisation among individuals undertaking a training programme (Collins et al., 2022).

The purpose of this study was, therefore, to explore the magnitude and variability in $\dot{V}O_{2max}$ change scores following exercise training prescribed relative to CP (threshold approach [THR]) and to $\dot{V}O_{2max}$ (traditional approach [TRAD]). Additionally, between THR and TRAD, we sought to explore the proportion of individuals experiencing a change in $\dot{V}O_{2max}$ beyond a study-specific technical error of measurement (TE) and a minimum important difference (MID; 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) (Bonafiglia et al., 2019; Hecksteden et al., 2018).

METHODS

Ethical approval

The study was approved by the University of Hertfordshire Health, Science, Engineering and Technology Ethics Committee and Delegated Authority (Protocol: LMS/PGR/UH/05138) and was conducted in accordance with the Declaration of Helsinki with the exception of database registration. All participants provided written informed consent before commencing participation.

Participants

Healthy males and females volunteered to take part in the study. Participants were 18+ years old, non-smokers, and free from any disease and musculoskeletal injury. Thirty-two individuals were recruited and started the study however four individuals (three from the exercise groups and one from the non-exercising control group) dropped out due to reasons related to time commitments. Characteristics of those completing the study are presented in **Table 6.1**.

Experimental design

All participants completed a series of exercise tests before, midway, and after a six-week training intervention (**Figure 6.1**). During each testing block, participants visited the laboratory on two separate occasions separated by a minimum of 48 hours. Testing day one included

anthropometric measurements including height and body mass, a graded maximal ramp exercise test (GXT), and a constant work rate exercise test (CWR). Testing day two included a further two CWRs. All exercise tests were performed on an electromagnetically braked cycling ergometer (Lode Excalibur Sport V2, Groningen, Netherlands). Following pre-intervention testing, participants were randomised into one of two groups using block randomisation (ABAB): THR, where exercise training was prescribed at an intensity relative to CP; and TRAD, where the intensity was prescribed relative to $\dot{V}O_{2max}$. Individuals serving as the non-exercising control group (CON) were those who desired to undertake the exercise tests but were not able to commit to the training protocol. The Lode Excalibur ergometer was used for all exercise testing and training sessions. An additional, electronically braked ergometer (Lode Corival, Groningen, Netherlands) was used for continuous training sessions but only in situations where the Lode Excalibur Sport could not be used. Pilot data collected in the present laboratory indicated no difference in training heart rate or rating of perceived exertion when cycling on either cycle ergometer maintaining the same absolute power output.

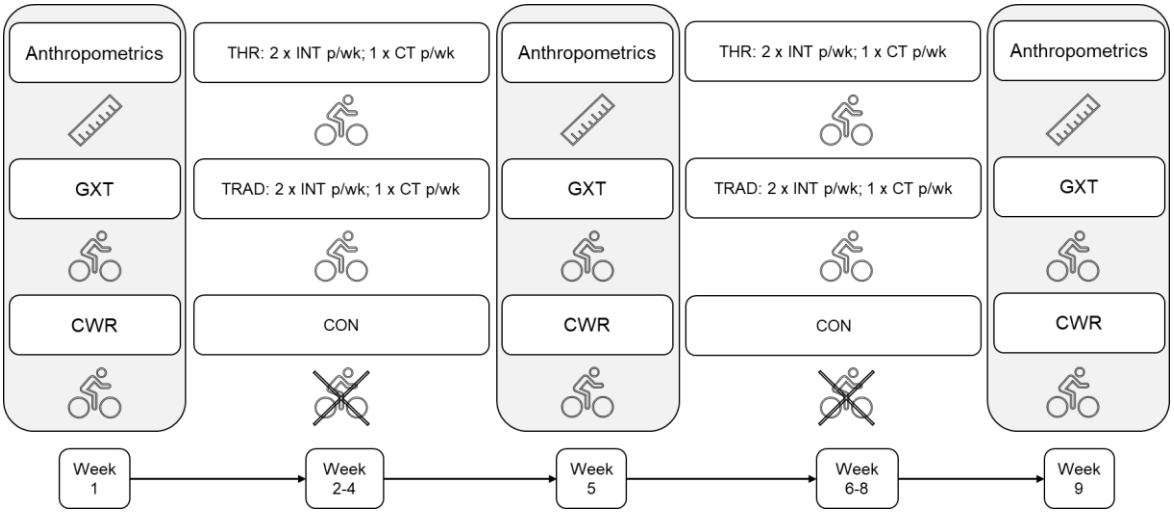

Figure 6.1. Overview of the study design. GXT: graded maximal ramp exercise test; CWR: constant work rate tests; THR: exercise training prescribed relative to critical power; TRAD: exercise training prescribed relative to maximum oxygen uptake; CON: non-exercising control group; INT: interval exercise; CT: continuous load exercise.

Pre-, mid-, and post-intervention measures

Graded maximal ramp exercise test (GXT):

Participants performed a GXT to determine peak oxygen uptake ($\dot{V}O_{2peak}$) and maximum heart rate (HR_{max}). Participants completed a standardised warm-up consisting of three min unloaded cycling at a self-selected cadence (60-100 rpm). Starting at 0 W, work rate increased continuously at rate of 30 $W \cdot min^{-1}$ until task failure. A ramp increment of 20 $W \cdot min^{-1}$ was used for individuals where an increment of 30 $W \cdot min^{-1}$ would likely elicit task failure below that of the intended test duration (approximately eight to twelve min; (Jamnick et al., 2018)). Task failure was defined as a decrease in cadence greater than 10 rpm below self-selected test cadence for more than 5 s. Breath-by-breath pulmonary gas exchange and heart rate (HR) data were collected continuously throughout the test and averaged over 10 s periods. $\dot{V}O_{2peak}$ was recorded as the highest mean $\dot{V}O_2$ during a 30 s period.

Constant work rate exercise tests (CWR):

To determine CP and work-prime (W′), participants performed three CWR (Muniz-Pumares et al., 2019). The first CWR was performed 45 min after the GXT on testing day one, and the second and third CWR trials were performed on testing day two separated by an intertrial recovery time of 45 min. Each CWR was intended to elicit task failure between 2-15 min, with at least a 5-min difference between the shortest and longest CWR duration (Jamnick et al., 2020; Jones et al., 2010). Participants completed a three min warm up at 25 W and at a self-selected cadence (60-100 rpm). Work rate was then increased to the target work rate and participants cycled to task failure at their self-selected cadence. As all CWR trials were severe-intensity, exhaustive bouts, and $\dot{V}O_2$ was measured throughout, the data from these trials were used to validate the $\dot{V}O_{2peak}$ achieved in the GXT. Calculation of CP and W′ were determined in accordance with General Methods (**Chapter 2**).

Training intervention

Both exercising groups undertook three training sessions per week for six weeks (**Figure 6.1**). Heart rate was recorded throughout all training sessions. The six weeks of training were split by the mid-intervention testing phase into two, three-week, training blocks. As $\dot{V}O_{2max}$ and CP were re-measured during the mid-intervention testing block, the new values were used to prescribe the subsequent TRAD and THR training sessions. All individuals performed two interval exercise sessions (INT) and one continuous exercise session (CT) per week. For CT sessions, individuals were prescribed 30, 40, and 45 min cycling in weeks one, two, and three, respectively, at 60% $\dot{V}O_{2max}$ in the TRAD group, and at 85% CP in the THR group. Increases in the duration of training sessions were subject to the previous CT session being completed, otherwise this session was performed until completion. In week four, individuals were told to complete the longest duration possible (i.e., 30, 40, or 45 min). If 45 min was completed, then this was repeated in weeks five and six otherwise sessions were increased as previously stated. For INT, individuals completed two sessions per week consisting of 5, 6, and 7 × 3 min intervals in weeks one, two, and three, respectively. Intervals were interspersed with 3 min of active recovery at 25 W. Progression of INT sessions were only implemented once the prescribed session was completed in full. In week four, individuals were told to complete as many intervals as possible (i.e., 5, 6, or 7 × 3 min). If all seven were completed, these were repeated in weeks five and six, otherwise the number of intervals were increased as previously stated. The intensity corresponded to 80% $\dot{V}O_{2max}$ in the TRAD group, and an intensity intended to elicit task failure in ~6 min were the bout to be continued to task failure in the THR group. This was calculated as follows:

$$PO_6 = (W' \div 360) + CP$$

Again, INT sessions were progressed only when the prescribed session was completed in full.

Statistical Analyses

Sample size calculation

Required sample size will be calculated given α, power, and an effect size calculated from the results presented in **Chapter 4** in which a large dataset of individual participant data was collated and categorised into training studies implementing exercise training prescribed relative to physiological thresholds or to a traditional intensity anchor.

Determination of $\dot{V}O_{2max}$ and study-specific technical error of measurement

In the GXT and CWR tests, $\dot{V}O_{2peak}$ was determined as the highest $\dot{V}O_2$ over a 30 s period. As $\dot{V}O_{2peak}$ was determined in both the GXT and CWR tests at each testing timepoint, the average $\dot{V}O_{2peak}$ across all tests was recorded and taken forward as the individuals overall $\dot{V}O_{2max}$. This helps account for the measurement error and day-to-day variability associated with $\dot{V}O_{2max}$ determination and increases the likelihood of observing true changes in the parameter thereafter. When only one measurement is taken, it is difficult to distinguish between true changes in $\dot{V}O_{2max}$ and those simply a manifestation of measurement error and day-to-day variability (Atkinson & Batterham, 2015; Hecksteden et al., 2018). Additionally, as $\dot{V}O_{2max}$ was determined from a minimum of four exhaustive bouts, the variation in $\dot{V}O_{2max}$ values across tests was calculated for each individual and averaged across groups to determine a study-specific technical error of measurement (TE).

Data analysis

Given the relatively small sample size used in the present study, a series of independent sample *t* tests were conducted to determine group changes in $\dot{V}O_{2max}$, CP, and W′ from testing timepoints (pre-, mid-, and post-intervention) within each group separately. Between-group comparisons were then made, again, using independent sample *t* tests. Of note, interpreting *p* values only may not always indicate a practical difference, for example a clinically important difference (Stapleton et al., 2009). Therefore, Cohen's *d* will also be considered and evaluated in addition to *p* values to identify potential between-group differences that may legitimately exist were a larger study implemented. Therefore, if medium (Cohen's d = 0.5-0.79) or large (Cohen's d = ≥0.8) effect sizes are observed these are identified in the results section.

The standard deviation of $\dot{V}O_{2max}$, CP, and W′ change scores were compared between THR and TRAD using the *F*-distribution. Taking into consideration the sample size of exercise groups in the current study, interpretation of the comparison between variances will consider both the *P*-value and the magnitude of the *F*-ratio as an indicator of the magnitude of difference. As the *F*-test is being used with exercise groups of n = 10, the *F*-statistic will be treated as an effect size estimator, and any ratio <0.33 will be considered of sufficient magnitude to indicate a lower change score variability in THR compared to TRAD that could potentially be significant with a larger sample (Chen & Chen, 2010).

The chi square test was used to compare the proportion of individuals demonstrating an increase in $\dot{V}O_{2max}$ >TE and >MID between intervention groups. Significance will be accepted when $P < 0.05$, however, given the small sample size, the effect size (Cohen's *d*) will also be considered (Stapleton et al., 2009). Linear regressions were conducted to determine any relationships between individual and training characteristics with changes in $\dot{V}O_{2max}$ and CP. An R^2 value of 0.20-0.39 = small, 0.40-0.59 = moderate, >0.60 = large association (Montgomery et al., 2021). Statistical analyses will be performed using SPSS (IBM Corp, Armonk, NY) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Individual characteristics

Table 6.1. Individual characteristics at pre-intervention testing phase.

Group	THR (n=10)	TRAD (n=10)	CON (n=7)
Sex (M, F)	7, 3	7, 3	5, 2
Age (years)	39 ± 15	35 ± 16	33 ± 7
Height (cm)	172 ± 11	171 ± 9	178 ± 6
Mass (kg)	73 ± 13	79 ± 20	79 ± 10
BMI ($kg \cdot m^2$)	24 ± 2	27 ± 6	25 ± 4

Data reported as mean ± SD. BMI: body mass index.

Sample size calculation

Required sample size was calculated to be n = 54, based on an α error of probability = 0.05, power (1 – β error probability) = 0.80, number of groups = 2 (given the primary objective in the present study is to compare the $\dot{V}O_{2max}$ change scores between THR and TRAD), number of measurements = 2 (given the primary comparison will be from pre- to post-intervention), and an effect size *f* = 0.197 calculated from the following data: mean and standard deviation of $\dot{V}O_{2max}$ change in threshold-based exercise studies 4.6 ± 2.9 $mL \cdot kg^{-1} \cdot min^{-1}$ (n = 343) and in traditionally prescribed exercise studies 3.4 ± 3.2 $mL \cdot kg^{-1} \cdot min^{-1}$ (n = 1105), this was associated with a Cohens *d* = 0.393 (**Chapter 4**). Given the number of individuals completing the exercise arms was n = 20, and therefore lower than the required sample size for a fully powered study (n = 54), the results of the present study are taken as preliminary findings, and thus, outcomes of statistical analyses are taken with caution.

Training characteristics

Training characteristics of exercise sessions are presented in **Figure 6.2** and **Figure 6.3**. In training weeks one to three, relative training intensity of INT was not different (8% [95% CI: -11 to 27%]; *p* = 0.202) between THR (126 ± 7% CP; 195 ± 57 W) and TRAD (134 ± 28% CP; 167 ± 48 W). In weeks four to six, relative training intensity of INT was also not different (7% [95% CI: -17 to 13%]; *p* = 0.403) between THR (119 ± 15% CP; 207 ± 55 W) and TRAD (123 ± 21% CP; 176 ± 59 W). In CT, from weeks one to three, relative training intensity of CT was no different (1% [95% CI: -10 to 11%]; *p* = 0.445) between THR (85 ± 0% CP; 131 ± 39 W) and TRAD (84 ± 16% CP; 108 ± 38 W). There was also no difference (8% [95% CI: -3 to 19%]; *p* = 0.081) in weeks four to six between THR (85 ± 0% CP; 146 ± 40 W) and TRAD (77 ± 17% CP; 111 ± 45 W).

Over the course of six weeks, there was no difference (-5% [95% CI: -20 to 11%]; *p* = 0.263) in the average training intensity of INT between THR (124 ± 6%) and TRAD (127 ± 24% CP). There was also no difference (4% [95% CI: -5 to 14%; *p* = 0.176) in the intensity of CT between THR (85 ± 0% CP) and TRAD (81 ± 14% CP).

Relative to peak power output attained in the GXT (PP_{GXT}), intensity of INT was no different (-3% [95% CI: -6 to 1%]; p = 0.051; Cohen's d = 0.8) between THR (75% PP_{GXT}) and TRAD (72% PP_{GXT}). In CT, relative to PP_{GXT}, the intensity of THR (52% PP_{GXT}) was higher (6% [95% CI: 2 to 10%]; p = 0.003) compared to TRAD (45% PP_{GXT}).

During the six weeks of INT training, there was no difference (2% [95% CI: -2 to 6%]; p = 0.147; Cohen's d = 0.5) in heart rate between THR (96% HR_{max}; 162 ± 12 b·min^{-1}) and TRAD (94% HR_{max}; 162 ± 22 b·min^{-1}). In CT, there was no difference (4% [95% CI: -5 to 12%]; p = 0.196) between THR (87% HR_{max}; 144 ± 13 b·min^{-1}) and TRAD (83% HR_{max}; 142 ± 20 b·min^{-1}).

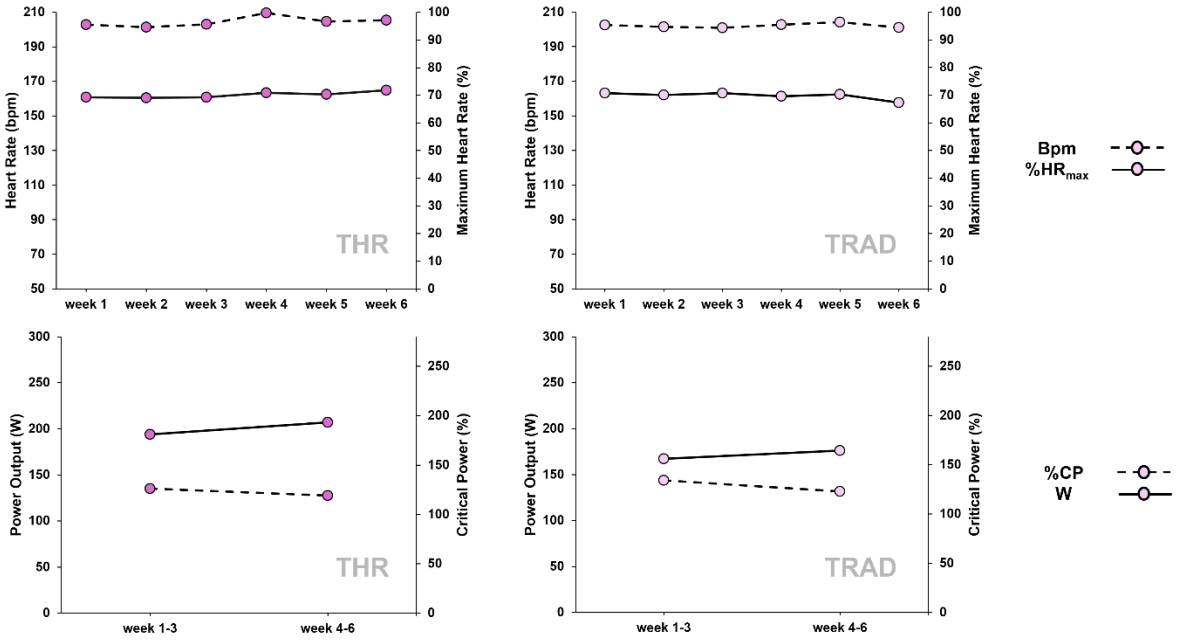

Figure 6.2. Training characteristics of INT in THR and TRAD. Top panel: average heart rate during working intervals expressed in absolute values (solid line; bpm) and relative to maximum heart rate (dashed line; %HR_{max}). Bottom panel: absolute power output (solid line; W) and relative to critical power (dashed line; %CP).

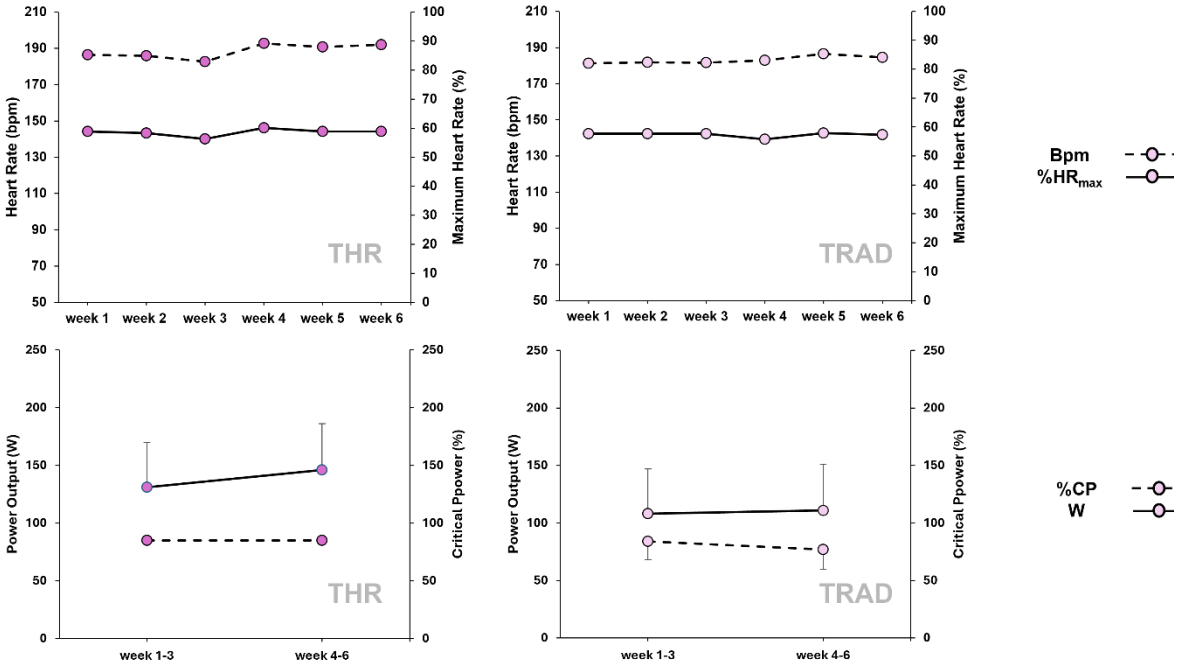

Figure 6.3. Training characteristics of CT in THR and TRAD. Top panel: average heart rate during working intervals expressed in absolute values (solid line; bpm) and relative to maximum heart rate (dashed line; $\%HR_{max}$). Bottom panel: absolute power output (solid line; W) and relative to critical power (dashed line; %CP).

