The Incidence of Cardiorespiratory Fitness Training and Cardiometabolic Risk Factor Responsiveness Following Individualised and Standardised Exercise Prescription

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Abstract

There is individual variability following cardiorespiratory fitness (CRF) training leading to the terminology of CRF 'responders' and 'non-responders,' yet the underlying cause of the variability is not well understood. Traditionally, a standardised approach to exercise prescription has utilised relative percentages of maximal heart rate (HR), heart rate reserve (HRR), maximal oxygen consumption (VO_2max), or VO_2 reserve to establish exercise intensity. This 'one size fits all' model fails to take into consideration individual metabolic responses to exercise and may be related to the variability in training responses. Therefore, the purpose of this thesis was to better understand training responsiveness following 12 weeks of CRF training between a standardised and individualised exercise intensity prescription.

A total of 49 and 20 inactive experimental and control participants, respectively, were recruited for the investigation from a community wellness program and the surrounding community via advertisement at the local university, newspaper, and word-of-mouth. In a subgroup of the main experimental participants, a TE of 4.7% in VO_2max was established from a coefficient of variability following repeated testing at baseline. Therefore, it was deemed that participants needed to have a $\%\Delta > +4.7\%$ in VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) to be considered a training responder following the 12-week intervention.

Training prescription in the individualised group was anchored based on the first (VT1) and second ventilatory threshold (VT2) with exercise intensity starting below VT1, increasing to between VT1 and VT2, and ending the exercise protocol with a HR above VT2. The standardised group had exercise intensity based on percentages of HRR with a progression from 40% to 65% of HRR throughout the 12 weeks. The control group was asked to maintain their regular day-to-day lifestyle.

In an analysis of time course changes, it was revealed that both groups had a significant change ($p<0.05$) at week 8 and 12 compared to baseline values. However, only the individualised group showed a significant increase from week 8 to 12. CRF responsiveness (measured by changes in VO_2max) was significantly different between groups with responsiveness of 100% and 60% for the individualised and standardised groups, respectively. VO_2max significantly increased for the standardised and individualised groups from 24.3±4.6 to 26.0±4.2 $ml \cdot kg^{-1} \cdot min^{-1}$, and 29.2±7.5 to 32.8±8.6

$ml \cdot kg^{-1} \cdot min^{-1}$, respectively. Absolute VO_2max significantly increased from 2.0±0.6 to 2.2±0.6 $L \cdot min^{-1}$, and 2.4±0.8 to 2.6±0.9 $L \cdot min^{-1}$ for the standardised and individualised groups, respectively. The overall changes in cardiometabolic factors were analysed based on changes in MetS z-scores (i.e. combination of fasting blood glucose, lipids, triglycerides, blood pressure, and waist circumference). However, MetS z-scores did not show a significant difference between individualised and standardised groups, but trends suggested that an individualised approach to the exercise prescription may have a positive effect on these outcomes.

The main finding of this thesis was that an individualised continuous aerobic exercise intensity prescription is superior to a standardised method when investigating training responsiveness. It is believed the mechanisms are related to an individualised approach taking into consideration individual metabolic characteristics.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any degree or diploma of a university or other institution of higher learning.

_____	10 April 2019
Ryan M Weatherwax	Date

Co-authored Works Arising from this PhD Thesis

Chapter	Publication reference	Contribution
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To my study participants: Without your sweat, blood (literally), and commitment to undergo at least 4 maximal exercise tests while training 3 days a week for 12 weeks, this study would not have been possible.

Ethical approval

All experimental studies contained within this thesis received ethics approval from Auckland University of Technology (16/264) on 1 August 2016 (Appendix A) and Western State Colorado University (HRC2016-01-90R6) on 5 July 2016 (Appendix B).

The study was registered with www.clinicaltrials.gov (NCT02868710) on 15 August 2016.