Maximum oxygen uptake

Pre-intervention, dispersion of $\dot{V}O_{2max}$ values across GXT and CWR trials was 1.7, 1.6, and 1.5 $mL \cdot kg^{-1} \cdot min^{-1}$ for THR, TRAD, and CON, respectively. Taking their average, TE was determined as 1.6 $mL \cdot kg^{-1} \cdot min^{-1}$. This threshold along with the MID (3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) was used to determine true and meaningful changes in $\dot{V}O_{2max}$, respectively.

In THR, $\dot{V}O_{2max}$ was unchanged (p = 0.420) from pre- to mid-intervention (+5%; 1.5 ± 2.8 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI: -1.2 to 4.1]), but increased by +8% (2.8 ± 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI: 0.3 to 5.4]) from mid- to post-intervention (p = 0.028), and by +13% (4.3 ± 3.1 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI: 1.4 to 7.1]) from pre- to post-intervention (p = 0.005) (**Table 6.2**). Seven individuals (70%) demonstrated an increase in $\dot{V}O_{2max}$ >TE, of whom, five (50%) demonstrated an increase >MID (**Figure 6.4**).

In TRAD, $\dot{V}O_{2max}$ increased by +6% (1.9 ± 1.4 mL·kg^{-1}·min^{-1} [95% CI: 0.6 to 3.1]) from pre- to mid-intervention (p =0.005), was unchanged (p = 0.557) from mid- to post-intervention (+3% (1.1 ± 2.3 mL·kg^{-1}·min^{-1} [95% CI: -1.1 to 3.3]), and increased by +9% (2.9 ± 2.0 mL·kg^{-1}·min^{-1} [95% CI: 1.1 to 4.8]) from pre- to post-intervention (p = 0.004) (**Table 6.2**). Eight individuals (80%) demonstrated an increase in $\dot{V}O_{2max}$ >TE, of whom, three (30%) demonstrated an increase >MID (**Figure 6.4**).

In CON, $\dot{V}O_{2max}$ was unchanged (p > 0.05) from pre- to mid-intervention (0%; 0.0 ± 2.3 mL·kg^{-1}·min^{-1} [95% CI: -2.8 to 2.9]), mid- to post-intervention (+5%; 1.9 ± 2.6 mL·kg^{-1}·min^{-1} [95% CI: -1.3 to 5.2]), and from pre- to post-intervention (+5%; 2.0 ± 2.2 mL·kg^{-1}·min^{-1} [95% CI: -0.9 to 4.8]) (**Table 6.2**). Four individuals (57%) demonstrated an increase in $\dot{V}O_{2max}$ >TE, of whom, two (29%) demonstrated an increase >MID (**Figure 6.4**).

Between THR and TRAD, the difference in $\dot{V}O_{2max}$ change scores from pre- to post-intervention (1.3 mL·kg^{-1}·min^{-1} [95% CI: -1.1 to 3.8]) was non-significant (p = 0.135; Cohen's d = 0.5). Similarly, the difference in change scores between THR and CON (2.3 mL·kg^{-1}·min^{-1} [95% CI: -0.6 to 5.2]) was non-significant (p = 0.056; Cohen's d = 0.8), as was the difference between TRAD and CON (1.0 mL·kg^{-1}·min^{-1} [95% CI: -1.2 to 3.2]), which was also non-significant (p = 0.179; Cohen's d = 0.5).

There was no difference in the variability of $\dot{V}O_{2max}$ change scores between THR and TRAD (F = 2.342; p = 0.221). There was also no difference in the proportion of individuals demonstrating a change in $\dot{V}O_{2max}$ >TE (p = 0.606) or >MID (p = 0.361) between THR and TRAD.

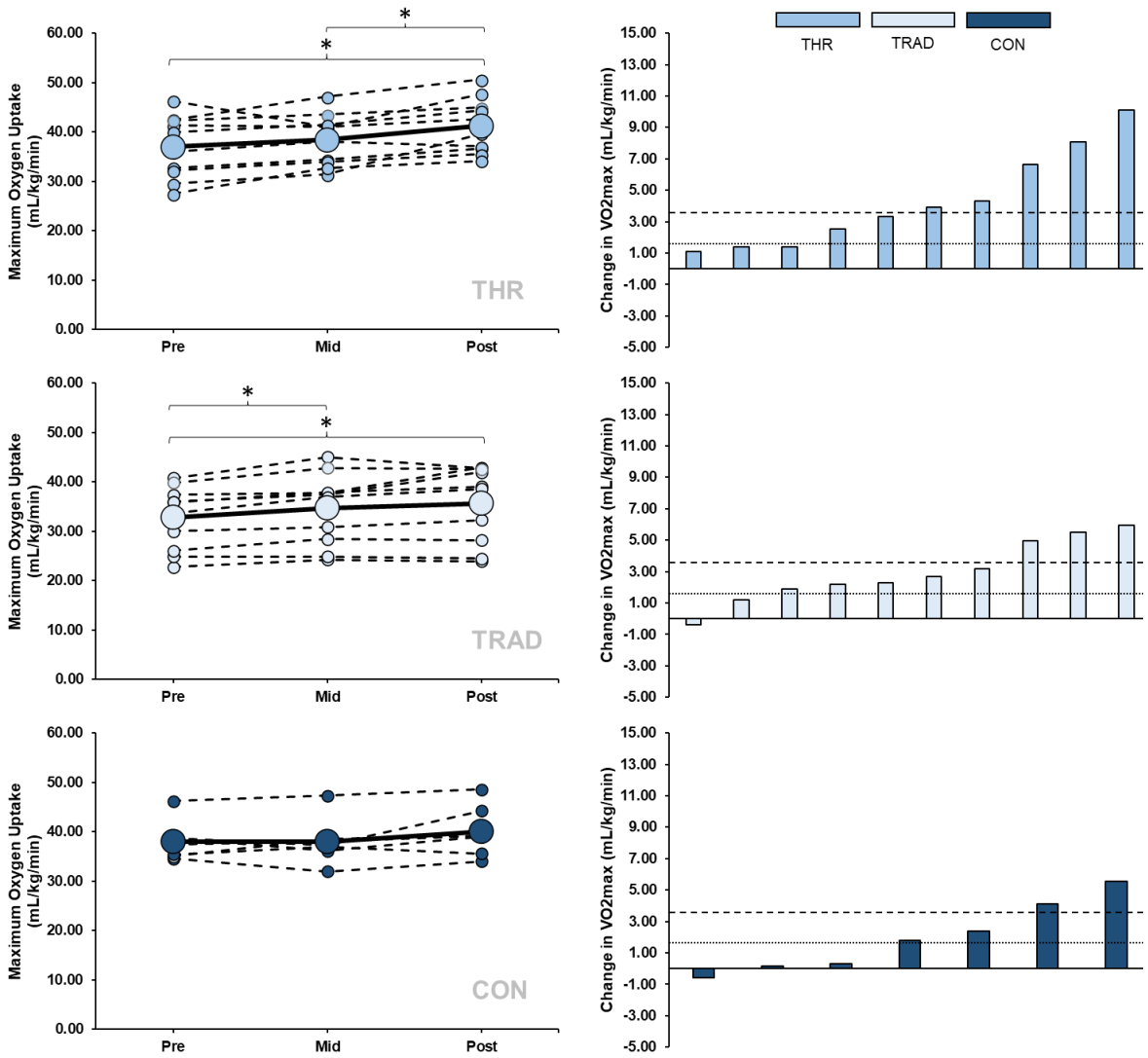

Figure 6.4. Left panel: group mean (solid line) and individual change profiles (dashed lines) in maximum oxygen uptake ($\dot{V}O_{2max}$) in THR (Top panel), TRAD (Middle panel), and CON (Bottom panel) at pre-, mid-, and post-intervention. Right panel: individual changes in $\dot{V}O_{2max}$ from pre- to post-intervention. Dotted and dashed lines represent a change in $\dot{V}O_{2max}$ of 1.6 $mL \cdot kg^{-1} \cdot min^{-1}$ (TE) and 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ (MID), respectively. * Represents a significant difference ($p < 0.05$) from timepoints.

Table 6.2. Change in variables determined during graded maximal ramp exercise tests and constant work rate tests at pre-, mid-, and post-intervention.

	THR			**TRAD**			**CON**		
	PRE	MID	POST	PRE	MID	POST	PRE	MID	POST
GXT									
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	36.5 ± 7.7	39.2 ± 4.8	42.9 ± 6.3	32.9 ± 6.1	34.9 ± 7.5	36.5 ± 8.1	36.9 ± 4.5	38.9 ± 4.7	39.8 ± 5.4
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.7 ± 0.8	2.9 ± 0.7	3.1 ± 0.8	2.5 ± 0.6	2.7 ± 0.6	2.8 ± 0.7	2.9 ± 0.5	3.1 ± 0.4	3.2 ± 0.6
HR_{max} ($b \cdot min^{-1}$)	171 ± 14	170 ± 9	171 ± 11	172 ± 20	167 ± 21	168 ± 24	180 ± 13	177 ± 14	172 ± 19
PO_{peak} (W)	260 ± 66	273 ± 66	289 ± 74	230 ± 63	242 ± 66	248 ± 71	282 ± 49	292 ± 55	289 ± 54
CWR									
CP (W)	155 ± 46	171 ± 47	181 ± 50	133 ± 54	147 ± 56	154 ± 53	172 ± 35	188 ± 29	190 ± 32
CP ($W \cdot kg^{-1}$)	2.1 ± 0.5	2.4 ± 0.6	2.5 ± 0.5	1.7 ± 0.5	1.9 ± 0.6	1.9 ± 0.6	2.2 ± 0.4	2.4 ± 0.3	2.4 ± 0.3
CP (%PO_{peak})	59 ± 5	62 ± 5	62 ± 6	56 ± 11	59 ± 9	62 ± 9	61 ± 7	65 ± 4	66 ± 3
W′ (kJ)	14.1 ± 5.2	12.9 ± 5.2	14.1 ± 5.9	13.3 ± 5.6	12.8 ± 4.3	13.6 ± 4.8	15.7 ± 4.8	15.8 ± 5.9	14.3 ± 5.1
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	37.2 ± 5.9	38.3 ± 5.5	40.8 ± 5.5	32.7 ± 6.6	34.5 ± 7.1	35.4 ± 7.7	37.2 ± 4.5	37.8 ± 4.8	40.0 ± 4.9
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.7 ± 0.7	2.8 ± 0.7	2.9 ± 0.7	2.5 ± 0.7	2.7 ± 0.7	2.7 ± 0.7	2.9 ± 0.4	2.9 ± 0.5	3.1 ± 0.5
HR_{max} ($b \cdot min^{-1}$)	170 ± 11	170 ± 8	170 ± 9	171 ± 19	168 ± 21	169 ± 19	177 ± 12	178 ± 13	176 ± 14

	THR			TRAD			CON		
	PRE	MID	POST	PRE	MID	POST	PRE	MID	POST
$\dot{V}O_{2max}$									
$mL \cdot kg^{-1} \cdot min^{-1}$	37.1 ± 6.3	38.5 ± 5.2	41.3 ± 5.6	32.7 ± 6.4	34.6 ± 7.2	35.7±7.7	38.0 ± 4.0	38.0 ± 4.6	40.0 ± 5.0
$L \cdot min^{-1}$	2.7 ± 0.7	2.8 ± 0.7	3.0 ± 0.8	2.5 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	3.0 ± 0.4	3.0 ± 0.4	3.1 ± 0.5

GXT: graded maximal ramp exercise test; $\dot{V}O_{2peak}$: peak oxygen uptake; $\dot{V}O_{2max}$: maximum oxygen uptake; HR_{max}: maximum heart rate; PO_{peak}: peak power output; CWR: constant work rate tests; CP: critical power; PRE: pre-intervention tests; MID: mid-intervention tests; POST: post-intervention tests; THR: threshold-based exercise training; TRAD: traditionally prescribed exercise training; CON: non-exercising control group. Data are mean ± SD.

Critical power

Changes in CP and W′ are presented in **Table 6.2**. In THR, CP increased by +12% (17 ± 14 W [95% CI: 3 to 30 W]) from pre- to mid-intervention (p = 0.017), was unchanged (p = 0.242) from mid- to post-intervention (+6%; 10 ± 16 W [95% CI: -5 to 24 W]), and increased by +18% (26 ± 17 W [95% CI: 10 to 42 W]) from pre- to post-intervention (p = 0.003). At all timepoints W′ was unchanged (p > 0.05).

In TRAD, CP increased (p = 0.027) by +12% (14 ± 14 W [95% CI: 2 to 27 W]) from pre- to mid-intervention, was unchanged (p = 0.142) from mid- to post-intervention (+7%; 7 ± 10 W [95% CI: -2 to 16 W]), and increased (p = 0.004) by +20% (21 ± 15 W [95% CI: 8 to 35 W]) from pre- to post-intervention. At all timepoints W′ was unchanged (p > 0.05). In CON, CP and W′ was unchanged (p > 0.05) at all timepoints.

There was no difference (p = 0.252) between THR and TRAD in CP change scores (5 W [95% CI: -10 to 20 W]) from pre- to post-intervention. The difference between THR and CON (14 W [95% CI: -4 to 31 W]) was non-significant (p = 0.057; Cohen's d = 0.8). The difference between TRAD and CON (7 W [95% CI: -7 to 25 W]) was non-significant (p = 0.126; Cohen's d = 0.5).

Relationship between individual and training characteristics and changes in maximum oxygen uptake

As illustrated in **Figure 6.5**, no significant relationships were observed between the relative change in $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) and individual and training characteristics. Additionally, no significant relationships (p > 0.05) were observed when data was split into separate THR and TRAD datasets.

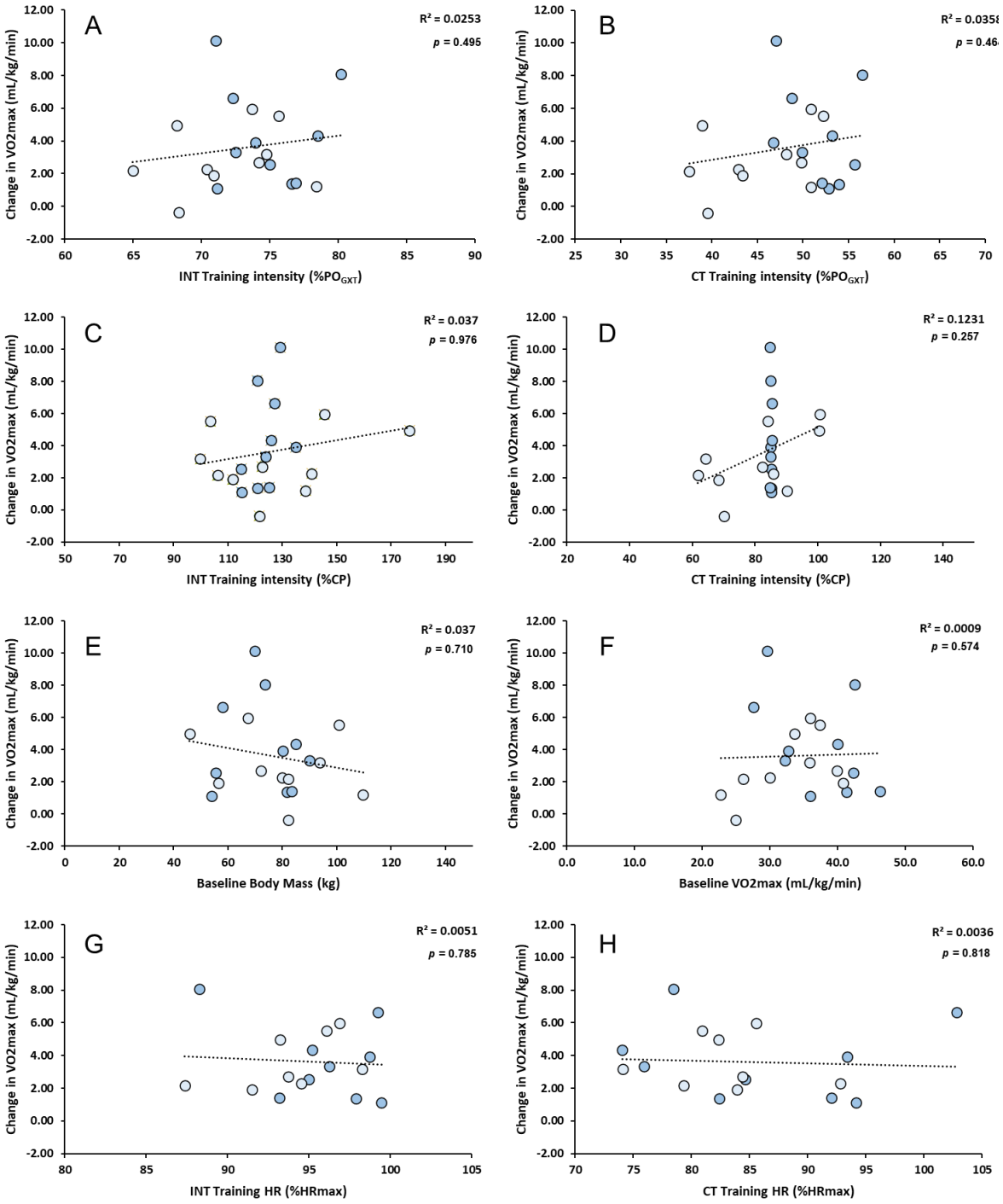

Figure 6.5. Relationship between relative training intensity expressed relative to peak power output in GXT (%PO_{GXT}) in INT (A) and in CT (B), relative training intensity expressed relative to critical power (CP) in INT (C) and in CT (D), baseline body mass (E), baseline $\dot{V}O_{2max}$ (F), relative training HR in INT (G), and relative training HR in CT (H), with the change

in $\dot{V}O_{2max}$ from pre- to post-intervention. Individuals in THR presented in dark blue, and TRAD in light blue.

Relationship between training characteristics and changes in critical power

As illustrated in **Figure 6.6**, no relationships were observed between the change in CP and the characteristics of training, apart from a small relationship between the relative training intensity of INT and percentage change in CP (R^2 = 0.255, p = 0.022). Additionally, no significant relationships (p > 0.05) were observed when data was split into separate THR and TRAD datasets.

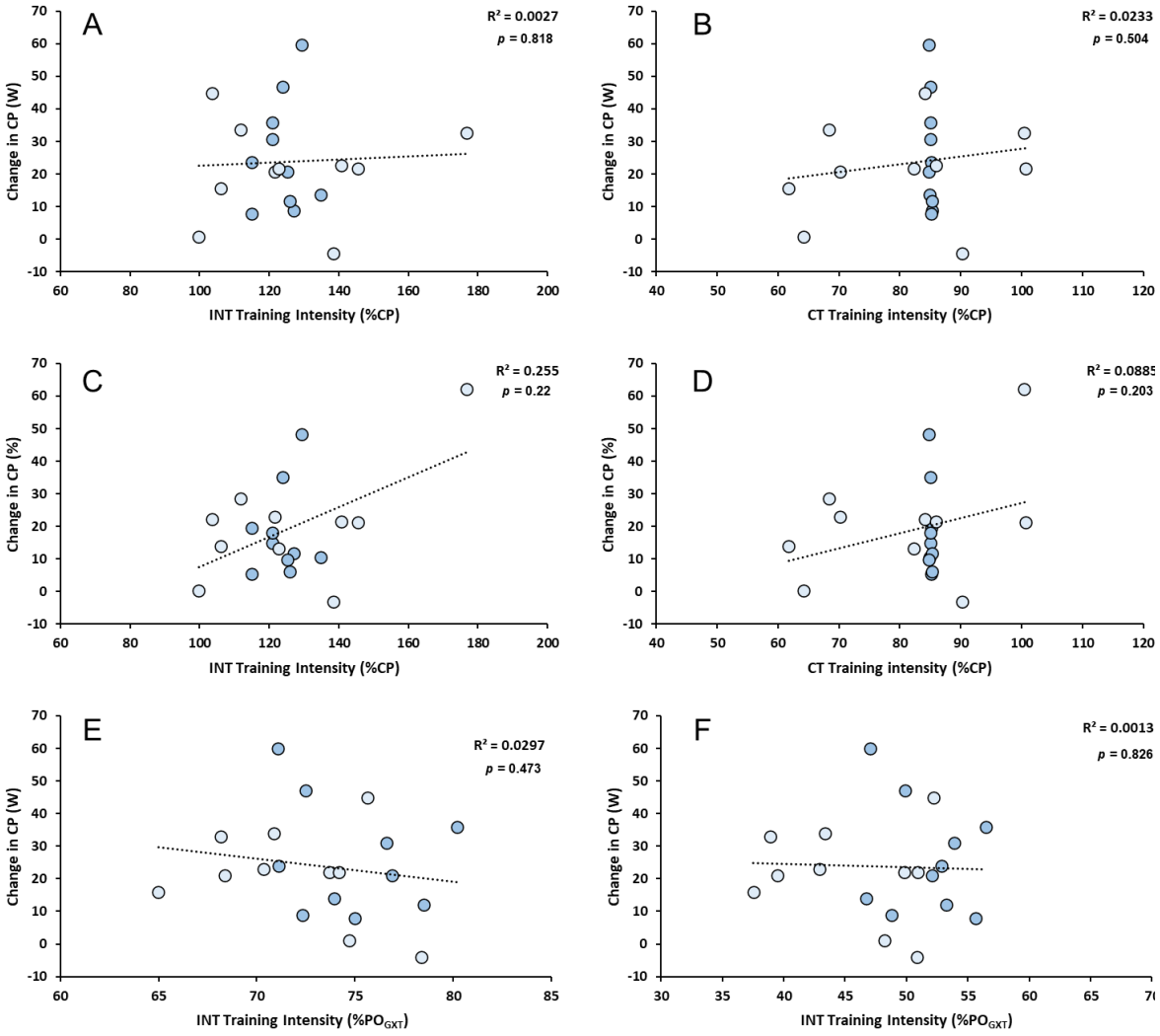

Figure 6.6. Relationship between training intensity, expressed relative to CP, in INT (A) and in CT (B) and change in CP (W). Relationship between training intensity in INT (C) and in CT (D) and change in CP (%). Relationship between training intensity, expressed relative to peak power output in GXT (PO_{GXT}), in INT (A) and in CT (B) and change in CP (W).