List of Abbreviations

Abbreviation	Definition
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CV	Coefficient of variability
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EE	Energy expenditure
GLM	General linear model
GXT	Graded exercise test
HDL	High-density lipoprotein cholesterol
HR	Heart rate
HR_{max}	Maximum heart rate
HRR	Heart rate reserve
IDF	International Diabetes Federation
IPAQ	International Physical Activity Questionnaire
Kcal	Kilocalorie
LDL	Low-density lipoprotein cholesterol
MAP	Mean arteriole pressure
MetS	Metabolic syndrome
MET	Metabolic equivalent of resting metabolic rate
RHR	Resting heart rate
RPE	Rate of perceived exertion
SBP	Systolic blood pressure
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TC	Total cholesterol
TE	Technical error
TG	Triglyceride
VE/VCO_2	Ventilatory equivalents of carbon dioxide
VE/VO_2	Ventilatory equivalents of oxygen
VO_2	Volume of oxygen consumption
VO_2max	Maximal oxygen consumption
VO_2peak	Peak oxygen consumption
VO_2R	Oxygen consumption reserve

Abbreviation	Definition
VT	Ventilatory threshold
VT1	First ventilatory threshold
VT2	Second ventilatory threshold
WC	Waist circumference
W_{max}	Wattage maximum
χ^2	Pearson's chi square

Chapter 1 - Introduction

1.1 Rationale

Heterogeneity in the response to exercise training was first recognised in the 1980s (1) with a series of standardised studies investigating trainability of sedentary adults. Among these studies was an investigation into responses of maximal aerobic power in which a large interindividual difference in the incidence of response ranging from an increase of 5% to 88% in maximal aerobic abilities was reported (2). Even though these original findings were reported over 30 years ago, individual variability of CRF remains poorly understood, but continues to be documented. For example, the following are some of the major findings throughout the years documenting the large variability in CRF training responsiveness:

- Individual improvements in VO_2max ($L \cdot min^{-1}$) ranged from 0 to +42% after 9-12 months of walking and/or running training (3)
- Endurance training elicited an average increase in VO_2peak of 8% ± 6% with a range of -5% to +22% (4)
- For groups working at a volume of 4, 8, and 12 $kcal \cdot kg^{-1} \cdot wk^{-1}$, there was an incidence of non-response of 44.9%, 23.8%, and 19.3%, respectively (5)
- A -8% to +42% increase in VO_2peak was found after a combined intervention of endurance and strength training (6)
- After 5 months of CRF training, there was a change of -5% to +23% in VO_2peak (7)

A major factor for the lack of understanding training responsiveness is due to the lack of a set definition in the literature regarding how a CRF training 'response' is determined (i.e. criteria to classify someone as a responder or non-responder). For example, criteria to determine incidence of response for changes in VO_2max have been established by classifying a fixed proportion of the lowest training response (8), absolute changes in pre- to post-intervention values (5,7), a change of more than one standard deviation (9), or a response that falls outside of a previously established biological variability and measurement error (10–12). This lack in a set definition increases the variability in how data are reported. Therefore, a robust and set definition regarding how to establish training responsiveness is needed to increase consistency among research findings.

Furthermore, in order to have an all-inclusive definition for incidence of response, the measurement error and day-to-day biological variability –accounting for the TE – must be taken into account (13). Therefore, biological variability and measurement error must be known for each outcome (i.e. establishing the CV for each outcome that will be used to categorised participants as responders or non-responder) to determine whether responses exceed the TE in a favourable direction. Three recent investigations of steady-state aerobic exercise (10–12) indeed used TE to determine training responsiveness. However, for these investigations, the TE was sourced from previously published work and were not specific to the cohort or site in which data were collected. This methodology alone may cause variability in how the data will be analysed.

Conventionally, results of exercise-based studies are reported as the group mean and standard deviation (14) and only illustrate the main effects and group based differences (15) of training responsiveness. Overall, there is a lack in attention to individual differences with these conventional methods of reporting data since nearly 32% of measurements (distributed normally) fall outside of 1 standard deviation. Recent literature proposes reporting not only the mean, standard deviation, and group differences, but also individual responses to the training program (14,15) or at least ranges of endurance changes (10) and changes that occur to cardiovascular risk factors. This approach will provide further insight on individual variability and strengthen the results and findings of training responsiveness studies.

From the HERITAGE Family Study (16), a large, well-controlled, 20-week standardised endurance training program, insight was gained on the incidence of response. It was reported that genetics may play a critical role in the incidence of response (17) with trainability of VO_2max linked to familial aggregation (18). However, with only about 50% of training variability associated with genetic factors, a large factor in the individual variability could be due to suboptimal methodology of exercise prescription. Indeed, due to the theoretical and physiological mechanisms of exercise prescription, utilization of a threshold measurement for establishing exercise intensity has been suggested to decrease the incidence of non-response and improve CRF and cardiometabolic factors compared to the traditional approach (relative percent concept) using intensities set relative to VO_2max, HR_{max}, VO_2R, or HRR (19). However, there have been few studies that have reported individual responses following training relative to a threshold measurement (14) with only two investigations reporting individual responses to training comparing set intensities based on VT1 and VT2 measurements and %HRR (11,12).

Indeed, caution has been advised for utilization of the relative percent method, specifically HR_{max} and VO_2max, as criteria to determine workload as they may not be sufficient methods to elicit the desired metabolic response (20,21). Furthermore, percentages for both HR_{max} and VO_2max correspond to a wide range of exercise intensities relative to threshold measurements (22). For example, with exercise intensities between 58% and 75% of VO_2max, some participants were found to be above while others were below their individual anaerobic threshold (23) and similar findings were noted by Scharhag-Rosenberger and colleagues (21) when investigating a 12-month jogging/walking program. In order to make the prescription of exercise intensity more individualised, many researchers have used percentages of HRR since this takes into consideration not only maximal HR, but also resting HR. However, aerobic thresholds were found to be at 70% ± 10% of HRR (24) indicating large variability in the metabolic stress across individuals at a set %HRR.

In summary, though individual variability in response to CRF training have been recognised since the 1980s, the specific factors explaining the non-response/response phenomenon remains poorly understood. Furthermore, it has been acknowledged as far back as the late 1970s that utilizing a relative percent method (i.e., %HRR) to establish exercise intensity fails to account for individual metabolic responses to exercise (20). Nevertheless, the relative percent concept remains the gold standard recommendation for exercise intensity (25). It is both plausible and practical to think that an intensity set based on an individual's threshold measurement (i.e. VT) will not only encourage more positive physiological adaptations but taking into consideration individual metabolic differences may account for some of the variability in training responsiveness.

1.2 Research Objectives

1.2.1 Overarching Research Question

This thesis was designed to address the following overarching research question:

Does an individualised exercise prescription increase CRF and cardiometabolic responsiveness compared to a standardised exercise prescription?

The chapters of this PhD are constructed of studies designed to address specific research aims and objectives central to the overarching research question.

1.2.2 Aims

The overarching aim of this research was to conduct a cohesive investigation into the incidence of training responsiveness following individualised and standardised exercise prescription. This thesis is constructed in three parts to explore the primary aim.

Part 1: Identification of VO_2max TE using a cohort and site-specific approach
Part 2: Understanding the time course changes (every 4th week) of VO_2max changes
Part 3: Quantifying the CRF training responsiveness (i.e. percent change in VO_2max) following a 12-week intervention with the use of a site- and cohort-specific TE

1.2.3 Specific Objectives

The specific objectives of this research were as follows:

1. To firstly present previous research on the topic of CRF training responsiveness and provide information on the concepts central to this thesis (**Chapter 2**).
2. Identify and report the robust methodology designed to understand multiple factors related to CRF training responders and non-responders (**Chapter 3**).
3. The next study objective is fundamental to understanding CRF training variability and involved the identification of a cohort- and site-specific TE for establishing training responsiveness related to CRF changes (i.e. changes in VO_2max) and retrospectively analyse two previously published training investigations to highlight the methodology used to quantify a response can have major implications to the overall study results (**Chapter 4**).
4. Identify when changes in VO_2max actually occur. If exercise professionals have a clear idea that VO_2max changes should occur by week X of a study or training program, it will allow for a more detailed interpretation of results and an opportunity to change the exercise methodology to improve or enhance the overall training outcome. Therefore, the next main objective was to explore the VO_2max time course changes every 4th week associated with individualised and standardised exercise prescriptions and to understand if a specific timing can be identified for when VO_2max changes occur (**Chapter 5**).
5. With the understanding that training responsiveness are more comprehensive than just focusing on one factor (i.e. VO_2max for the majority of this PhD), the use of a MetS z-score to identity whether or not severity of MetS factors was explored. This objective was identified to understand the feasibility of using a MetS z-score

to investigate training responsiveness of cardiometabolic factors (SBP, DBP, HDL, TG, fasting BG, and WC) following a standardised and individualised exercise intensity prescription (**Chapter 6**)

6. The novel and primary objective of the overall study for the PhD was to identify the incidence of CRF training responsiveness and the differences between a standardised and individualised methodology of exercise intensity prescription using the cohort and site-specific TE (**Chapter 7**).
7. To summarise, discuss and conclude the findings of the research conducted, and present suggestions for future research directions (**Chapter 8**).