DISCUSSION

This study compares changes in physiological parameters following exercise training prescribed relative to $\dot{V}O_{2max}$, and to CP, a marker of intensity demonstrated to be superior in normalising exercise intensity among individuals. Six weeks of training comprised of two INT and one CT session a week increased $\dot{V}O_{2max}$ by 11% (3.6 ± 2.6 mL·kg^{-1}·min^{-1}). When training was prescribed relative to CP and to $\dot{V}O_{2max}$, $\dot{V}O_{2max}$ increased by 13% (4.3 ± 3.1 mL·kg^{-1}·min^{-}

^{1}) and 9% (2.9 ± 2.0 mL·kg^{-1}·min^{-1}), respectively. The proportion of individuals demonstrating an increase in $\dot{V}O_{2max}$ >MID (and >TE) was 50% (70%), 30% (80%), and 29% (57%) in THR, TRAD, and CON, respectively.

Magnitude of change in $\dot{V}O_{2max}$

Whilst $\dot{V}O_{2max}$ increased as a result of both training programmes, there was no significant difference between the magnitude of $\dot{V}O_{2max}$ change scores between THR and TRAD. It is worth noting that the small sample size of the present study limits the estimation of the magnitude of difference between groups as indicated by the 95% confidence intervals presented herein. As such, effect sizes (Cohen's *d*) were considered in addition to *p* values to elucidate differences that might legitimately reveal were a larger study conducted. For example, no significant difference ($p > 0.05$) was observed between $\dot{V}O_{2max}$ change scores in THR and TRAD (1.3 mL·kg^{-1}·min^{-1} [95% CI: -1.1 to 3.8]) yet a medium effect size was observed (Cohen's $d = 0.5$). Should a difference indeed exist between the approaches of exercise prescription scrutinised herein, it could range from very small to as much as 3.8 mL·kg^{-1}·min^{-1} with a central tendency in the order of 1.3 mL·kg^{-1}·min^{-1}.

Additionally, whilst the mean difference in $\dot{V}O_{2max}$ change scores between exercise groups and CON were non-significant ($p > 0.05$), the mean difference between THR and CON and TRAD and CON are worth noting. Given TRAD demonstrated a +9% increase in $\dot{V}O_{2max}$, when you consider the mean difference in $\dot{V}O_{2max}$ change scores between TRAD and CON (1.0 mL·kg^{-1}·min^{-1}), the effect of the training intervention appears to be somewhat similar to that of CON (+5%). In comparison, given the difference in $\dot{V}O_{2max}$ change scores between THR and CON (2.3 mL·kg^{-1}·min^{-1}) and the effect size (Cohen's $d = 0.8$), the THR training programme appears to be more effective than the TRAD when compared to the changes observed in CON despite the differences being non-significant ($p > 0.05$). Furthermore, in both the TRAD and CON groups, the proportion of individuals demonstrating a change in $\dot{V}O_{2max}$ >MID was ~30%

compared to 50% in THR, again, indicating that the added benefit of TRAD over CON was perhaps not meaningful whereas that of THR appears more apparent.

The changes in $\dot{V}O_{2max}$ following THR (+13%) align well with those previously reported following six weeks of interval and/or continuous exercise training. For example, taking only the six-week studies from those reported elsewhere (Milanović et al., 2015), and in **Chapter 5** the average increase in $\dot{V}O_{2max}$ was ~13%. In the present study, the TRAD training programme falls short of this change and highlights a potential superiority of the CP-based approach. It is previously shown that using CP as an anchor of intensity creates a more homogenous exercise stimulus among individuals compared to when intensity is prescribed relative to $\dot{V}O_{2max}$ (**Chapter 5**), potentially explaining the present preliminary findings presented herein. In **Chapter 5**, the variability in acute physiological responses to exercise, and exercise tolerance, was lower when acute bouts of exercise were prescribed relative to CP. As such, using CP better controlled exercise intensity, ensuring exercise sessions were undertaken in the intended intensity domain, important given each domain is associated with domain-specific homeostatic perturbations (Black et al., 2017). If individuals undertaking the same prescribed training are incidentally exercising in different intensity domains to one another, as is a common issue when training is prescribed relative to $\dot{V}O_{2max}$ (Scharhag-Rosenberger et al., 2010), the physiological demand experienced by each individual may be markedly different. It is plausible, but currently unknown, that the acute response heterogeneity elicited by traditional approaches manifests as chronic heterogeneity regarding changes in physiological parameters. This may explain the common observation of large individual variability in training-induced adaptations following training interventions which, coincidentally, predominantly implement traditional approaches to exercise intensity prescription (Bonafiglia et al., 2022; Milanović et al., 2015; Williams et al., 2019). If true, a consequence of this might be that the outcomes of traditionally prescribed exercise studies are in some cases unknowingly influenced or confounded by a poorly controlled exercise

programme. This however needs elucidating on with much larger studies that have sufficient power to draw conclusions regarding individual response variability (Swinton, 2023).

When compared to volume-matched exercise training prescribed relative to heart rate reserve (an example of a traditional prescription approach), prescribing exercise intensity relative to alternative physiological thresholds (i.e., ventilatory thresholds) has previously been shown to induce greater improvements in $\dot{V}O_{2max}$ and a greater proportion of individuals attaining increases in $\dot{V}O_{2max}$ beyond a study-specific response threshold (Byrd et al., 2019; Dalleck et al., 2016; Weatherwax et al., 2019; Wolpern et al., 2015a). As such, the advocation of using threshold-based approaches to exercise prescription has increased (**Chapter 2**). Whilst the preliminary findings of the present study point towards the direction of a superiority in threshold-based approaches, this requires further exploration before more conclusive conclusions can be made.

In TRAD, $\dot{V}O_{2max}$ increased by 1.89 $mL \cdot kg^{-1} \cdot min^{-1}$ from pre- to mid-intervention but only by 1.05 $mL \cdot kg^{-1} \cdot min^{-1}$ from mid- to post-intervention. Following the mid-intervention testing phase, the new training stimulus appears to have been less effective in eliciting further increases in $\dot{V}O_{2max}$ compared to THR whereby marked increases were demonstrated from mid- to post-intervention (+2.82 $mL \cdot kg^{-1} \cdot min^{-1}$). Were the training programme extended, it would have been interesting to determine whether a further plateau in $\dot{V}O_{2max}$ was evident in TRAD and whether this plateau was also experienced in THR, or whether further gains were in fact realised thereafter. Additionally, were it feasible to do so, it would have been interesting to randomise those experiencing no, or a minimal change in their $\dot{V}O_{2max}$ from mid- to post-intervention into an extended programme where they either continued with their current programme or switched to the alternative programme (i.e., TRAD to THR, and vice versa). This would elucidate on whether changing the stimulus, created by the prescription approach, has a differing effect among individuals. This would provide useful information regarding the optimisation and personalisation of exercise intensity prescription for different individuals.

Variability in $\dot{V}O_{2max}$ change scores

Contrary to that expected, there was no difference in the variability of $\dot{V}O_{2max}$ change scores between THR and TRAD. A methodological factor which may explain these findings, at least in part, may concern the chosen exercise intensities for TRAD. In **Chapter 5**, greater variability among individuals in acute physiological responses and exercise tolerance were observed following INT prescribed at 85% $\dot{V}O_{2max}$ compared to 110% CP. However, only 20% of individuals were able to finish the INT session prescribed at 85% $\dot{V}O_{2max}$ where the completed duration of the session ranged between 17-100%. In contrast, 100% of individuals were able to complete the INT session at 110% CP. In the present study, the intensity of INT in TRAD was reduced to 80% $\dot{V}O_{2max}$ to increase the likelihood of training sessions being more attainable, feasible, and worthwhile for participants. Despite a reduction in the intensity of INT sessions, it was speculated that just a 5% reduction would still elicit marked variability in the exercise stimulus, however this does not seem to be the case. In fact, the intensity of INT in both THR and TRAD was incidentally very similar (124% vs 127% CP, respectively). Were 85% $\dot{V}O_{2max}$ prescribed, shown to elicit a more heterogenous exercise stimulus among individuals, differences in the variability of $\dot{V}O_{2max}$ change scores may have been observed.

Additionally, in **Chapter 5**, when prescribed 20 min of exercise at 75% $\dot{V}O_{2max}$, the duration of the session completed ranged between 387-1200 s, with only 30% able to complete the full task (i.e. 1200 s of exercise). Considering the response to the above prescribed exercise sessions at 75% $\dot{V}O_{2max}$ and 85% $\dot{V}O_{2max}$ in **Chapter 5**, and 80% $\dot{V}O_{2max}$ in the present study, this highlights the issue of using the %$\dot{V}O_{2max}$ approach whereby large variations in exercise tolerance can be expected despite using the recommended intensities (64-90% $\dot{V}O_{2max}$) for eliciting heavy (or vigorous) intensity exercise (American College of Sports Medicine, 2017). Fortunately, for the current cohort, 80% $\dot{V}O_{2max}$ was in fact appropriate for completing the prescribed INT sessions.

Changes in CP and W′

Both THR and TRAD programmes were effective in eliciting significant increases in CP (18% and 20%, respectively). However, no changes in W′ were observed in either group which is a common finding (Collins et al., 2022; Gaesser & Wilson, 1988; Griffin et al., 2018; Thomas et al., 2020). Changes of ~13-16% and ~15-28% in CP have previously been reported following continuous and interval-based exercise training programmes, respectively, with no additional change in W′ (Collins et al., 2022; Gaesser & Wilson, 1988). Thus, those observed in the present study provide further evidence of increased CP with training occurs with no concomitant change in W′. Whilst changes in $\dot{V}O_{2max}$ are central to the present study, increases in CP are also important. Increasing CP is a key attribute for improved endurance performance, whereby increasing ones CP allows higher intensities of exercise to be sustained for longer periods of time before fatigue. In turn, from an endurance performance perspective, it can be more telling to monitor and evaluate changes in CP than changes in $\dot{V}O_{2max}$ (Podlogar et al., 2022), particularly as differences in CP can be used to differentiate performance among individuals with relatively homogenous characteristics such as $\dot{V}O_{2max}$ (Loftin & Warren, 1994) and that $\dot{V}O_{2max}$ in world-class marathon runners have been reported to differ by up to 22 $mL \cdot kg^{-1} \cdot min^{-1}$ (Jones et al., 2020).

Recently, Collins et al. (2022) found that individuals training at a higher intensity when expressed relative to their CP as opposed to their $\dot{V}O_{2max}$, as is commonly the case, experienced the greater gains in CP. This relationship was not observed in the present study. However, the study of Collins et al. (2022), had an additional two weeks of training which may have allowed more time for adaptations and changes in performance to manifest. It would have been interesting to determine whether the results would have been more consistent with that of Collins et al. (2022), were a longer training period implemented in the present study. Despite no such relationship being observed in the present study (**Figure 6.6**), the present findings regarding the combination of greater changes in $\dot{V}O_{2max}$ and CP following a THR

exercise training, compared to those reported following TRAD, all point towards the notion that exercise may be more effectively prescribed relative to CP than to $\dot{V}O_{2max}$.

Experimental considerations

Were a large sample achieved, it would have been interesting to determine whether there were sex differences regarding training-induced changes in $\dot{V}O_{2max}$ and to explore factors explaining such changes, however, a greater number of both males and especially females was warranted to draw on such conclusions. Whilst recent evidence indicates that there are no sex differences regarding changes in $\dot{V}O_{2max}$ specifically following high intensity interval training (Lock et al., 2023), it is also shown that females typically experience lesser gains in $\dot{V}O_{2max}$ compared to males (Diaz-Canestro & Montero, 2019). This may be explained by a series of methodological and biological factors (**Chapter 2**), but notably, the predominant pathways of adaptation may differ somewhat between sexes (Ansdell et al., 2020). For example, females tend to display greater changes in peripheral factors such as enhanced oxygen extraction and mitochondrial respiration (Cardinale et al., 2018; Montero et al., 2018), changes which typically manifest over a longer period of time compared to central adaptations (i.e., blood volume) (Lundby et al., 2017), changes experienced more so by males(Ansdell et al., 2020). If a larger sample of male and females was feasible, it would be interesting to have determined whether the time course of changes in $\dot{V}O_{2max}$ differed between sexes, and were more equipment accessible, whether the physiological changes driving subsequent changes in $\dot{V}O_{2max}$ also differed between sexes.

Of note, we conducted two CWR tests per day during the testing phases in order to fit all required tests in the space of a week as this was most practical for participants. It has previously been shown that as little as 30 min of inter-test recovery time is required to minimise the effect of previous maximal exercise efforts on the determination of CP (Triska et al., 2021). However, as noted by Collins et al. (2022), the impact of previous same-day CWR tests on subsequent W′ determination is unclear. To err on the side of caution, and to implement a testing format that was realistic for participants, a 45 min inter-test recovery period was chosen

in the present study. It is worth pointing out, however, that endurance trained individuals were used in the study of Triska et al. (2021), and thus, compared to the non-endurance trained nature of individuals participating in the present study, it may be that CWR tests were impacted more so by the previous exhaustive trials. However, as the format of GXT and CWR tests remained consistent during each testing phase, the effect of previous exhaustive exercise also remained consistent between pre-, mid-, and post-intervention testing.

Considering the standard deviation of $\dot{V}O_{2max}$ change scores between intervention groups (THR: 3.1; TRAD: 2.0; CON: 2.2 $mL \cdot kg^{-1} \cdot min^{-1}$) highlights the uncertainty and complexity of evaluating $\dot{V}O_{2max}$ change scores regarding individual response variability. Given that the standard deviation of change scores in TRAD is less than that in the CON group, were only one test conducted at each timepoint, it would have been difficult to distinguish true changes in $\dot{V}O_{2max}$ with that simply a result of measurement error and day-to-day variability (Atkinson & Batterham, 2015). However, as a minimum of four exhaustive bouts were completed at each testing timepoint, in which a maximum measure of $\dot{V}O_{2peak}$ was attained (Poole & Jones, 2017), a more conservative measure of $\dot{V}O_{2max}$ could be attained. This in turn increases the likelihood that observed changes in $\dot{V}O_{2max}$ were indeed 'true' changes. As the standard deviation of $\dot{V}O_{2max}$ change scores was higher in THR than that of CON, this may point towards evidence of an interaction effect of the individual and the training (i.e., trainability). However, much larger sample sizes are needed to rigorously investigate individual response variability and methods of doing so remain equivocal (Swinton, 2023).

CONCLUSION

Six-week training programmes comprised of interval and continuous exercise sessions prescribed relative to CP and to $\dot{V}O_{2max}$ were effective in increasing $\dot{V}O_{2max}$. The increase in $\dot{V}O_{2max}$ following THR appears to be superior to that of TRAD, with a larger proportion of individuals experiencing a change in $\dot{V}O_{2max}$ >MID, however, further exploration with larger samples of males and females is warranted to elucidate on this.

PERSPECTIVE

If results persisted in this manner, this could elucidate on the most effective means of exercise intensity prescription for future training programmes given that the dominant method of controlling exercise intensities is to prescribe intensity relative to a traditional intensity anchor. These preliminary findings are interesting and warrant further exploration via larger well-powered studies. If the number of individuals experiencing what can be considered a meaningful increase in $\dot{V}O_{2max}$ (≥3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) is greater following THR training programmes, this could have profound implications for a variety of populations where increasing $\dot{V}O_{2max}$ is vital for performance and/or health-related goal.

CHAPTER 7 – GENERAL DISCUSSION

This thesis aimed to compare and evaluate the acute and chronic responses to exercise prescribed relative to traditional anchors of intensity, and to physiological thresholds. Currently, exercise training programmes (e.g., those implemented in research studies) are predominantly prescribed relative to traditional markers of intensity such as maximum oxygen uptake ($\dot{V}O_{2max}$) or maximum heart rate (HR_{max}). However, among individuals, such approaches are consistently shown to elicit marked variability in acute responses despite undertaking the 'same' prescribed exercise bouts (Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010). Whilst undoubtedly effective for some, the ability to control and normalise exercise intensity among a variety of individuals using this approach is poor. It was thus speculated that this may, in part, contribute to the commonly observed $\dot{V}O_{2max}$ response variability demonstrated among individuals following a period of exercise training. Tackling this heterogeneity in $\dot{V}O_{2max}$ change scores, and specifically, reducing the number of individuals experiencing un-meaningful changes in $\dot{V}O_{2max}$ following a period of training, is important given that this has implications for a variety of populations. For example, there exists a strong association between cardiorespiratory fitness (i.e., $\dot{V}O_{2max}$) and mortality risk (R. Ross et al., 2016), fitness for surgery and postoperative outcomes (Richardson et al., 2017), and endurance performance (Bassett & Howley, 2000). Thus, ensuring changes in $\dot{V}O_{2max}$ are indeed experienced following training can have marked implications for health and sporting performance.

Prescribing exercise intensity relative to physiological thresholds, which, unlike traditional approaches, accounts for metabolic differences among individuals, is shown to create a more homogeneous exercise stimulus and better control exercise within intended exercise intensity domains. In turn, using a threshold-based approach may be a more appropriate means of prescribing exercise intensity for training programmes, reducing the likelihood of exercise being undertaken in un-intended intensity domains or the elicited exercise stimulus being under- or over-stimulating for a given individual.

Therefore, the aim of the first experimental chapter (**Chapter 4**) was to investigate how the approach used to prescribe exercise intensity influences the magnitude and variability of changes in $\dot{V}O_{2max}$ following exercise training. This was done by systematically meta-analysing, using individual participant data (IPD), $\dot{V}O_{2max}$ change scores following traditionally prescribed and threshold-based exercise training. The findings of **Chapter 4** demonstrated that the magnitude of change in $\dot{V}O_{2max}$, and the number of individuals achieving meaningful changes in $\dot{V}O_{2max}$, was greater following threshold-based exercise training compared to traditionally prescribed exercise training.

In light of this, it was of interest to determine whether the reason for this superiority in threshold-based exercise training was attributable to the elicitation of the exercise stimulus at the acute level. Therefore, **Chapter 5** aimed to compare the variability in exercise tolerance and the acute physiological responses elicited by acute bouts of exercise prescribed relative to critical power (CP) and the gas exchange threshold (GET), and to $\dot{V}O_{2max}$. This study aimed to detect whether prescribing moderate, heavy and severe intensity exercise using $\dot{V}O_{2max}$ (traditional approach) or GET and CP (Threshold-based approach) truly elicited moderate, heavy, and severe intensity exercise among individuals. Of note, CP was used throughout the thesis to represent the boundary between the heavy and severe intensity domains. Whilst other physiological thresholds can be used to approximate this transitional boundary (i.e., maximal lactate steady state (MLSS) and respiratory compensation point (RCP)), mounting evidence supports the use of CP particularly due its capability of delineating between steady and non-steady state exercise (Nixon et al., 2021; Poole et al., 2020).