1.3 Thesis Overview

1.3.1 Thesis Organisation

This thesis is presented as a sequential progression of studies arranged in a series of chapters. Chapter 2 is a narrative review of the 'training responsiveness' topic related to steady state aerobic exercise training. Chapter 3 was developed from a publication in the journal Trials (26) in which I published the original thesis methodology. Chapter 3 has since been updated and is a modified version of the Trials paper to reflect changes that were made during the study when issues or previously unconsidered situations occurred.

Chapters 4-7 have been prepared as separate chapters for publication in peer-reviewed journals. Therefore, some repetition of information occurs. Although the chapters are close in content to their published or submitted for review journal articles, limited deviations from the published form do occur. However, all data, outcomes, and interpretations are identical to the published version. Preludes for each chapter serve to link and outline the progression of studies to read as one cohesive document. The purpose of Chapter 8 is to assemble all of the key study findings and outcomes and helps to provide an answer to the overreaching research question. Furthermore, this final chapter helps to identify the contributions to the advancement in knowledge related to training responsiveness stemming from this thesis and considers the implications of this research on increasing VO_2max training responsiveness and the adoption of the methodology for the development of exercise prescriptions by exercise professionals.

References are standardised throughout this thesis to the National Library of Medicine (US) format, which may differ from referencing styles used in the respective journals where articles have been published or are under review.

1.3.2 Thesis Methodology

One of the goals of this thesis was to collect data in a setting that represented a more 'real world' scenario. Often times, experimental research is conducted in a very controlled environment, for very just reason, but can sometimes lack real world application. Therefore, experimental participants were recruited with participants signing up for a community wellness program at a local university and from the surrounding area. The target population were individuals between the ages of 30 and 75 years, who participated in 30 min of moderate intensity exercise on 3 days a week or less, and were considered low-to-moderate risk based on recommended standards (25). All participants underwent

an individual consultation in which a detailed medical history questionnaire and thorough follow-up questions were completed to ensure inclusionary criteria were met. Sample size was projected with change in VO_2max as the main outcome variable. The means and standard deviations of a previous study (11) were examined and the effect size for this research study was calculated. Assuming a power of 0.80 was needed and the calculated effect size for change in VO_2max was 0.30, it was determined that approximately 16 participants would be needed for each group (27). It was assumed there would be an approximate 20% dropout rate, so the aim was to achieve 20 participants per group.

The control group was recruited as a convenience sample separate from the experimental participants due to the moral and ethical considerations of withholding a known physiological and psychological benefit (i.e. an exercise intervention), similar to previous research (28,29). The control participants were recruited by advertising and word-of-mouth looking for individuals that were interested in the various health indices from the laboratory testing, but not interested in increasing regular exercise or physical activity. Control participants had to meet the same inclusion/exclusion criteria previously mentioned and completed all the same laboratory testing at baseline and 12 weeks as the experimental groups.

Chapter 3 provides a detail explanation of the experimental protocol, but in summary, the thesis was a randomised control trial which was comprised of smaller studies. A sub group of the main experimental participants were first analysed to establish a CV to be used as the TE and the threshold to determine VO_2max training responsiveness. Experimental participants were then randomised to one of two groups: individualised or standardised groups with exercise intensity prescribed based on VTs or %HRR, respectively. At baseline and every 4^{th} week, experimental participants completed laboratory testing which involved basic anthropometric measure (height, weight, BMI, and WC), a blood profile (TC, HDL, LDL, TG, and fasting BG), and a maximal GXT with a verification procedure to confirm a true VO_2max.

1.3.3 Candidate Contribution

This thesis fulfils the terms of an Auckland University of Technology Doctoral Degree through a significant, original contribution to knowledge regarding the VO_2max and cardiometabolic training responsiveness of sedentary adults through an objective narrative of existing literature and the completion of systematic quantitative investigations.