Subsequently, based on the findings in **Chapter 5** whereby greater homogeneity in individual responses at the acute level were observed following threshold-based exercise, **Chapter 6** aimed to explore the responses at the chronic level (i.e., adaptations to training) following a period of exercise training prescribed relative to CP and to $\dot{V}O_{2max}$. The findings of **Chapter 6** indicated that changes in $\dot{V}O_{2max}$ and the number of individuals experiencing meaningful changes in $\dot{V}O_{2max}$ was greater when exercise training was prescribed relative to CP, further

supporting the use of threshold-based exercise prescription and advocate the use of CP as the primary anchor of exercise intensity.

Overall, the findings presented within this thesis provide evidence pertaining towards the superiority of using physiological thresholds to prescribe exercise intensity for exercise training programmes. Using such approaches appears to better normalise exercise intensity among individuals, and increases the probability that an individual will experience the desired benefits of exercise.

SUMMARY OF MAIN FINDINGS

Chapter 4

In this chapter a large scale (n = 1544) meta-analysis, using IPD, was conducted comparing $\dot{V}O_{2max}$ change scores between studies implementing traditionally prescribed and threshold-based exercise training. To do this, two databases of IPD were created comprised of controlled and non-controlled studies. In controlled studies, change in $\dot{V}O_{2max}$ was greater following threshold-based exercise training and a greater proportion of individuals demonstrated an increase in $\dot{V}O_{2max}$ above a minimum important difference. There was, however, no difference in the variability of $\dot{V}O_{2max}$ change scores between threshold-based and traditionally prescribed exercise training. In the analyses of non-controlled studies, $\dot{V}O_{2max}$ change scores were also greater in studies implementing threshold-based training programmes compared to those implanting traditionally prescribed training programmes. However, again, there was no difference in the variation of such changes. These findings indicate that superior gains in $\dot{V}O_{2max}$ are attained following exercise training prescribed relative to physiological thresholds compared to when traditional anchors of exercise intensity are used. Furthermore, a greater number of individuals can be expected to demonstrate an increase in $\dot{V}O_{2max}$ beyond that of a minimum important difference.

Chapter 5

Considering the results of **Chapter 4**, reasons for this superiority were sought, focussing on the ability of intensity prescription methods to control and normalise exercise intensity among individuals. In this experimental chapter, the variability in exercise tolerance and physiological responses to acute bouts of exercise prescribed relative to GET and CP, and relative to $\dot{V}O_{2max}$ were compared. There were no differences in exercise tolerance or acute response variability between moderate intensity exercise sessions prescribed relative to GET or to $\dot{V}O_{2max}$. All individuals completed the heavy intensity exercise session prescribed relative to GET and CP, whereas only 30% of individuals were able to complete the session when it was prescribed relative to $\dot{V}O_{2max}$. Notably, work rates associated with heavy intensity exercise prescribed relative to GET and CP were below CP. When heavy intensity exercise was prescribed relative to $\dot{V}O_{2max}$, work rates were below CP for only 30% of individuals. All individuals completed severe intensity interval sessions prescribed relative to CP whereas only 20% completed the interval sessions when prescribed relative to $\dot{V}O_{2max}$. Accordingly, the variability in peak and average blood lactate responses was lower in the interval session prescribed relative to CP compared to when prescribed relative to $\dot{V}O_{2max}$. The variability in work-prime (W′) depletion (the finite work capacity above CP) after the final interval bout was also lower when intervals were prescribed relative to CP compared to when prescribed relative to $\dot{V}O_{2max}$. These data indicate that using physiological thresholds, namely CP, to prescribe exercise intensity reduces the heterogeneity in exercise tolerance and physiological responses to exercise spanning the boundary between the heavy and severe intensity domains. Therefore, these findings advocate the use of physiological thresholds, and particularly CP, over the %$\dot{V}O_{2max}$ approach, to increase the precision of exercise intensity prescription.

Chapter 6

Based on the findings of **Chapter 4,** whereby threshold-based exercise training elicits superior gains in $\dot{V}O_{2max}$ following a period of training, and those of **Chapter 5,** whereby using CP to anchor exercise intensity better controls and normalises the acute exercise stimulus among

individuals, **Chapter 6** aimed to compare the efficacy of using CP as an anchor of intensity for a period of exercise training. In turn, this approach was compared to that of a traditionally prescribed training programme whereby the subsequent magnitude and variability in $\dot{V}O_{2max}$ changes that manifested following each training programme were compared. The results, of which, suggested that training-induced gains in $\dot{V}O_{2max}$ and the number of individuals demonstrating a meaningful increase in $\dot{V}O_{2max}$ appears to be greater following the CP-based training programme.

As anticipated, post-intervention, $\dot{V}O_{2max}$ increased following exercise training prescribed relative to CP and also when prescribed relative to $\dot{V}O_{2max}$. There was, however, no such change in the non-exercising control group. Whilst the magnitude of change in $\dot{V}O_{2max}$ appeared to be greater following exercise training prescribed relative to CP compared to when prescribed relative to $\dot{V}O_{2max}$, this difference was not statistically significant. It is important to note that the present experimental study was underpowered. Due to time constraints and the practicality of running a training intervention, the current sample size completing the study was n = 27, falling short of that required for statistical power (n = 54). Therefore, in **Chapter 6**, effect sizes were also considered alongside *p* values to identify differences that may legitimately exist were a larger study implemented. As such, the greater gain in $\dot{V}O_{2max}$ elicited by training prescribed relative to CP observed in this study may indeed be meaningful given the large effect size associated with the mean difference. Following suit, the proportion of individuals demonstrating an increase in $\dot{V}O_{2max}$ above the minimum important difference was 50% when exercise was prescribed relative to CP, 30% when prescribed relative to $\dot{V}O_{2max}$, and 37% in the control group. Whilst changes in $\dot{V}O_{2max}$ was the primary parameter of interest, it is worth noting that CP increased following both exercise programmes but not in the control group. Changes in CP are important given this demonstrates an enhanced exercise capacity compared to that before the training intervention. The present findings demonstrate that six-week training programmes comprised of interval and continuous exercise sessions prescribed relative to CP and to $\dot{V}O_{2max}$ are effective in increasing $\dot{V}O_{2max}$ and CP. However, exercise

training prescribed relative to CP appears to be the more effective training programme regarding changes in $\dot{V}O_{2max}$ with a larger proportion of individuals experiencing a change in $\dot{V}O_{2max}$ above the minimum important difference. However, such conclusions need to be confirmed via larger, well-powered studies.

PRACTICAL APPLICATION AND INTEGRATION OF FINDINGS

Practical application of threshold-based exercise prescription

In accordance with the findings of the present thesis, using physiological thresholds to prescribe exercise intensity is advocated. This is to ensure that individuals exercise in the intended intensity domain, which, in turn, might increase the likelihood of achieving marked increases in $\dot{V}O_{2max}$. As discussed in **Chapter 4**, **Variability in $\dot{V}O_{2max}$ change scores**, changes in $\dot{V}O_{2max}$ are primarily dictated by the relative intensity of exercise, whereby the higher the exercise intensity, the greater the magnitude of change in $\dot{V}O_{2max}$ (Collins et al., 2022; Daussin et al., 2008; Gormley et al., 2008; Inglis et al., 2024; MacInnis & Gibala, 2017; McNicol et al., 2009; Milanović et al., 2015). As such, high intensity INT training is consistently shown to elicit greater training-induced changes in $\dot{V}O_{2max}$ compared to lower intensity CT (Milanović et al., 2015). However, in a study by Collins et al. (2022), when prescribing exercise intensity for CT and INT at 44% and 80% of the maximum power output achieved during a graded exercise test, respectively, there were instances where individuals in the CT group were exercising at higher intensities to those in the INT group when the intensities were instead expressed relative to CP. As a result, those exercising at a higher percentage of their CP, regardless of whether they were in the INT or CT group, were the ones experiencing the greatest training-induced adaptations (Collins et al., 2022). This emphasises that whilst exercise intensity is important for inducing marked changes in $\dot{V}O_{2max}$; you need an appropriate means of prescribing exercise intensity to ensure intensity is high relative to CP and not just relative to a marker such as $\dot{V}O_{2max}$. Using TRAD approaches to prescribe exercise intensity does not guarantee the intensity that is in fact elicited, is appropriate. When considering the commonly observed incidence of individuals not experiencing meaningful

changes in markers such as $\dot{V}O_{2max}$ compared to their fellow counterparts (Bacon et al., 2013; Bouchard et al., 1999; Williams et al., 2019), this might be explained by a high exercise intensity being prescribed relative to a maximum physiological value, but low when expressed relative to CP (Collins et al., 2022). This study reiterates the findings of **Chapter 5** whereby TRAD approaches lack the ability to control and normalise exercise intensity among individuals and further advocates the use of thresholds, such as CP, to instead anchor exercise intensity too. By doing so, exercise intensity is prescribed considering the position of an individual's first and second physiological threshold and their associated intensity domains which dictate subsequent physiological responses to exercise.

From a practical point of view, using physiological thresholds as an anchor of exercise intensity requires some means of additional testing or data collection is needed. To determine the first threshold, this might be through a step or ramp incremental exercise test which can be used to determine the lactate threshold (LT) or GET. For the second threshold, a series of constant work rate (CWR) exercise tests, time trials, or habitual training data can be used to determine CP (**Chapter 2**, **Prescription of exercise intensity**).

Moderate intensity exercise

To prescribe moderate intensity exercise, determination of the first physiological threshold is needed. Determining this transitional boundary asserts the upper limit of the moderate intensity domain and thus ensures that the intensity prescribed falls below (Poole & Jones, 2012; Poole & Richardson, 1997). As such, GET or LT needs to be determined. To determine GET, a step or ramp incremental exercise test needs to be performed, during which, gas exchange data (e.g., oxygen uptake [$\dot{V}O_2$] and carbon dioxide production [$\dot{V}CO_2$]) needs to be collected (**Chapter 2, Gas exchange threshold**). To do this a stationary or portable gas analyser is needed. Alternatively, blood lactate can be measured during a step incremental exercise test and used to determine LT (**Chapter 2, Lactate threshold**). To do this, a means of blood collection and analyses is required to measure blood lactate concentrations. When GET or LT is used as the intensity anchor, an example cycling-based exercise session could

be a prolonged bout of cycling performed at a percentage below the work rate associated with GET or LT, for example a power output (W) corresponding with 90% GET which was implemented in **Chapter 5** and in Black et al. (2017). For running-based exercise, a pace (e.g., $min \cdot km^{-1}$) or speed ($m \cdot s^{-1}$) below that associated with GET or LT can be prescribed for a prolonged period of time. Alternatively, if heart rate is also measured throughout the given test, target heart rates can be prescribed that fall below the heart rate associated with GET or LT providing that the individual has access to a means of heart rate monitoring (i.e., a heart rate monitoring strap or smart watch).

Heavy intensity exercise

To prescribe heavy intensity exercise, intensities corresponding with GET and LT can be used to assert the bottom of the heavy intensity domain. Additionally, to assert the top of the heavy intensity domain, CP should be determined.

To use CP as an anchor of exercise intensity, a recommendation generated by the findings of the present thesis, determination of CP is of course needed. Traditionally, this requires the completion of ~3-5 CWR tests performed to maximal exertion and task failure (Muniz-Pumares et al., 2019). This is of course time consuming; however, completing multiple trials per day, as was done in the present study (**Chapter 5** and **6**), are evidenced to be suitable in both sporting and health environments (Goulding et al., 2017; Triska et al., 2021). Therefore, it is appropriate for an individual to perform two CWR tests per day over two separate days, which greatly reduces the burden of determining CP from say five CWR tests, completed on five separate days, as is recommended (Muniz-Pumares et al., 2019).

Alternative methods of CP determination have been generated, for example, the 3-min all-out test which was established as a time-efficient alternative to the traditional means of determining CP (Burnley et al., 2006; Vanhatalo et al., 2007). However, the 3-min all-out test requires large amounts of motivation, and a familiarisation session is recommended in order to obtain reliable data thereafter (Vanhatalo et al., 2007). Additionally, it may not be viable to expect individuals deemed as unhealthy to undertake a effort 3-min all-out test which requires

maximal exertion and large amounts of motivation to complete correctly. Alternatively, determining critical speed (CS), the running equivalent of CP, is somewhat easier as this can be determined from training data (i.e., performance or training bests for a given distance) which does not require laboratory equipment beyond a stopwatch and a measure of distance (Smyth & Muniz-Pumares, 2020b). However, studies have now demonstrated that CP and CS, can be estimated through the collection of habitual training data and maximal effort time trials (B. Hunter et al., 2023; Smyth & Muniz-Pumares, 2020b). For example, Hunter et al. (2023) were able to derive running-based CP and CS estimates using the best 3-, 7-, and 12-minute segments recorded over the course of six training weeks (CS: 3.44 $m \cdot s^{-1}$, CP: 281 W) and the best 3-, 7-, and 12-minutes maximal effort time trials completed in weeks seven and eight (3.42 $m \cdot s^{-1}$, CP: 290 W). Similar findings have also been demonstrated in cycling (Karsten et al., 2013b) whereby three all-out cycling tests were performed for durations of 3-, 7-, and 12-minutes at an outdoor cycling velodrome and were compared to laboratory-based CWR tests performed at 80%, 100%, and 105% of maximal aerobic power. Findings revealed no differences in CP values between laboratory and field-based CP testing (Karsten et al., 2013b).

Once CP (or CS) has been determined, different options are available regarding how to prescribe exercise sessions. In **Chapter 5**, heavy intensity cycling exercise was prescribed at the midpoint power output between GET and that corresponding with CP, this is referred to as the delta method, an example of which is implemented in a study by Ghiarone et al. (2019) where instead of using CP to assert the upper limit of the heavy intensity domain, the second breakpoint in blood lactate (i.e., LT2: second lactate threshold) is used. The cycling session is prescribed at a power output (W) associated with 50% of the difference between LT and LT2. Alternatively, a percentage of CP can be used to target heavy intensity exercise, examples of which are implemented in **Chapter 6** where cycling exercise was prescribed at a power output (W) associated with 85% CP, in Black et al. (2017) where cycling exercise was prescribed at a power output (W) associated with lower boundary of the 95% confidence limit for the

determined CP parameter, and in B. Hunter et al. (2021) where treadmill running was prescribed at a velocity ($m \cdot s^{-1}$) associated with 95% of critical velocity minus one standard error of estimation.

Severe intensity exercise

Finally, severe intensity exercise, undertaken above CP, needs only to consider this parameter in order to determine the lower limit of the severe intensity domain; however, multiple approaches of using CP to prescribe severe intensity exercise exist. Typically, severe intensity exercise is going to be structured as high intensity interval training (HIIT) in order to accrue a large component of exercise undertaken at high intensities. In **Chapter 5**, HIIT was prescribed at 110% CP for 5 x 3 min work intervals. However, in **Chapter 6**, a different approach was used whereby the finite work capacity that exists at intensities above CP (i.e., work prime [W′]) was utilised. As such, HIIT was prescribed as 5 x 3 min work intervals at an intensity (PO_6) that, based on the below equation, should elicit task failure in ~6 min were the bout to be continued. This was calculated as follows:

$$PO_6 = (W' \div 360) + CP$$

This approach can be implemented in running by replacing CP with CS, work prime (W′) with distance prime (D′), and PO_6 in W with $m \cdot s^{-1}$.

Pettitt (2016) highlights the utility of using CS to prescribe HIIT in running based exercise, although this can of course be implemented with cycling-based parameters as well. Once CS and D′ (which represents the finite work capacity available above CS) have been determined, time limits (t_{LIM}) can be predicted for given speeds and distances. As such, to prescribe running intervals, the following equation can be used:

$$Interval\ t_{LIM} = (D - [0.6\ x\ D']) \div CS$$

Where D is distance and 0.6 is the intended fractional depletion of D′ (Pettitt, 2016). As well as prescribing sessions on a desired interval length, the equation can be adapted to prescribe sessions based on an intended running speed (S) using the following equation:

$$Interval\ S = \ ([D'\ x\ 0.6] \div t_{LIM}) + \ CS$$

For a review on using CS to prescribe high intensity interval exercise see Pettitt (2016). An example based on this approach was implemented in a study by E. J. Thomas et al. (2020). In the study, running sessions were created using a pre-determined running speed (140% CS) and a calculated interval time that should induce a fractional D′ depletion of 70% using the following equation:

$$t_{LIM} = \ 0.7\ x\ D'\ \div (1.4\ x\ CS - CS) = 0.7\ x\ \ D' \div (0.4\ x\ CS)$$

The example provided by E. J. Thomas et al. (2020) explains that for an individual with a CS of 3.5 m·s^{-1} and a D′ of 160 m, the t_{LIM} prescribed would need to be 80 s. As such, when running at 140% of 3.5 m·s^{-1} (4.9 m·s^{-1}) it would take ~80 s to deplete D′ by 70%.

For the other running group, interval sessions were prescribed with a pre-determined t_{LIM} of 90 s and the following calculation was used to determine the speed at which the running bouts should be performed at to induce a fractional D′ of 70%:

$$S = \ ([0.7\ x\ D'] \ \div 90\ s) + CS$$

The example given by E. J. Thomas et al. (2020) notes that for an individual with a CS of 3.2 m·s^{-1} and a D′ of 180 m intervals would be prescribed at a running speed of 4.6 m·s^{-1} in order to deplete D′ by 70% in 90 s.

In cycling, it is common for individuals to know their Functional Threshold Power (FTP), a power output sustainable for one hour without the onset of fatigue (A. Hunter & Coggan, 2010). The intensity at FTP is determined by either a one hour test or estimated by scaling the average power output of a 20 min test (A. Hunter & Coggan, 2010). Its conceptualisation is supposed to resemble the second physiological threshold (i.e., CP) such that exercising above FTP elicits non-steady state exercise (A. Hunter & Coggan, 2010). However, FTP is consistently evidenced not to equate to markers of the boundary between the heavy and severe intensity domain such as CP (Karsten et al., 2021; Morgan et al., 2019), RCP

(Barranco-Gil et al., 2020; Sitko et al., 2022), and MLSS (Inglis et al., 2020; Lillo-Beviá et al., 2022), which, considering it is a test performed over an arbitrary length of time (1 h) as opposed to specifically determining a threshold between steady and non-steady state exercise, is not surprising Click or tap here to enter text. (2012. As such, due to its measurement protocol, it is performed in the heavy intensity domain but cannot determine the upper boundary of this domain (Chorley & Lamb, 2020).

Regardless, FTP has been widely adopted as a measure of endurance performance in cycling, and indeed among professional cyclists (Van Erp & Sanders, 2021). Furthermore, FTP is widely used to inform exercise intensity prescription and determine training zones, approaches which are commonly adopted by popular training software applications such as Garmin Connect and Zwift (Chorley & Lamb, 2020). However, as noted by Chorley & Lamb (2020), such approaches should be used with caution as FTP does not necessarily delineate the heavy and severe intensity domains, and thus, determining training zones of this single value is erroneous. It is proposed that CP can account for these methodological flaws by accurately determining the position of this transitional boundary between the heavy and severe intensity domains, and thus, along with data surrounding the LT or GET, exercise intensity can instead be prescribed pertaining to an individual's intensity domains and the desired physiological responses elicited by them (Chorley & Lamb, 2020).

Of note, when using CP to prescribe high intensity interval training, consideration of W′ is necessary (Chorley & Lamb, 2020). Using CP in isolation does not account for the finite work capacity available above the intensity at CP (i.e., W′) which can be similar among individuals with different CP values and vice versa. As explained by Chorley & Lamb (2020), take individual A who has a CP of 375 W, a W′ of 13 kJ, and a body mass of 78 kg, and individual B who has a CP of 305 W, a W′ of 13 kJ, and a body mass of 64 kg. Undertaking a 3 min interval session at 120% CP would leave individual B with >2 kJ of W′ remaining, a depletion of 15%, whilst for individual A, would likely fail to complete the session due to the depletion of W′. Informing a session based on both CP and W′ would allow for more appropriate and

individualised exercise prescription, for example, reducing the interval intensity to 436 W (from 450 W = 120% CP) for 3 min would leave 2 kJ of W′ remaining, equating to a 15% depletion (Chorley & Lamb, 2020). However, it is worth noting that the optimal method used to model W′ reconstitution is still a working progress and currently, the application of such models are hindered due to asepcts such as how W′ recovers following differing exercise protocols and indeed by progressive fatigue (Chorley & Lamb, 2020), and finally, is the added complexity of large variability in the rate of W′ recovery among individuals (Skiba et al., 2012, 2015; Skiba & Clarke, 2021).

The above examples, whilst not exhaustive, provide individuals with examples of how exercise sessions can be prescribed using threshold-based approaches. Notably, using CP (or CS) to prescribe exercise sessions boasts great utility and offers individuals a creative tool for designing and prescribing CP-based high intensity interval sessions where individuals can experiment with the manipulation of interval durations, repetitions, work rates, and intended W′ (or D′) depletion.

When considering the implementation of threshold-based exercise prescription across different populations, for example clinical populations, it is acknowledged that implementing threshold-based exercise might not always be appropriate due to the requirement of preliminary exhaustive exercise testing. However, it is worth noting that cardiopulmonary exercise testing (CPET) is routinely performed in clinical settings (Mezzani et al., 2013; R. Ross et al., 2016). Using gas exchange data from these tests (e.g., $\dot{V}O_2$ and $\dot{V}CO_2$) or blood lactate date, one can readily use this data to prescribe exercise intensity in place of using $\dot{V}O_{2max}$ or HR_{max}. For example, moderate intensity exercise can be prescribed at a HR or work rate (i.e., W or $km \cdot h^{-1}$) associated with a given percentage of GET. Using such an approach would ensure moderate intensity exercise was indeed being undertaken, controlling, and normalising exercise intensity among different individuals, whilst also increasing the safety of the exercise whereby the prescription of inappropriate intensities is thus avoided.

Of note, more recent studies are exploring the use of self-assessed threshold tools, which roughly reflect one's laboratory measured physiological thresholds. Examples of which are rate of perceived exertion and the 'Talk Test' which can be used to mimic a more practical and accessible approach to threshold-based exercise training (Berggren et al., 2004; Gillespie et al., 2015; Jeans et al., 2011; Lyon et al., 2014; Reed & Pipe, 2014; Rodríguez-Marroyo et al., 2013; Sørensen et al., 2020; Zanettini et al., 2013). This is an interesting avenue aiming to encourage the rollout of individualised, population-wide approaches of exercise prescription that do not require access to laboratory facilities (Lehtonen et al., 2022; Mezzani et al., 2013). Additionally, the benefit of using such approaches is also being realised for use in various clinical populations (Anselmi et al., 2021b; D'Ascenzi et al., 2022; Mezzani et al., 2013; Pymer et al., 2020).

The talk test, for example, was generated on the basis of one's ability to talk and hold conversation at different intensities of exercise. The rationale for which was founded on the marked increase in ventilatory drive needed to sustain work rates exceeding that of the first physiological threshold (Poole & Jones, 2012; Poole & Richardson, 1997). Since speech only occurs during the expiratory phase of breathing, the change in breathing patterns to meet increasing gas exchange demands leads to a progressive reduction in expiratory time, and thus, capacity to talk (Rotstein et al., 2004; Zanettini et al., 2013). This results in a conflict between metabolic and phonatory functions, and the capacity to speak at high intensities is inhibited (Rotstein et al., 2004; Zanettini et al., 2013). The talk test has thus been evidenced to provide an alternative non-invasive protocol for determining the first physiological threshold (Dehart-Beverley et al., 2000) and has since been used as a prescriptive tool in healthy individuals (Dehart-Beverley et al., 2000; Foster et al., 2008; Persinger et al., 2004), in athletes (Recalde et al., 2002), and in individuals with cardiovascular disease (Brawner et al., 2006; Voelker et al., 2002). As such, this offers a simple, practical, and adequately precise tool for implementing an exercise prescription tool, based on a threshold-based approach, and an approach that negates the need for preliminary exercise testing and sophisticated monitoring

strategies (Persinger et al., 2004). This might be particularly useful when prescribing exercise intensity for unhealthy or clinical populations whereby intensity of exercise can be monitored and controlled based on the individual's ability to talk and hold conversation, adopting non-invasive approaches in place of invasive approaches which might be unappealing or unfeasible in such environments. For example, the talk test was demonstrated as an effective and safe tool for prescribing exercise intensity in individuals who had recently undergone myocardial revascularisation (Zanettini et al., 2013). In this study, good reliability was observed when using the talk test to assert exercise below and above the first physiological threshold (Zanettini et al., 2013). Additionally, in a study by Foster et al. (2008), the first threshold was established via an incremental exercise test using gas exchange data and then again using the talk test parameters. In this instance, at the end of each incremental stage, individuals were asked to recite a standardised paragraph and answer the question of "Can you still speak comfortably?" choosing from the following answers "yes", "I'm not sure", or "no". When exercise intensity was evaluated as comfortable, this was associated with moderate intensity exercise, and when exercise was evaluated as uncomfortable, this meant that the intensity had exceeded that of the first physiological threshold. Based on the premise that such approaches offer a non-invasive alternative to invasively determining physiological thresholds, future studies might aim to compare acute physiological responses and training adaptations to exercise prescribed relative to various anchors of exercise intensity including those related to self-assessed thresholds.

Alternatively, this is where prescription tools such as the talk test and rating of perceived exertion (RPE) might hold their greatest premise (Lehtonen et al., 2022). When using the 6-20 Borg scale, it is evidenced that the first physiological threshold occurs at ~11-14 among both trained and untrained individuals (Elsangedy et al., 2013; Fabre et al., 2013) and that changes in training status are reflected by RPE. For example, Swaine et al. (1995) found that the first physiological threshold as determined by gas exchange data occurred at higher heart rates in trained (142 beats·min^{-1}) versus untrained (128 beats·min^{-1}) individuals, but the RPE

associated with this threshold was not different between trained (RPE: 13) and untrained individuals (RPE: 13). The Borg CR10 scale can also be used which uses a scale of 1-10 (Monnier-Benoit et al., 2009). As noted in Lehtonen et al. (2022), ratings of ≤13 and ≤4, 14-16 and 5-6, and ≥17 and ≥7 using the Borg 6-20 and Borg CR10 scales would reflect exercise below the first physiological threshold (i.e., moderate intensity exercise), between the first and second threshold (i.e., heavy intensity exercise), and above the second physiological threshold (i.e., severe intensity exercise), respectively (Hydren & Cohen, 2015).

Whilst this thesis does not necessarily apply directly to clinical populations, the findings of the thesis are worth consideration, and it is hoped that the findings might promote future research pertaining to the efficacy of using threshold-based exercise prescription in clinical populations as a tool for increasing individuals' cardiorespiratory fitness.

Using physiological thresholds to better prescribe exercise intensity in research studies

Given the findings of **Chapter 5** whereby the intensity of exercise is better controlled and normalised among individuals when prescribed relative to CP, and that in comparison, the elicited exercise stimulus resulting from prescribing exercise relative to $\dot{V}O_{2max}$ is largely heterogenous, research studies implementing the $\%\dot{V}O_{2max}$ approach may unknowingly be confounding the findings of their study due to a poorly controlled exercise programme. For example, a hypothetical experiment is investigating the effect of heavy (or vigorous) intensity exercise, that is, exercise training below CP, on the change in the hypothetical variable 'x'. As is commonly done, exercise is prescribed within the range of 64-90% $\dot{V}O_{2max}$, say 75%, and thus sitting within the recommend range for heavy (or vigorous) intensity exercise (American College of Sports Medicine, 2017). However, as was found in **Chapter 5**, whilst exercising at 75% $\dot{V}O_{2max}$ will elicit exercise below CP for a number of individuals, for others such an intensity will elicit exercise undertaken above ones CP. Consequently, within this hypothetical experiment, some of the participants in this cohort are indeed undertaking heavy intensity exercise training, whereas another portion of the cohort are undertaking their training in the

severe intensity domain (i.e., above their CP). Given the aim of the hypothetical study is to determine the effect of heavy intensity exercise on 'x', the true effect of such exercise is unknown, confounded by a poorly controlled exercise training programme.

In turn, prescribing exercise relative to physiological thresholds in research studies may provide more clarity on research findings which manifest in response to a given exercise training intervention. This is because moderate, heavy, and severe intensity exercise can be accurately prescribed using such approaches, and thus, effects of exercising in each of these domains can be discretely evaluated.

Using physiological thresholds to prescribe exercise intensity in clinical populations

It is acknowledged that the experimental chapters within this thesis have all been conducted on healthy individuals; however, the impact of the present findings may have implications noteworthy for their translation into clinical settings. It is strongly recommended that the findings of the present study are built upon and used to investigate the efficacy of using physiological thresholds in unhealthy populations.

An increasing body of evidence has established that the risk of developing various diseases and disorders (i.e., cardiovascular disease and various cancers) as well as all-cause mortality is increased with low levels of cardiorespiratory fitness (R. Ross et al., 2016). In turn, individuals demonstrating low levels of cardiorespiratory fitness are more likely to die prematurely, primarily due to greater rates of developing cardiovascular disease and/or cancer (Blair, 1989). Additionally, $\dot{V}O_{2max}$ is a highly predictive measure of future fatal and non-fatal cardiac events, even more so than traditional risk factors such as poor lipid profiles, smoking, diabetes, and hypertension (Laukkanen et al., 2004; Sui et al., 2007). As such, interpretation of ones $\dot{V}O_{2max}$ can be used as a powerful tool for identifying 'at-risk' individuals.

Those who do demonstrate a poor level of cardiorespiratory fitness and are identified as needing to increase their $\dot{V}O_{2max}$, should thus be recommended, and hopefully prescribed, exercise given that $\dot{V}O_{2max}$ responds most profoundly to exercise training. However, given the

discussion and interpretation of the findings of the present thesis, a critical factor determining the subsequent change in $\dot{V}O_{2max}$ is going to relate to the effectiveness of the exercise programme undertaken. In combination with the results of Collins et al. (2022), just because exercise is prescribed at a high intensity relative to $\dot{V}O_{2max}$, this does not mean the intensity of exercise is high relative to the individuals' physiological thresholds and intensity domains. Therefore, an effective means of intensity prescription is needed to ensure that exercise intensity is elicited in the intended intensity domain, eliciting the desired metabolic stress. To ensure this is the case, and as evidenced in this thesis and previously published work (Collins et al., 2022; Inglis et al., 2024), a threshold-based approach is vital.

Based on the findings presented herein, the likelihood of an individual experiencing a meaningful change in their $\dot{V}O_{2max}$ is increased when the exercise programme is prescribed relative to a physiological threshold (**Chapter 4** and **Chapter 6**). As such, it seems appropriate that exercise programmes are indeed prescribed using such approaches and specifically, future exploration of the use of CP as the primary anchor of intensity within larger studies across different populations is highly encouraged. Whilst the determination of physiological thresholds requires additional laboratory visits and tests, considering that the outcomes of the exercise training could indeed have profound implications to health, the added effort and time is arguably justified.

Within clinical settings, exercise programmes may be undertaken as prehabilitation or rehabilitation (Assouline et al., 2021; Dunne et al., 2016; G. H. Huang et al., 2016b; Levett et al., 2018; Palma et al., 2021b; Richardson et al., 2017; Rose et al., 2022; Sawatzky et al., 2014; Sheill et al., 2020; West et al., 2015, 2019). For example, improvements in systemic O_2 consumption may be targeted such that the increased O_2 demand associated with the perioperative period can be met (Rose et al., 2022). If one's system is not able to meet such demands imposed for example by the physiological insult of a surgical procedure, an O_2 deficit is created. The severity of this deficit ultimately dictates subsequent postoperative outcomes, hospitalisation, and the inducement of subsequent organ failure (**Figure 7.1**) (Rose et al.,

2022). Improving cardiorespiratory fitness (i.e., $\dot{V}O_{2max}$) is thus paramount for a variety of individuals identified as unfit for surgery (Steffens et al., 2021).

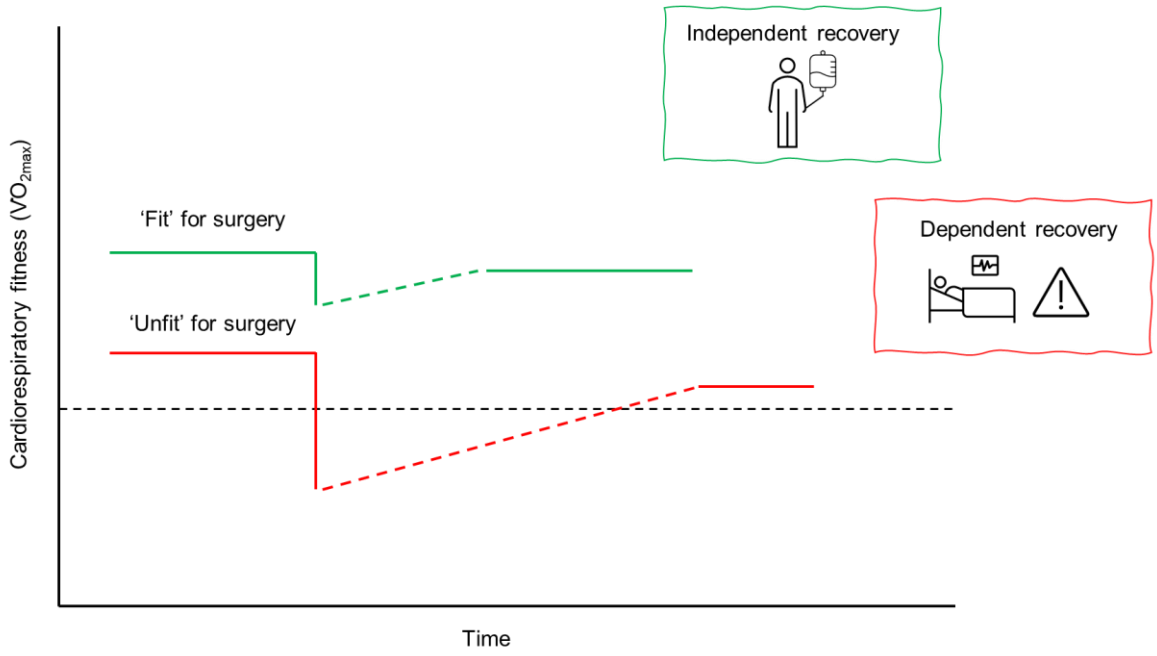

Figure 7.1. Physiological insult of surgery and potential discrepancies in recovery. Patient deemed fit (green) and unfit (red) for surgery and hypothetical recovery profiles. Dashed line represents the threshold between independent (e.g., ward-based care) and dependent recovery (e.g., high dependency or intensive care unit). Adapted from Rose et al. (2022) and Clegg et al. (2013).

In a meta-analysis conducted by Assouline et al. (2021), preoperative exercise training, with the aim of improving preoperative functional capacity and cardiorespiratory fitness, reduced postoperative pulmonary complications by 48% when compared with standard care. Additionally, factors such as hospital stay length and pneumonia cases were also reduced in those undertaking prehabilitative exercise. Accordingly, prehabilitative exercise was shown to reduce hospital stay length, and reduced postoperative complication rates by half in patients with lung cancer (Steffens et al., 2018).

Notably, it is common for prehabilitation studies to adopt continuous exercise training prescribed relative to traditional anchors of intensity. For example, exercise intensities have been prescribed at ranging between 40-85% heart rate reserve (Dronkers et al., 2010; Rosenfeldt et al., 2011; Timmerman et al., 2011) and 50-85% $\dot{V}O_{2max}$ (Sawatzky et al., 2014; Stefanelli et al., 2013; Tung et al., 2012). Interval based exercise training has also been prescribed, again, commonly anchored relative to traditional anchor of intensity such as maximum work rates achieved in a graded exercise test or $\dot{V}O_{2max}$ (Dunne et al., 2016; Licker et al., 2017). Consistent with that seen in healthy populations (**Chapter 5**) (Lansley et al., 2011; Meyer et al., 1999; Scharhag-Rosenberger et al., 2010), using such approaches poorly controls exercise intensity among individuals (Anselmi et al., 2021b; Mezzani et al., 2013; Pymer et al., 2020; Vonbank et al., 2022). Anselmi et al. (2021) reported that using fixed percentages of HR_{max} and $\dot{V}O_{2max}$ misclassified exercise intensity whereby $\dot{V}O_2$ at the first threshold (i.e., that demarcating the moderate and heavy intensity domains) corresponded with heavy rather than moderate intensity exercise when referring to the 2020 European Society of Cardiology guidelines (Pelliccia et al., 2021). Furthermore, values at the second threshold (i.e., that demarcating the heavy and severe intensity domains) corresponded with severe rather than heavy intensity exercise. Therefore, the authors concluded that shifting to a threshold-based approach was advised when working with cardiac patients to define appropriate exercise intensities (Anselmi et al., 2021b). Consistent with such findings, Pymer et al. (2020), found that over half of patients with coronary heart disease displayed their first physiological threshold outside the predicted range of heart rate reserves used for training in the moderate intensity domain. In turn, they concluded that using heart rate reserve to prescribe exercise intensity is likely inaccurate for a large proportion of patients undergoing cardiac rehabilitation (Pymer et al., 2020). In patients with interstitial lung disease, Vonbank et al. (2022), reported marked variability in the heart rates associated with patients first physiological threshold when expressed relative to their HR_{max} providing further evidence of the inability of such approaches to control and normalise exercise intensity among individuals.

Using physiological thresholds to control and better normalise exercise intensity may thus be more effective in eliciting beneficial impact across a variety of populations undertaking exercise training. As Mezzani et al. (2013) nicely portray, given the increasing body of evidence indicating that exercise may be more homogenously and effectively prescribed when informed by a threshold-based approach, a finding further supported by the results of the present thesis, this may encourage a shift from a traditional to a threshold-based approach to exercise intensity prescription. In turn, this could maximize the benefits obtainable by the use of aerobic exercise training. Given the findings of the experimental chapters in the present thesis, the results provide further evidence supporting this notion. Furthermore, the finding of an increased proportion of individuals demonstrating meaningful increases in cardiorespiratory fitness following threshold-based training (**Chapter 4** and **Chapter 6**) is profound given the positive impact this may have regarding the improvement in postoperative outcomes, hospitalisation, and health care costs (**Figure 7.2**).

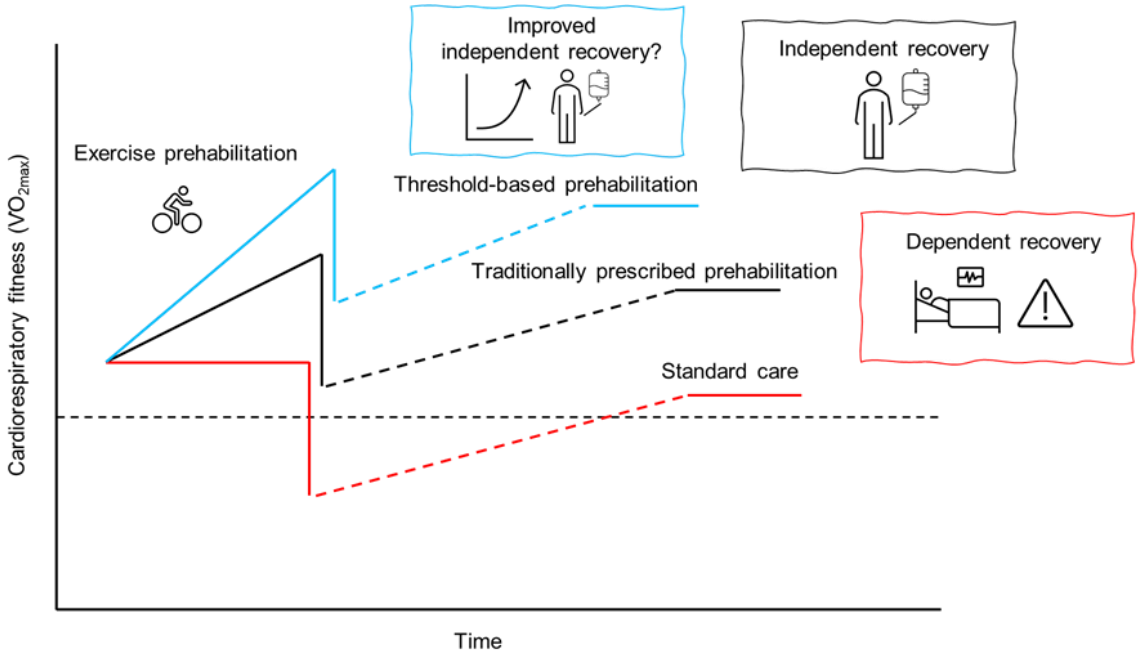

Figure 7.2. Hypothetical effect of threshold-based (blue) and traditionally prescribed (black) exercise prehabilitation. Compared to the effect of standard care (red), increases in cardiorespiratory fitness reduce the risk of postoperative complications and facilitate enhanced recovery (black). This may be further augmented following threshold-based prehabilitation (blue). Dashed line represents the threshold between independent (e.g., ward-based care) and dependent recovery (e.g., high dependency or intensive care unit). Adapted from Rose et al. (2022) and Clegg et al. (2013).