The development of the research questions was solely undertaken by the candidate. The main research questions were formed in response to a disconnect between recommendations of previous literature on the use of threshold as markers for exercise intensity prescription and the avoidance of these procedures in more current literature and within the main nationally recognised organisations in the field of exercise science and physiology. Further development of the research occurred after a review of the literature which helped to identify significant knowledge gaps.

The candidate designed the overall study, was responsible for all of the data collection, supervised the training interventions, and statistically analysed the data. The participation in data collection was an essential element of the PhD and allowed the candidate to develop research measurement techniques, interpersonal skills, and enhanced understanding of the underlying mechanisms associated with individual variability in training responsiveness.

Through the process of independent work, the ensuing chapters demonstrate developed application of research skills, critical analysis, and application. In addition, on-going dissemination of research findings to the international academic community is being conducted in the form of peer-reviewed journal articles.

Chapter 2 - Cardiorespiratory Fitness Training Responders and Non-Responders Following Steady State Aerobic Exercise: A Narrative Review

2.1 Prelude

This chapter serves to provide insight on the topic of individual variability following steady-state aerobic exercise related to responses in VO_2max and cardiometabolic factors since this has been widely recognised in the literature, but there is an overall lack of understanding as to why it occurs. Within this review, the overall topic of training responsiveness is explored, key investigations are highlighted, and gaps in the literature are identified. Information from this review will shape the studies of this PhD thesis. It should be noted that some of the information within this chapter has been adopted in subsequent chapters and implemented into peer-review journal articles.

2.2 Introduction

Low CRF has been shown to be a predictor of future CVD incidence and mortality (30), but substantial evidence exists showing that increasing physical activity and exercise can increase CRF (i.e. VO_2max) and mitigate adverse health effects (31). However, since the 1980s (1), it has been known that considerable individual variability in CRF training responsiveness occurs following a structured steady-state aerobic exercise program. Thus, the terms training 'responder' (exhibiting changes in a favourable direction) and 'non-responder' (an overall lack in change or a change occurring in an unfavourable direction) have been used. With the heterogeneity in responses, it is speculated that not all individuals receive the same beneficial health outcomes from the same exercise intervention. This variability in CRF adaptations has since been shown in a variety of populations including healthy, but untrained adults (8–12), post-menopausal women (5), and overweight and obese men and women (7) and shown to occur in VO_2max (5,8,10–12) and cardiometabolic factors (13,32). Despite knowledge that individual variability in training responsiveness occurs, the causative mechanisms are not fully understood. Through the HERITAGE studies, it was found that age, sex, race, and initial fitness do not significantly effect changes in VO_2max response to standardised exercise training (33), but there is a significant genetic component with a maximal heritability estimate of 47% (18). Therefore, it has been proposed that the methodology of exercise prescription

could play a critical role in eliciting a desired or undesirable change in VO_2max and cardiometabolic factors. In the late 1970s, it was shown that utilizing a relative percent method (i.e. %HRR, %VO_2max, %HR_{max}, etc.) for prescribing exercise intensity fails to consider individual metabolic differences (20), yet this still remains the gold-standard recommended approach (25). Recent investigations have proposed a more individualised exercise prescription using VTs to personalize a training regime based on individual metabolic responses (11,12) and, therefore, enhance the potential benefits of regular physical activity.