By using a threshold-based approach, whilst the variability in responses to exercise will not be abolished, the likelihood if an individual not attaining a meaningful increase in $\dot{V}O_{2max}$ is reduced. The results obtained from using CP as the primary anchor of exercise intensity in **Chapter 5** and **Chapter 6** encourages future consideration and use of this intensity marker due to the improved ability to control and normalise exercise intensity among individuals. Additionally, the usability and flexibility of using the CP model to generate both continuous and interval-based exercise sessions (as demonstrated in **Chapter 5** and **Chapter 6**) presents CP as a highly innovative training tool. Considering that a series of CWR trials are recommended when determining CP, such an approach is likely unfeasible in routine clinical settings

(Mezzani et al., 2009). However, given that an association exists between CP and RCP which can be obtained from a single GXT (i.e., a CPET, a routinely performed clinical exercise stress test), RCP might be used as a surrogate for CP, and when combined with GET (which can also be obtained from a single GXT), an individual's intensity domains can be evaluated and used to inform tailored exercise prescription. For example, in cardiac rehabilitation patients, it is strongly encouraged that exercise testing, in the form of GXTs (or CPETs), is a foundational part of the initial patient assessment, further using this information for risk stratification, exercise training evaluation, and tailoring exercise prescription (American Association of Cardiovascular & Pulmonary Rehabilitation, 1999; Arena et al., 2007; Corra et al., 2010; Mezzani et al., 2009, 2013). Future research is thus highly encouraged exploring the use of CP and RCP as representatives of the boundary between the heavy and severe intensity domains and their efficacy as anchors of exercise intensity in clinical populations. This would provide valuable information as to the best means of conducting threshold-based exercise prescription in clinical populations and whether beneficial impacts of exercise training are realised to a greater extent in these populations when threshold-based exercise training is undertaken.

Is prescribing exercise intensity by means of threshold-based approaches an example of a subtractive solution to improved exercise intensity prescription?

Whilst acknowledging that several biological and methodological factors underpin the observation of $\dot{V}O_{2max}$ response variability including factors relating to measurement error and day-to-day biological variability (Bonafiglia et al., 2022), interventions aiming to tackle response variability, and increase response rates (i.e., the number of individuals attaining a change in $\dot{V}O_{2max}$ surpassing a predefined threshold), have commonly implemented additive approaches (**Figure 7.3**) (Adams et al., 2021; Picard, 2022). For example, augmenting the exercise stimulus (i.e., increasing training volume, frequency, and/or intensity) often proves effective in increasing response rates (Montero & Lundby, 2017; R. Ross et al., 2015; Sisson et al., 2009), explained primarily by greater group mean increases in $\dot{V}O_{2max}$ (Bonafiglia et al.,

2021). Reducing response variability elicited by the initial stimulus, an example of a subtractive approach (**Figure 7.3**) (Adams et al., 2021), is thus desired given this negates the need to exhaust the training dose. Based on the findings of **Chapter 4** and **Chapter 6**, the mean $\dot{V}O_{2max}$ increase was greater following threshold-based exercise training compared to traditionally prescribed exercise training. These data thus provide support for using threshold-based approaches as a means of increasing group mean changes in $\dot{V}O_{2max}$ which in turn, increases the likelihood of an individual's attaining an increase in their $\dot{V}O_{2max}$ surpassing a given response threshold. Whilst it is unlikely that this abolishes the variability in $\dot{V}O_{2max}$ responses, augmenting the number of individuals surpassing the given response threshold in turn means that the number of individuals experiencing no change, or an unmeaningful change in their $\dot{V}O_{2max}$ is reduced.

In the context of the present thesis, response variability is the 'problem' in **Figure 7.3** given that some individuals demonstrate no change, or an unmeaningful change in $\dot{V}O_{2max}$ following a period of exercise training. The most common approach to tackle this is to increase training load (i.e., increasing the volume, intensity, and/or frequency of training) in order to increase group mean changes in $\dot{V}O_{2max}$ (Montero & Lundby, 2017; R. Ross et al., 2015; Sisson et al., 2009)which in turn inflates the number of individuals demonstrating an increase in $\dot{V}O_{2max}$ above a predefined response threshold (Bonafiglia et al., 2021). Given the findings presented herein, whereby exercise intensity is more effectively and homogenously prescribed relative to physiological thresholds, a more potent and appropriate exercise stimulus may be elicited such that more individuals demonstrate a meaningful increase in $\dot{V}O_{2max}$ to the initial stimulus, negating the need to exhaust the training dose thereafter. It is recognised however, that further work is needed to elucidate on this notion.

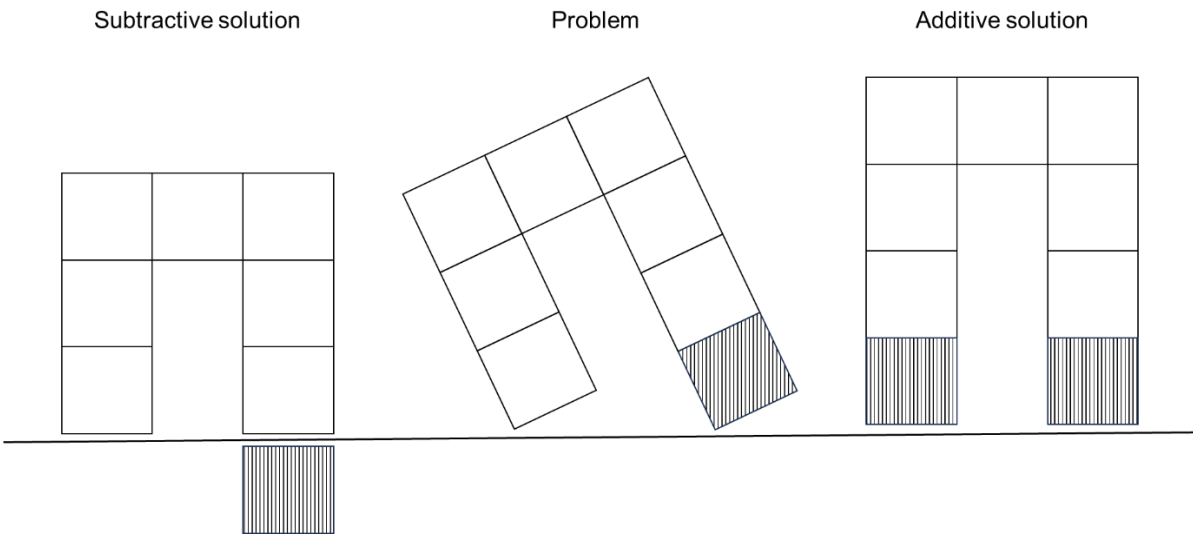

Figure 7.3. Illustration of subtractive and additive solutions to a given problem. Adapted from Picard (2022).

EXPERIMENTAL LIMITATIONS

Regarding **Chapter 5**, future studies are warranted to confirm whether the greater homogeneity in acute physiological responses to exercise bouts prescribed relative to CP are also consistent among additional metabolic disturbances. For example, future studies are encouraged to investigate the variability in intramyocyte perturbations such as, as purported by Poole and Jones (2023), changes in creatine phosphate, inorganic phosphates, adenosine diphosphate, and glycogen. Additionally, in **Chapter 6**, the physiological mechanisms underpinning observed changes in $\dot{V}O_{2max}$ were not explored. Were resources available, investigating the effect of acute responses to exercise, for example measuring acute metabolic disturbances, and how these related to training-induced adaptations would have been interested. Given that training-induced adaptations are the product of the upregulation of signalling pathways which are shown to differ depending on exercise intensity, it would have been interesting to determine if the mismatch in normalised exercise intensity resulting from traditionally prescribed exercise, explains a portion of the variability in $\dot{V}O_{2max}$ change scores. Additionally, conclusions on the primary contributor to changes in $\dot{V}O_{2max}$ cannot be confirmed. For example, as discussed in **Chapter 2**, increases in $\dot{V}O_{2max}$ are primarily attributable to

central adaptations over peripheral adaptations, particularly in untrained individuals. It would have been interesting to measure changes in such factors to elucidate on what physiological mechanisms underpinned the observed changes in $\dot{V}O_{2max}$ and whether these changes varied among individuals and response profiles.

Additionally, it is of interest to determine whether the magnitude and variability in acute responses to exercise bouts, and indeed training-induced adaptations, are consistent between males and females, something that was not able to be explored in the present thesis due to the limited sample sizes available. Previously, sex was acknowledged to account for only a very small portion (~3%) of $\dot{V}O_{2max}$ response variability (Sarzynski et al., 2017). However, this was generated from the HERITAGE study where a TRAD approach to exercise intensity prescription was implemented (Bouchard et al., 1999). It would be interesting to determine whether differences in changes to $\dot{V}O_{2max}$ remain consistent following the completion of a THR based exercise training programme among males and females. As is noted by Ansdell et al. (2020), females are consistently shown to experience inferior changes in $\dot{V}O_{2max}$ following training compared to their male counterparts (Diaz-Canestro & Montero, 2019), yet the training prescribed to females is heavily informed by studies dominated by male participants. It is known that the LT and GET (i.e., the delineators of the moderate and heavy intensity domains) typically position themselves higher relative to $\dot{V}O_{2max}$ than males (Ansdell et al., 2020; Iannetta et al., 2021; Vainshelboim et al., 2020) and thus, considering the findings of Collins et al. (2022), when intensity is prescribed using TRAD approaches, the intensity might be high relative to a maximum value such as $\dot{V}O_{2max}$ for both males and females, but low for females when expressed relative to the individuals CP. As such, females undertaking TRAD might consistently experience an inferior metabolic stress compared to males undertaking the same exercise. It would therefore be interesting to determine whether this is in fact the case and whether following a THR endurance training programme, females experience similar changes in $\dot{V}O_{2max}$ to males.

Of note, the experimental study in **Chapter 6** was underpowered regarding identifying differences in $\dot{V}O_{2max}$ change scores between groups. Compared to the computed sample size of n = 54 required to identify such changes, 27 individuals completed the study. To accommodate for this, measures of effect size were considered and interpreted in addition to exclusively relying on *p* vales. This approach allows for the identification of differences that may legitimately exist but need to be confirmed using larger well-powered studies. Due to time constraints, resources, and undertaking this thesis during the coronavirus pandemic, it was not possible to extend the running of this experimental study and despite best efforts regarding participant recruitment, the sample size fell short of that recommended through the power analysis. As such, the preliminary findings of **Chapter 6** should be taken with caution and the results need to be confirmed by implementation of larger well-powered studies.

When determining $\dot{V}O_{2max}$ and CP, same-day testing procedures were conducted. This was primarily done to accommodate individuals participating in the experimental studies (**Chapter 5** and **6**) whereby conducting single tests across separate days would not have been feasible for a large proportion of individuals. Conducting intra-day testing bouts was considered appropriate based on previous findings (Goulding et al., 2017; Triska et al., 2021). Goudling et al. (2017) found that performing heavy intensity exercise (i.e., “priming” exercise) prior to CP determination does not alter subsequent CP outcomes, speed up $\dot{V}O_2$ kinetics and thus does not alter CP outcomes in upright cycling (Goulding et al., 2017). It has also been shown that just 30 min is required between tests to minimise the effect of previous maximal exercise efforts on the determination of CP (Triska et al., 2021). As such, inter-test recovery times of tests performed on the same day were set at 45 min (**Chapter 5**) and 1 hr (**Chapter 6**). It is worth noting that endurance trained individuals were used in the study of Triska et al. (2021) and thus, compared to the generally non-endurance trained nature of individuals participating in the present study, it may be that tests used to determine CP in the present thesis were impacted more so by the previous exhaustive trials. However, as was the case in **Chapter 6**, the format of maximal ramp exercise tests and constant work rate tests remained consistent

during each testing phase (i.e., pre-, mid-, and post-intervention), the effect of previous exhaustive exercise on subsequent $\dot{V}O_{2max}$ and CP determination also remained consistent. It is, however, unknown as to the practicality of implementing such a testing protocol across unhealthy populations given that the present findings were confirmed only in a healthy population. Considering the points discussed within this chapter, using CP undoubtedly has its benefits regarding improved exercise intensity prescription, and thus, exploring its usability and appropriateness across different populations is encouraged.

FUTURE DIRECTIONS

In the present thesis, healthy individuals were exclusively used within experimental chapters. As such, the findings presented herein require further exploration to elucidate on the effectiveness of using threshold-based approaches across unhealthy populations. In order to do so, the application of such approaches need to be trialled and potentially adapted to determine their practicality if to be used across various populations.

It is acknowledged that accurately determining physiological thresholds requires specialised equipment which is not always available or accessible to all. Future research should therefore aim to determine the magnitude of variability in exercise tolerance and acute physiological responses to exercise prescribed relative to gold standard measures of physiological thresholds (i.e., laboratory determined CP) in comparison to exercise prescribed relative to self-assessed threshold tools such as rating of perceived exertion or the ‘Talk Test’ (deemed to approximate laboratory-determined physiological thresholds). Results of such studies would help elucidate on potentially more appropriate approaches to exercise intensity prescription that can be used at the population level and not just to for those with access to laboratories and specialised equipment. There are, however, approaches which require sub-maximal efforts to determine CP and indeed do not require means beyond the ability to self-assess effort perception (Nakamura et al., 2008). Such approaches have shown promising results, demonstrating relatively high accuracy in estimating CP without requiring an individual to exercise to exhaustion (Nakamura et al., 2008); however, further studies are required to

corroborate these findings and explore the implementation of such approaches in exercise training regimens. This might be of particular interest in the exploration of, and potential role out of, threshold-based exercise in sedentary, unhealthy, and/or clinical populations.

The additional parameter of the power-duration relationship is work-prime (W'), which represents the finite work capacity available when working above ones CP (Jones et al., 2010; Poole et al., 2016; Skiba et al., 2012; Skiba & Clarke, 2021). As such, the depletion of W' reflects exhaustion within the severe intensity domain (Skiba & Clarke, 2021) and can be used to prescribe intermittent exercise (Clark et al., 2013; Pettitt, 2016; Pettitt et al., 2015; Thomas et al., 2020). Specifically, the W' parameter can be used whereby prescribed exercise intensity is dictated by a desired interval length, a desired interval intensity, a given W' depletion, a power output intended to elicit exhaustion in an approximate time (as was done in **Chapter 6**), or simply as a percentage of CP (as was done in **Chapter 5**). However, one challenge presenting is accurately modelling the reconstitution of W' among individuals (i.e., modelling the individual recovery of W' regarding its speed and trajectory). It is well established that W' depletes when exercise is undertaken above CP, and when intensity is reduced below CP, W' is able to recovery. However, the capacity of the system to do so will thus dictate the amount of W' remaining for subsequent bouts of exercise, and a model best predicting this is still being researched. Whilst several approaches have been developed and proposed, more work is needed to elucidate the most effective and accurate model (Skiba & Clarke, 2021). Additionally, it is currently unknown as to the most effective means of prescribing exercise utilising the W' concept. As such, future studies might look to compare the variability in exercise tolerance and acute and chronic responses to exercise prescribed using these different approaches to interval-based exercise prescription using W'. This would provide valuable insight into optimising exercise intensity prescription for interval-based exercise.

In **Chapter 5** the exercise stimulus elicited by exercising relative to CP was more homogenous compared to that elicited when exercising relative to $\dot{V}O_{2max}$. Indeed, other physiological thresholds exist (discussed in **Chapter 2**), some of which do not require additional testing

beyond a test used to determine $\dot{V}O_{2max}$. With a limitation of using CP concerning the added time and effort needed for its determination, it would be interesting to compare the variability in the exercise stimulus elicited by an approach utilising an alternative physiological threshold determined during a maximal graded exercise test (e.g., gas exchange thresholds). This would elucidate on whether there is an added marked benefit of determining CP regarding its ability to control and normalise exercise intensity or whether using threshold markers attained from $\dot{V}O_{2max}$ determination provide a sufficient alternative. Similarly, in **Chapter 6**, CP was the primary anchor of intensity used to prescribe exercise training. It would be interesting to compare the effect of using this approach against exercise training prescribed relative to an alternative physiological threshold. Again, if using an alternative physiological threshold that can be determined during $\dot{V}O_{2max}$ determination provides greater benefit to that of using the % $\dot{V}O_{2max}$ approach for example, this will provide information regarding the most effective, but also the most practical method of exercise intensity prescription. In situations where CP testing may not be deemed feasible yet conducting a $\dot{V}O_{2max}$ test is, it could be that using thresholds determined from a $\dot{V}O_{2max}$ test provides an effective and practical approach, superior to that of the traditional approach whereby percentages of $\dot{V}O_{2max}$ would likely be used. This, again, would be an interesting avenue of research which would improve the application and feasibility of threshold-based exercise training which might be up taken by a greater number of individuals across varying levels of health and fitness.

CONCLUSION

The most common means of exercise intensity prescription remains to be dominated by traditional approaches. The findings of the present thesis provide general support for a shift from using traditional means of exercise intensity prescription, to a threshold-based approach, increasing the proportion of individuals experiencing a change in $\dot{V}O_{2max}$ above a predefined meaningful response threshold.

In this thesis, prescribing acute bouts of exercise relative to $\dot{V}O_{2max}$ (perhaps the most commonly used approach to exercise prescription) consistently overestimated the boundary

between the heavy and severe intensity domains when used across a group of homogenous individuals. Compared to when CP was used to anchor exercise intensity, this caused greater heterogeneity in exercise tolerance and the metabolic responses to exercise. The ability to control and normalise exercise intensity among individuals was thus superior when exercise intensity was prescribed relative to CP. Specifically, the findings presented in **Chapter 5** advocate the use of CP as a primary anchor of exercise intensity.

Preliminary results of **Chapter 6** further advocate the use of CP to prescribe exercise intensity for periods of exercise training. Compared to when exercise training was prescribed relative to $\dot{V}O_{2max}$, greater increases in $\dot{V}O_{2max}$ were observed and the number of individuals demonstrating an increase in $\dot{V}O_{2max}$ above a predefined meaningful response threshold was increased when exercise training was prescribed relative to CP. If results persisted in this manor, this could elucidate on the most effective means of exercise intensity prescription for future training programmes.

Overall, the results of the present thesis provide evidence to justify a shift from traditional to threshold-based exercise intensity prescription. Mounting evidence is presented demonstrating the superiority in using threshold intensity anchors to prescribe exercise, and that the number of individuals demonstrating marked increases in $\dot{V}O_{2max}$ is increased when threshold-based exercise training is prescribed. If the number of individuals experiencing what can be considered a meaningful increase in $\dot{V}O_{2max}$ is greater following threshold-based training programmes, this could have profound implications for a variety of populations where increasing $\dot{V}O_{2max}$ is vital for attaining performance and/or health-related benefits.

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APPENDIX

Supplementary file for **Chapter 6**

CHANGES IN CARDIORESPIRATORY FITNESS FOLLOWING EXERCISE TRAINING PRESCRIBED RELATIVE TO TRADITIONAL INTENSITY ANCHORS AND TO PHYSIOLOGICAL THRESHOLDS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF INDIVIDUAL PARTICIPANT DATA

PRISMA IPD

Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

PRISMA-IPD Section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2-3
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	

		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	7
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	7
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	7-8
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	8-9
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8-9
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	8-9
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	8-9

		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	8-9
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	8-9
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	8-9
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	8-9
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and t^2). • How studies providing IPD and not providing IPD were analysed together (where applicable). • How missing data within the IPD were dealt with (where applicable).	10-11

Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	12
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	10-11
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	11
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	12-16
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	12
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	Suppl.
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	17-20
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	17-20

		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	Suppl.
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarise the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	17-20
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	21
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	21-25
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	21-25
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	21-25
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	4

Risk of Bias

The inter-reviewer reliability for the reviewers was found to be k=0.798 (p < 0.001), indicating 'substantial' agreement between reviewers. There were no important issues when checking IPD integrity. Categorisation of k statistic, 0.01-0.2 is slight; 0.21-0.40 is fair; 0.41-0.60 is moderate; 0.61-0.80 is substantial; 0.81-1.00 is almost perfect agreement. Results of the RoB are presented in Figure 1. The ROBINS-I tool was used for non-randomised and/or uncontrolled studies. Studies: (Bouchard et al., 1999; Casaburi et al., 1987a; Dalleck et al., 2008; Granata et al., 2016; Jacques et al., 2021; Landen et al., 2021; Nicolini et al., 2019; Nio et al., 2020; Scharhag-Rosenberger et al., 2012; Vanhatalo et al., 2008; Vollaard et al., 2009; Yan et al., 2017) were all deemed (authors SM and DM) as low risk with only domain 6 (Bias in measurement of outcomes) highlighting as 'some concerns' due to outcome assessors being aware of the intervention received by study participants, as is typically the nature of exercise intervention studies.

Search strategy

Below is the example search terminology used to search electronic databases.

(((((((((high intensity interval training[Title/Abstract]) OR (continuous training[Title/Abstract])) OR (endurance training[Title/Abstract])) OR (exercise[Title/Abstract])) OR (training[Title/Abstract])) AND (maximum oxygen uptake[Title/Abstract])) OR (maximal oxygen uptake[Title/Abstract])) OR (VO2max[Title/Abstract])) OR (cardiorespiratory fitness[Title/Abstract])) AND (healthy adults)

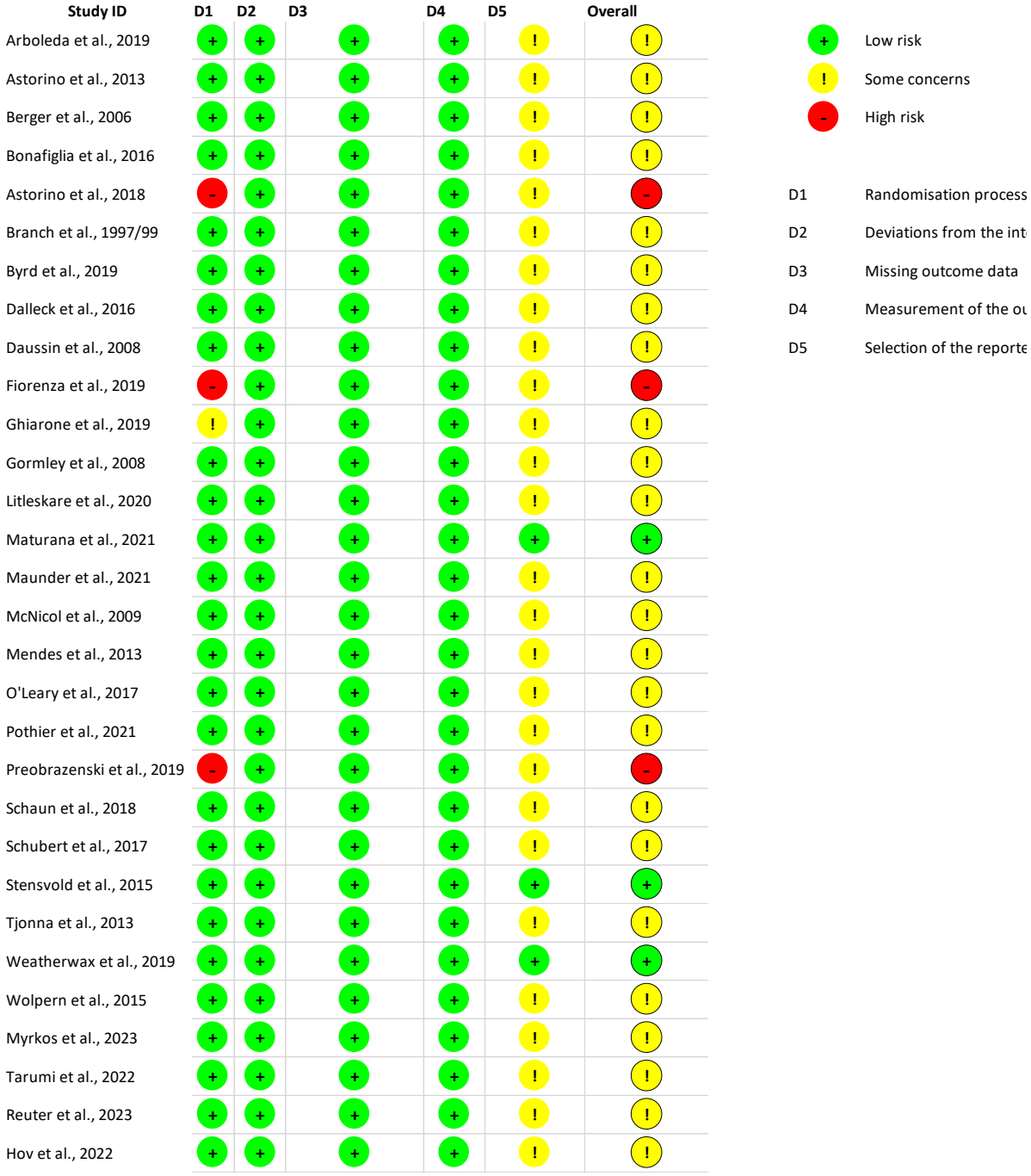
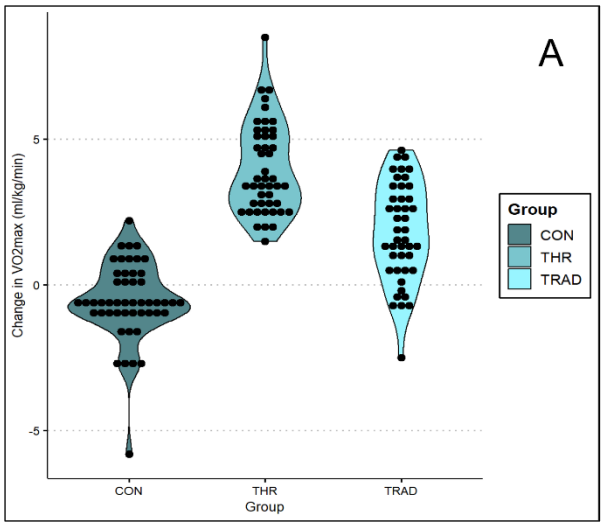
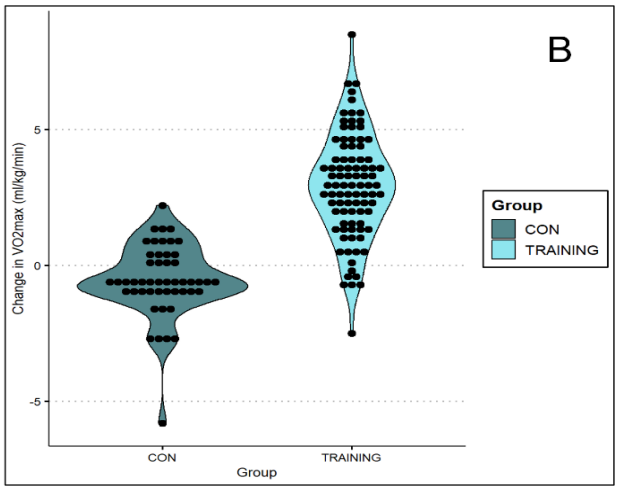


Figure 1. Results of the Cochrane Risk of Bias (RoB) tool.

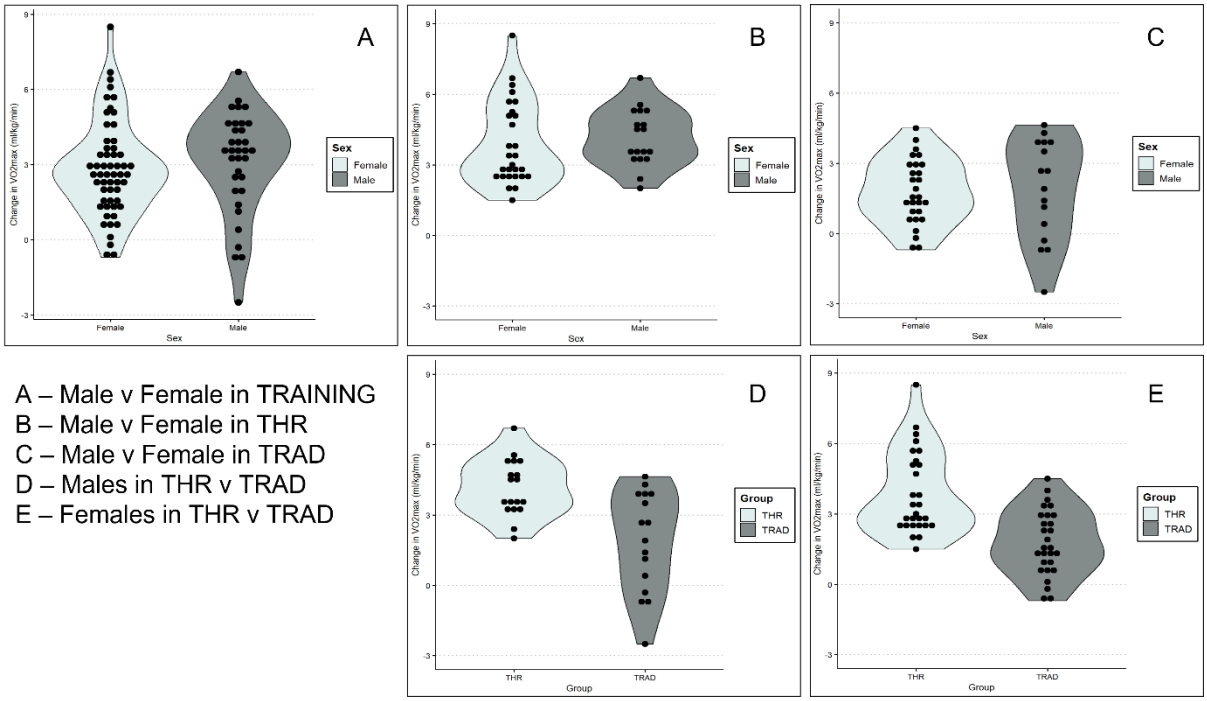
Data visualisation



Change in $\dot{V}O_{2max}$ (ml·kg^{-1}·min^{-1}) in controlled THR and TRAD exercise groups and non-exercising control group (CON). MID: minimum important difference, THR: exercise training prescribed relative to physiological thresholds, TRAD: exercise training prescribed relative to traditional intensity anchors.

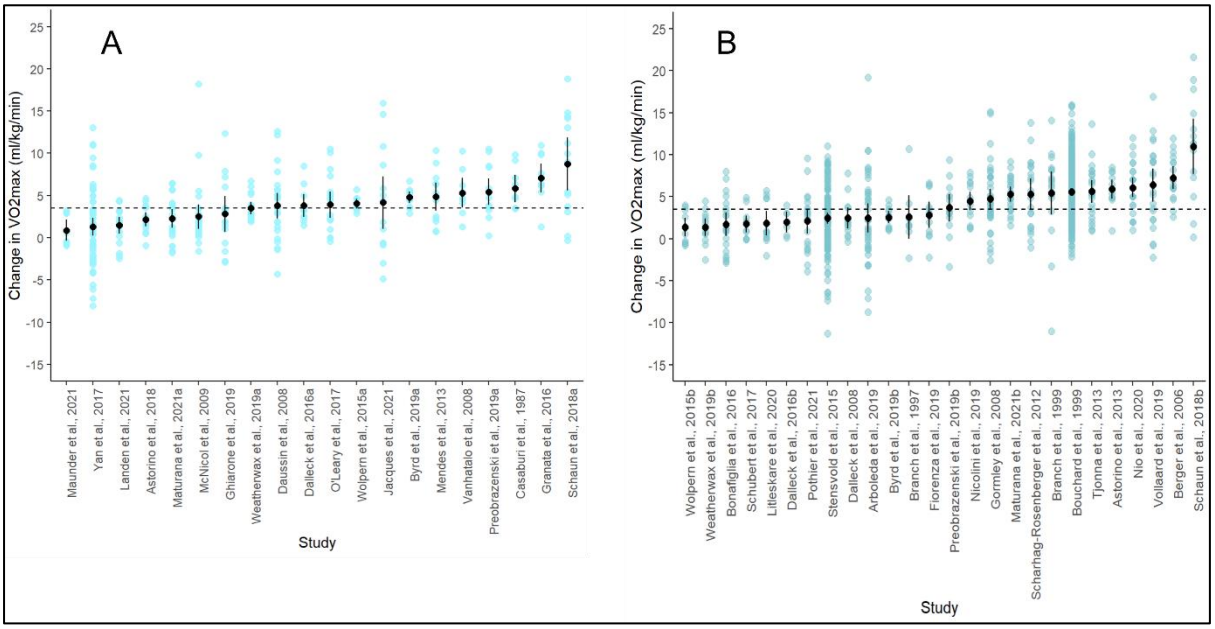


Change in $\dot{V}O_{2max}$ (ml·kg^{-1}·min^{-1}) in combined THR and TRAD controlled exercise groups (TRAINING) and in non-exercising control group (CON) (B). MID: minimum important difference.

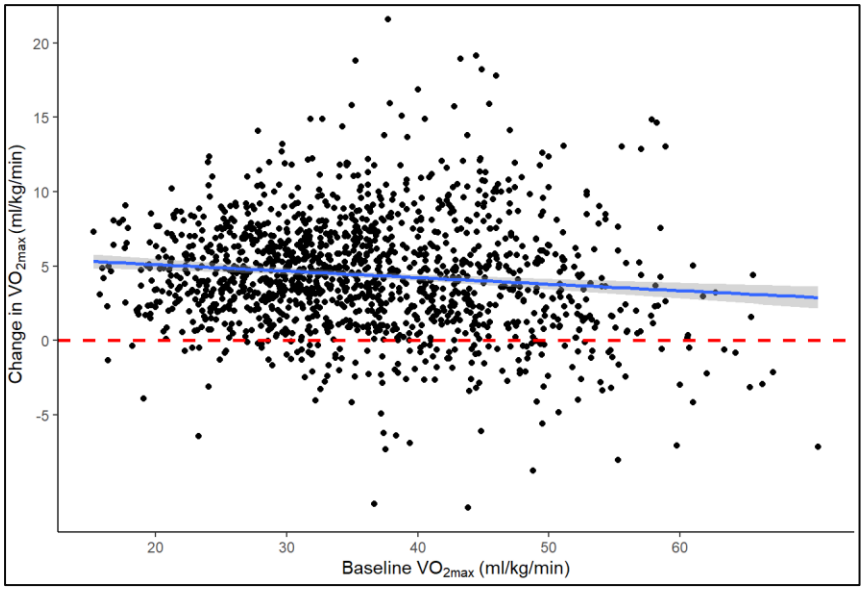


A – Male v Female in TRAINING
B – Male v Female in THR
C – Male v Female in TRAD
D – Males in THR v TRAD
E – Females in THR v TRAD

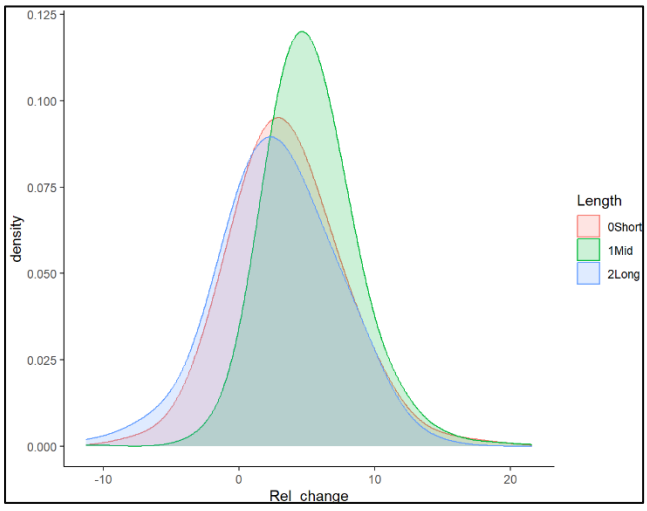
Change in $\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) in males and females in controlled THR and TRAD controlled studies combined (A), in THR only (B), in TRAD only (C), in males (D), and in females (E). THR: exercise training prescribed relative to physiological thresholds, TRAD: exercise training prescribed using traditional intensity anchors.



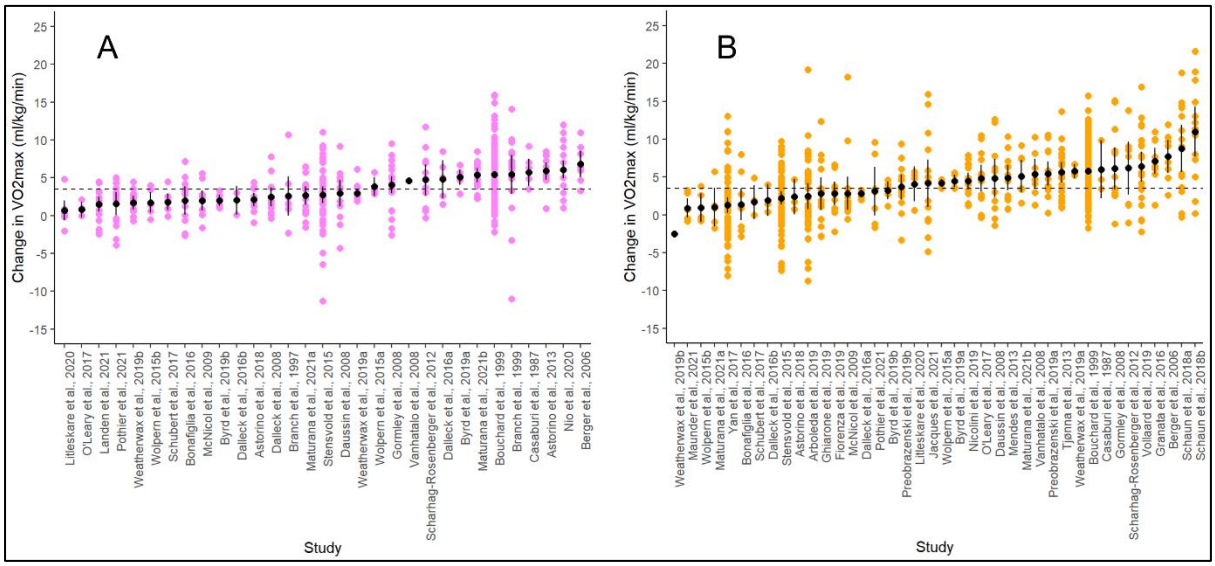
Changes in $\dot{V}O_{2max}$ (ml·kg^{-1}·min^{-1}) across all THR (A) and TRAD (B) studies. Dashed line is the MID (3.5 ml·kg^{-1}·min^{-1}).

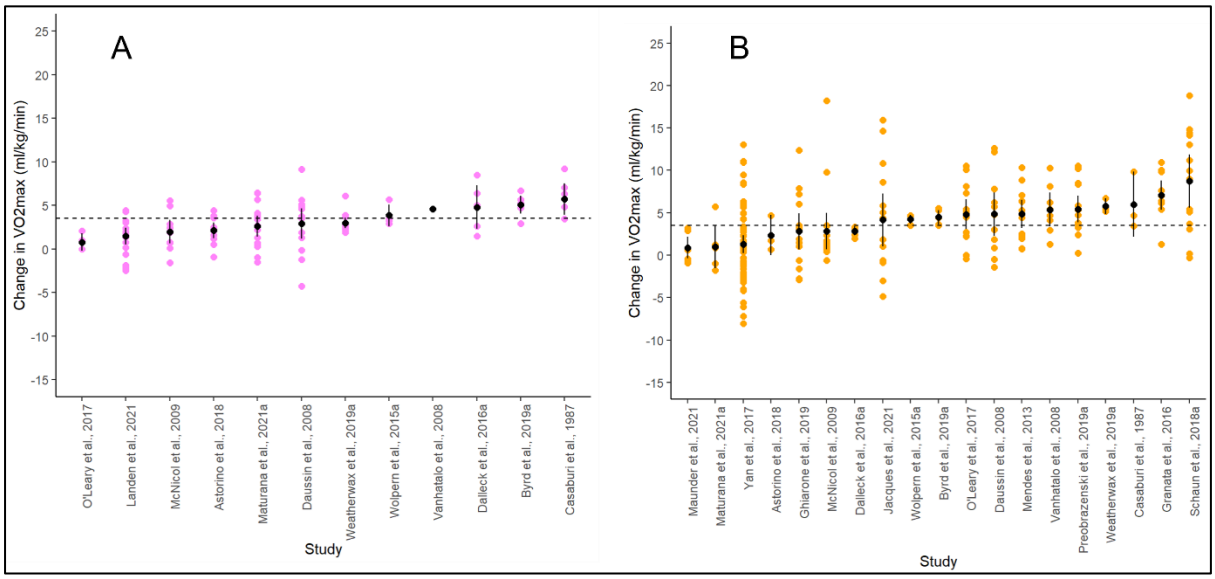


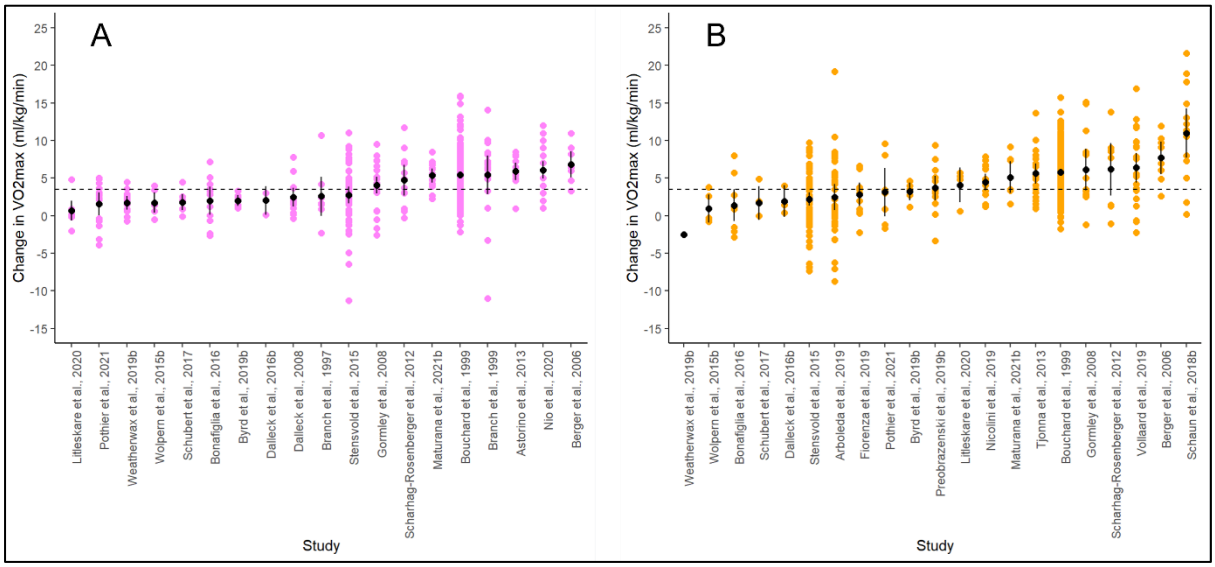
Relationship between baseline $\dot{V}O_{2max}$ and subsequent $\dot{V}O2max$ change score (ml·kg^{-1}·min^{-1}).