In 2013, an opinion paper was published on moving toward exercise a as personalised medicine (15). Undeniably, this concept and thought process was well overdue based on the impact regular physical activity and exercise have on the overall health of an individual and the ability to prevent future adverse events (30,31,34–37). Within the opinion paper, the authors outline 5 critical strategies toward the goal of personalised exercise as medicine with 2 of the 5 strategies directly related to individual variability to exercise training: 1) evaluating participant responses at the individual as well as a group level and 2) identifying sources of variability in responsiveness to training. Indeed, the identification and understanding of individual variability in training responsiveness is the key component to moving forward with exercise as a medicine. For example, when receiving standard 'western medicine,' when patients receive a medication for a particular ailment, they also receive information on the dosage, when to take the medicine (i.e. morning, midday, or night), frequency (per day and overall), special considerations (taking with food or water), and are provided with detailed information related to the side effects. Furthermore, patients are encouraged to reconnect with the provider if they experience any unusual symptoms or if the problem does not go away. Unfortunately, when it comes to exercise prescription as a 'medication,' patients receive a standard statement of how to improve their overall health with exercise and physical activity coming from the accepted guidelines on exercise per week: "30-60 min·d^{-1} on 5 d·wk^{-1} to accumulate a minimum of 150 min·wk^{-1} of moderate intensity exercise or 20-60 min·d^{-1} on 3 d·wk^{-1} of vigorous intensity exercise to accumulate a minimum of 75 min·wk^{-1}" (38). This standard statement does not provide the critical information to the patient on how to actually exercise and gain health outcomes. There is no information on how to set intensity and if intensity information is provided, it is often based on percentages of HR_{max}. Therefore, having specific information related to individualizing exercise

prescription (especially exercise intensity), will help to add critical insight on how to use exercise as a medication and to the standard of commonly prescribed pharmaceuticals.

2.3 Identification of 'Responders' and 'Non-Responders'

Another fundamental issue of understanding individual variability following CRF training is a lack in accepted criteria for what is considered to be a response to quantify 'responders' and 'non-responders', as noted in Table 2.1. Commonly, training responsiveness has been quantified based on absolute changes from baseline to post-intervention, but this method does not take into consideration normal day-to-day fluctuations in biological variability and the measurement error of the equipment being used (10,13,14). It has been proposed that in order to have an all-inclusive definition for incidence of response, the TE (biological variability and measurement error) must be taken into consideration (13). However, often times when TE has been used to quantify training responsiveness, the value has been sourced from previous literature rather than developing one that is specific to the site and cohort being analysed (10–12). Such application of identical group TE criteria (i.e. one based on a uniform biological variability metric and sourced from the literature) for the categorization of responders and non-responders disregard individuality. Furthermore, many training investigations only report the group mean ± standard deviation which fails to address individual participants. Therefore, when only group differences are reported, there could be a misrepresentation of the effect the exercise prescription on the overall training response.

2.4 Incidence of Response: VO_2max

There has been considerable individual variability reported in the literature related to the response of CRF measurements (specifically, VO_2max and VO_2peak). Overall, there is a lack of understanding as to why this heterogeneity occurs. Table 2.1 outlines the key studies involved with the investigation of CRF response. Only investigations that provided a set criterion for incidence of response or specifically reported the individual variability were included within this table. There is minimal consistency in methodology and the criteria for determining incidence of response leading to the overall findings indicating there are overall changes in training responsiveness of -33.2% to +88%.

Table 2.1 Key investigations evaluating incidence of response to cardiorespiratory fitness capacity that included a set definition for response rate or included individual variability