Distribution of $\dot{V}O_{2max}$ change scores in relation to study training duration. Training duration: Short, 3 to 11 weeks; Mid, 12 to 20 weeks; Long, 21 to 52 weeks.


A
B
Change in VO2max (ml/kg/min)
Study


A
B
Change in VO2max (ml/kg/min)
Study


A
B
Change in VO2max (ml/kg/min)
Study

Change in V̇O2max in females and males across all exercise groups (Top: A, B), THR only (Middle: A, B), and TRAD only (Bottom: A, B). Dashed line is the MID (3.5 $ml \cdot kg^{-1} \cdot min^{-1}$).

Ethics approval Notification: **Chapter 5**

University of Hertfordshire UH

HEALTH, SCIENCE, ENGINEERING AND TECHNOLOGY ECDA

ETHICS APPROVAL NOTIFICATION

TO	Samuel Meyler
CC	Daniel Muniz
FROM	Dr Simon Trainis, Health, Science, Engineering & Technology ECDA Chair
DATE	14/10/2021

Protocol number: **LMS/PGR/UH/04708**

Title of study: Comparison of acute responses to exercise prescribed relative to maximum physiological values and physiological thresholds.

Your application for ethics approval has been accepted and approved with the following conditions by the ECDA for your School and includes work undertaken for this study by the named additional workers below:

no additional workers named

General conditions of approval:

Ethics approval has been granted subject to the standard conditions below:

Permissions: Any necessary permissions for the use of premises/location and accessing participants for your study must be obtained in writing prior to any data collection commencing. Failure to obtain adequate permissions may be considered a breach of this protocol.

External communications: Ensure you quote the UH protocol number and the name of the approving Committee on all paperwork, including recruitment advertisements/online requests, for this study.

Invasive procedures: If your research involves invasive procedures you are required to complete and submit an EC7 Protocol Monitoring Form, and copies of your completed consent paperwork to this ECDA once your study is complete.

Submission: Students must include this Approval Notification with their submission.

Validity:

This approval is valid:

From: 18/10/2021

To: 30/04/2022

Ethical Approval Notification: **Chapter 5**

University of Hertfordshire UH

HEALTH, SCIENCE, ENGINEERING AND TECHNOLOGY ECDA

ETHICS APPROVAL NOTIFICATION

TO	Samuel Meyler
CC	Daniel Muniz
FROM	Dr Rebecca Knight, Health, Science, Engineering & Technology ECDA Vice Chair
DATE	02/11/2022

Protocol number:	**LMS/PGR/UH/05138**
Title of study:	Inter-individual responses to exercise training prescribed relative to maximum oxygen uptake and to critical power

Your application for ethics approval has been accepted and approved with the following conditions by the ECDA for your School and includes work undertaken for this study by the named additional workers below:

no additional workers named

General conditions of approval:

Ethics approval has been granted subject to the standard conditions below:

Permissions: Any necessary permissions for the use of premises/location and accessing participants for your study must be obtained in writing prior to any data collection commencing. Failure to obtain adequate permissions may be considered a breach of this protocol.

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Invasive procedures: If your research involves invasive procedures you are required to complete and submit an EC7 Protocol Monitoring Form, and copies of your completed consent paperwork to this ECDA once your study is complete.

Submission: Students must include this Approval Notification with their submission.

Validity:

This approval is valid:

From: 02/11/2022

To: 31/08/2023

Health Screen: **Chapter 4** and **Chapter 5**

Participant Full Name:

Please do not partake in this study if you have any Covid-19 symptoms, listed below:

- A high temperature. This means you feel hot to touch on your chest or back (you do not need to measure your temperature).
- A new, continuous cough. This means coughing a lot for more than an hour, or 3 or more coughing episodes in 24 hours (if you usually have a cough, it may be worse than usual).
- A loss or change to your sense of smell or taste. This means you've noticed you cannot smell or taste anything, or things smell or taste different to normal.

If you have tested positive for Covid-19 then you should self-isolate. If you live with someone who tests positive, but you have been double vaccinated, then you do not need to self-isolate (as a precaution, you should get tested before coming onto campus).
If the above applies to you, please let us know and we will cancel your appointment.

It is important when having volunteered as subject for this study and having read the briefing sheet for subjects that you answer the following questions. Please do not answer any questions if you consider them intrusive.

1. Do you suffer from high blood pressure, or any heart problems?	Yes	No
2. Do you often get dizzy, or do you know that you have low blood pressure?	Yes	No
3. **When** and **what** did you last eat?		
4. Are you under the influence of alcohol or any other psycho-active substance?	Yes	No
5. Have you had a cold or flu in the last two weeks?	Yes	No
6. Are you suffering from any musculo-skeletal injury?	Yes	No
7. Are you currently taking any medication (over the counter, or prescription)? (you do not need to answer "Yes" if you are only taking oral contraceptives, or if you are an asthmatic with an inhaler available)	Yes	No
8. Do you, or have you suffered from any blood related disorders, or have you any issues related to blood taking?	Yes	No
9. Have you ever been told that you should not exercise?	Yes	No
10. Do you feel fully fit, and eager to act as subject?	Yes	No
11. Is there any reason, not stated above, why you cannot take part as a subject in this practical?	Yes	No

Participant Signature: **Date:**

Checked by (Member of Staff):

Participant information sheet: **Chapter 4**

University of Hertfordshire UH Ethics Committee

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET

1 **Title of study**

Comparison of acute responses to exercise prescribed relative to maximum physiological values and physiological thresholds

2 **Introduction**

You are being invited to take part in a study. Before you decide whether to do so, it is important that you understand the study that is being undertaken and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. The University's regulation, UPR RE01, 'Studies Involving the Use of Human Participants' can be accessed via this link:

https://www.herts.ac.uk/about-us/governance/university-policies-and-regulations-uprs/uprs
(after accessing this website, scroll down to Letter S where you will find the regulation)

Thank you for reading this.

3 **What is the purpose of this study?**

The purpose of this study is to determine whether prescribing exercise relative to physiological thresholds provides a more homogenous exercise stimulus among individuals than when prescribed relative to an individual's maximum heart rate. The findings of this study will provide insight in to whether such prescription methods in turn lead to more homogenous training adaptations observed within a group, such that the occurrence of 'non-responders' to exercise training can be minimized.

4 **Do I have to take part?**

It is completely up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not affect any treatment/care that you may receive (should this be relevant).

5 **Are there any age or other restrictions that may prevent me from participating?**

Eligibility criteria is as follows:

- Aged 18+ years old
- Male or female
- No history of, or not currently experiencing, high or low blood pressure, heart problems, dizziness, respiratory problems, or hematological disorders

- Absent of any musculoskeletal injuries
- Non-obese (BMI < 30 kg/m^2)
- Not suffering from any known diseases

Each participant will be subject to health screening.

6 **How long will my part in the study take?**

If you decide to take part in this study, you will be involved in it for 3 weeks (consisting of 7 visits to the laboratory).
Week 1 will involve 3 visits separated by 24 hours.
Visit 1 will include anthropometric measurements and a VO2max test (test intended to last < 20 min)
Visit 2 and 3 will include 2 x constant work rate tests per day (each of which intended to last between 2 and 15 min with an intertrial recovery time of 1 hour)
Week 2 will then require a further 2 visits.
Visit 4 will include moderate-intensity continuous cycling exercise (MICE; 20 min) and a high-intensity interval session (HIIT; 15 min), with an intertrial recovery time of 1 hour
Visit 5 will include heavy intensity continuous cycling exercise (HICE; 20 min) and severe intensity continuous cycling exercise (SICE), with an intertrial recovery time of 1 hour
Week 3 will then require a further 2 visits.
Visit 6 will involve another MICE and HIIT, with an intertrial recovery time of 1 hour
Visit 7 will involve another HICE and SICE, with an intertrial recovery time of 1 hour

7 **What will happen to me if I take part?**

After details of the study have been understood, and consent provided, you will be invited to the physiology laboratory in the Institute of Sport on De Havilland Campus. On your first visit, anthropometric data will be collected including height and weight and after that you will perform an incremental test to task failure (VO2max test) on a cycle ergometer. This test is intended to last up to 20 min and will involve physiological measurements including gas analysis and heart rate monitoring. This test should be completed to task-failure (when cadence drops below a predefined threshold) and will be used to estimate your VO2max and gas exchange threshold.

On visits 2 and 3, you will perform 2 constant work rate tests per visit, intended to last between 2-15 min each, with an intertrial recovery time of 1 hour. During the 1-hour recovery period you are free to undertake any other activities at rest (e.g., check emails, social media etc.). These constant work rate tests should be completed to task-failure (same as above) and will be used to estimate your critical power and W'.

Following exercise testing, you will complete two batteries of exercise sessions. Battery 1 and 2 will both include 1 x MICE, HIIT, HICE and SICE, but the exercise in battery 1 will be prescribed at an intensity relative to your maximum heart rate (HRmax) whereas battery 2 will be prescribed relative to your gas-exchange threshold (GET) and critical power (CP). You will complete both batteries of exercise over the course of 4 visits (2 weeks) (see Q6.). The aforementioned physiological measurements will be taken during all exercise sessions with the addition of blood lactate analysis. To analyze blood lactate, small samples of capillary blood will be collected from the border of your fingertip through a small pinprick.

8 **What are the possible disadvantages, risks or side effects of taking part?**

- Cycling exercise testing - as with any exercise that is undertaken to a maximal effort, it is possible that you may experience a degree of exertional exhaustion, dizziness, nausea, musculoskeletal soreness or injury, or collapsing. As a participant you will be under constant supervision by a researcher with considerable experience of exercise physiology and exercising testing. The researcher is also first aid trained. As part of the testing protocol, you will undergo a standardized warm-up and cool-down to minimize the above risks. You will have also completed a health screen questionnaire, which will be used to minimize such risks.
- Capillary blood samples - with any form of blood collection there is a risk of cross-contamination or infection of pathogenic organisms. Such risks are very rare, and full precautions are taken during all testing and exercise to minimize such risks. A qualified researcher will be taking blood samples under standard laboratory conditions using single kit equipment for each test. The researcher is first aid trained and will adhere to strict protocols regarding the collection and handling of blood samples.

9 **What are the possible benefits of taking part?**

- Accurate measurement of VO2max representing your aerobic capacity (important for endurance performance) and cardiorespiratory fitness (a strong predictor of all-cause mortality).
- Determine your critical power and W' which has large associations with endurance performance and exercise capacity.
- Experience being involved in a scientific research project and using state of the art equipment.
- Experience different types of cycling sessions that can be used to improve aerobic capacity and cardiorespiratory fitness.
- Learn first-hand about how your body responds to different types of exercise.

10 **How will my taking part in this study be kept confidential?**

Raw data from testing will be kept confidential with no names linking data to an individual. Instead, subject ID's will be used. Any personal data such as contact details will be used only when necessary (e.g., to contact participants and schedule laboratory visits).

11 **What will happen to the data collected within this study?**

- Any personal data collected will be stored electronically, in a password-protected environment, for up to 24 months, after which time it will be destroyed under secure conditions.
- Study data will be anonymized prior to storage.
- Findings and anonymized data from the study will be published in a peer-reviewed journal article and presented at relevant conferences. Data may also be used in other relevant studies within the area; however, data will strictly be anonymized and individuals will be unidentifiable.

12 **Will the data be required for use in further studies?**

- Data collected may be re-used or subjected to further analysis as part of a future ethically approved study; the data re-used will be strictly anonymized and un-identifiable.

13 **Who has reviewed this study?**

This study has been reviewed by:

- The University of Hertfordshire Health, Science, Engineering and Technology Ethics Committee with Delegated Authority

The UH protocol number is < LMS/PGR/UH/04708 >

14 **Factors that might put others at risk**

Please note that if, during the study, any medical conditions or non-medical circumstances such as unlawful activity become apparent that might or had put others at risk, the University may refer the matter to the appropriate authorities and, under such circumstances, you will be withdrawn from the study.

15 **Who can I contact if I have any questions?**

If you would like further information or would like to discuss any details personally, please get in touch with me, in writing, by phone or by email:

Sam Meyler
07495739477
s.meyler2@herts.ac.uk

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University's Secretary and Registrar at the following address:

Secretary and Registrar
University of Hertfordshire
College Lane
Hatfield
Herts
AL10 9AB

Thank you very much for reading this information and giving consideration to taking part in this study.

Participant information sheet: **Chapter 5**

University of Hertfordshire UH Ethics Committee

UNIVERSITY OF HERTFORDSHIRE

ETHICS COMMITTEE FOR STUDIES INVOLVING THE USE OF HUMAN PARTICIPANTS ('ETHICS COMMITTEE')

FORM EC6: PARTICIPANT INFORMATION SHEET

1 **Title of study**

Inter-individual responses to exercise training prescribed relative to maximum oxygen uptake and to critical power

2 **Introduction**

You are being invited to take part in a study. Before you decide whether to do so, it is important that you understand the study that is being undertaken and what your involvement will include. Please take the time to read the following information carefully and discuss it with others if you wish. Do not hesitate to ask us anything that is not clear or for any further information you would like to help you make your decision. Please do take your time to decide whether or not you wish to take part. The University's regulation, UPR RE01, 'Studies Involving the Use of Human Participants' can be accessed via this link:

https://www.herts.ac.uk/about-us/governance/university-policies-and-regulations-uprs/uprs
(after accessing this website, scroll down to Letter S where you will find the regulation)

Thank you for reading this.

3 **What is the purpose of this study?**

The purpose of this study is to determine whether prescribing exercise relative to critical power reduces the variability of training-induced adaptations compared to when using maximum oxygen uptake to anchor exercise intensity. The findings of the present study will help inform the optimization of exercise prescription to increase the likelihood of individuals obtaining meaningful changes in their cardiorespiratory fitness following training.

4 **Do I have to take part?**

It is completely up to you whether or not you decide to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Agreeing to join the study does not mean that you have to complete it. You are free to withdraw at any stage without giving a reason. A decision to withdraw at any time, or a decision not to take part at all, will not affect any treatment/care that you may receive (should this be relevant).

5 **Are there any age or other restrictions that may prevent me from participating?**

Eligibility criteria is as follows:

- Aged 18+ years
- Male or female
- No history of, or not currently experiencing, high or low blood pressure, heart problems, dizziness, respiratory problems, or hematological disorders
- Absent of any musculoskeletal injuries

- Non-obese (BMI < 30 kg/m^2)
- Not suffering from any known diseases

Each participant will be subject to health screening.

6 **How long will my part in the study take?**

If you decide to take part in this study, the duration of the study will span ~9 weeks, this will comprise of the following:

Week 1: Testing block #1 – Visit the laboratory on 2 x days for approx. 2 hours per visit, however one of these hours each visit will be a recovery period where you are free to do as you please

Week 2-4: Training block #1 – 3 x training sessions per week, for 3 weeks including 'cardio' and high intensity interval (HIIT) sessions.

Week 5: Testing block #2 – same as testing block #1

Week 6-8: Training block #2 – same as training block #1

Week 9: Testing block #3 – same as testing block #1

7 **What will happen to me if I take part?**

After details of the study have been understood, and consent provided, you will be invited to the physiology laboratory in the Institute of Sport on De Havilland Campus. On your first testing visit, anthropometric data will be collected including height and weight and after that you will perform an incremental exercise test ($\dot{V}O_{2max}$ test) on a cycle ergometer. This test is intended to last no more than 15 min and will involve physiological measurements including gas analysis and heart rate monitoring. This test is completed to task-failure, i.e., the resistance gets harder and harder until you cannot maintain a given cycling cadence. Following an hour recovery period you will then perform a second exercise test intended to last < 5 min, this is again performed to task failure.

On testing visit 2 you will perform a further 2 exercise tests, intended to last between 2-15 min each, again with an intertrial recovery time of 1 hour. During the 1-hour recovery period you are free to undertake any other activities at rest (e.g., check emails, social media, watch television etc.).

Following exercise testing, you will be randomized into one of two groups, exercise group 1 or exercise group 2. Exercise groups 1 and 2 will both undertake 3 weeks of training consisting of 1 x cardio session and 2 x high intensity interval sessions per week. Following this 3-week period all groups will then undertake a second testing block followed by a further 3 weeks of training before the final testing block.

8 **What are the possible disadvantages, risks or side effects of taking part?**

- Cycling exercise testing - as with any exercise that is undertaken to a maximal effort, it is possible that you may experience a degree of exertional exhaustion, dizziness, nausea, musculoskeletal soreness, injury, or collapsing. As a participant you will be under constant supervision by a researcher with considerable experience of exercise physiology and exercising testing. The researcher is also first aid trained. As part of the testing protocol, you will undergo a standardized warm-up and cool-down to minimize the above risks. You

will have also completed a health screen questionnaire, which will be used to minimize such risks.

9 **What are the possible benefits of taking part?**

- Accurate measurement of $\dot{V}O_{2max}$ representing your aerobic capacity (important for endurance performance) and cardiorespiratory fitness (a strong predictor of all-cause mortality). It is likely that this will also be improved following the training intervention which may contribute to improved health and well-being and performance capacity.
- Determine and improve your critical power and W' which has large associations with endurance performance and exercise capacity.
- Experience being involved in a scientific research project and using state of the art equipment.
- Experience different types of cycling sessions that can be used to improve aerobic capacity and cardiorespiratory fitness.
- Learn first-hand about how your body responds to different types of exercise.

10 **How will my taking part in this study be kept confidential?**

Raw data from testing will be kept confidential with no names linking data to an individual. Instead, subject ID's will be used. Any personal data such as contact details will be used only when necessary (e.g., to contact participants and schedule laboratory visits).

11 **What will happen to the data collected within this study?**

- Any personal data collected will be stored electronically, in a password-protected environment, for up to 24 months, after which time it will be destroyed under secure conditions.
- Study data will be anonymized prior to storage.
- Findings and anonymized data from the study will be published in a peer-reviewed journal article and presented at relevant conferences. Data may also be used in other relevant studies within the area; however, data will strictly be anonymized and individuals will be unidentifiable.

12 **Will the data be required for use in further studies?**

- Data collected may be re-used or subjected to further analysis, in future research studies in this area and by the same investigators. In any case, data will be strictly anonymized and un-identifiable, and used exclusively for research purposes.

13 **Who has reviewed this study?**

This study has been reviewed by:

- The University of Hertfordshire Health, Science, Engineering and Technology Ethics Committee with Delegated Authority

The UH protocol number is < LMS/PGR/UH/05138>

14 **Factors that might put others at risk**

Please note that if, during the study, any medical conditions or non-medical circumstances such as unlawful activity become apparent that might or had put others at risk, the University may refer the matter to the appropriate authorities and, under such circumstances, you will be withdrawn from the study.

15 **Who can I contact if I have any questions?**

If you would like further information or would like to discuss any details personally, please get in touch with me, in writing, by phone or by email:

Sam Meyler
07495739477
s.meyler2@herts.ac.uk

Although we hope it is not the case, if you have any complaints or concerns about any aspect of the way you have been approached or treated during the course of this study, please write to the University's Secretary and Registrar at the following address:

Secretary and Registrar
University of Hertfordshire
College Lane
Hatfield
Herts
AL10 9AB

Thank you very much for reading this information and giving consideration to taking part in this study.