Study	Participants	Training Variables/methodology	Criteria for response rate	Response Rate
Chmelo et al., 2015 (7)	40 (M & W) 69.0 ± 3.6 yr	• 60 months • 4 days·wk^{-1} • Walked at 60-70% HRR, 30 min	No change or a decline in function after the intervention	27 of 31 responded positively to the training intervention
Dalleck et al., 2016 (12)	46 (M & W) 64.9 ± 8.4 yr	• 13 weeks • 3 days·wk^{-1} for 25 to 50 min·d^{-1} • Intensity based on HRR or ventilatory thresholds	Analysed percent change in relative VO_2max from previous literature on biological variability • Responders: $\Delta > 5.9\%$ • Non-responders: $\Delta \leq 5.9\%$	• 64.3% responders in HRR group • 100% responders in ventilatory threshold group
Hautala et al., 2006 (4)	73 (M & W) 42 ± 5 yr	• 2 weeks • 5 days·wk^{-1} • 30 min cycling at 70-80% HRmax	No set criteria, but evaluated percent change in pre- and post-measurements	Average increase in VO_2peak was 8 ± 6% with a range of -5% to 22% improvement
Leifer et al., 2014 (39)	1870 (M & W) 59 yr (median)	• 12 weeks • 3 days·wk^{-1} • 15-30 min at 60% HRR and progressed to 30-35 min at 70% HRR • Encouraged to complete 2 days·wk^{-1} at home after the 18th session	Used the control group to determine SD of change to set criteria of a negative responder having a decrease of at least 2 SD (i.e. decrease of 5 ml/kg/min)	9 subjects (0.9%) were negative responders
Lortie et al., 1984 (2)	24 (M & W) 25 ± 4 yr	• 20 weeks • 4 increasing to 5 days·wk^{-1} • 60% increasing to 85% HRR cycling	No set criteria, but evaluated percent change from pre- to post-measurements	Increases of 5% to 88%
McPhee et al., 2010 (9)	53 (W) 21 ± 4 yr	• 6 weeks of cycling intervals • 3 days·wk^{-1} for 45 min • Week 1: moderate intensity at 75% HRmax • Week 2: 6 min at 75% HRmax followed by 2 min at 90% HRmax • Week 3-6: 6 min at 75-80% HRmax followed by 3 min at 90%	1 SD outside of the Ratio$_{1:2}$ (single leg VO_2peak: two leg VO_2max)	Did not report individual results for response rates
Montero & Lundby, 2017 (40)	78 (M) 26.2 ± 3.4 yr	• 6 weeks • 1, 2, 3, 4, or 5 days·wk^{-1} for 60 min·d^{-1} • Average of 65% Watt Max • Non-responders after 6 weeks completed a second 6 weeks with 2 extra days a week	Responder = Δ watt max > 3.96%	• 69%, 40%, 29%, 0%, and 0% of participants were considered non-responders for 1, 2, 3, 4, and 5 exercise sessions a week, respectively • 100% responders after second 6-week intervention

Values are reported as mean ± standard deviation unless otherwise stated.

Δ, change; BMI, body mass index; CV, coefficient of variability; HR, heart rate; HR_{max}, maximal heart rate; HRR, heart rate reserve; M, men; SD, standard deviation; SIT, sprint interval training; VO_2, aerobic capacity; VO_2max, maximal aerobic capacity; VO_2peak, highest achieved VO_2 during a test; VT1, first ventilatory threshold; VT2, second ventilatory threshold; W, watts; and W, women.

Table 2.1 (Continued) Key investigations evaluating incidence of response to cardiorespiratory fitness capacity that included a set definition for response rate or included individual variability

Study	Participants	Training Variables/methodology	Criteria for response rate	Response Rate
Scharhag-Rosenberger et al., 2012 (10)	18 (M & W) 42 ± 5 yr	• 50 weeks of jogging or walking • 3 days·wk^{-1} for 45 min • Constant HR at 60% HRR or HR at LT (used the higher of the two measurements – training intensity was 62 ± 9% pre-training VO_2max)	Non-responder = %Δ < CV • 7.5% for resting HR • 2.7% for exercise HR • 5.6% for VO_2max • 1.9% for lactate threshold	• 8 subjects - improved all 4 variables • 8 subjects - one variable did not change • 2 subjects - two variables did not change
Sisson et al., 2009 (5)	464 (W) 57.3 ± 6.4 yr	• 6 months • 3-4 days·wk^{-1} • HR associated to 50% VO_2max • 3 experimental groups: 4, 8, and 12 kcal·kg^{-1}·wk^{-1}	Post-training minus baseline values with non-responders Δ ≤ 0	• VO_2max non-response rate was 44.9%, 23.8%, and 19.3% for 4, 8, and 12 kcal·kg^{-1}·wk^{-1}, respectively • About 32% of the subjects were non-responders
Vollaard et al., 2009 (8)	24 (M) 24 ± 2 yr	• 6 weeks • 4 days·wk^{-1} for 45 min • 70% VO_2max cycling	Absolute changes in VO_2max and listed low, moderate and high responders as a change in VO_2max of 4 ± 3%, 13 ± 4%, and 23 ± 5%, respectively	• Classified 8 participants in low, 8 in moderate, and 8 in high responder categories • Did not have set criteria for response
Wolpern et al., 2015 (11)	12 (M & W) 33.5 ± 7.0 yr	• Pre and post testing. No intervention (control)	Analysed percent change in relative VO_2max from previous literature on biological variability • Responders: Δ > 5.9% • Non-responders: Δ ≤ 5.9%	• HRR: 58.3% non-responders • ACE-3ZM: 100% responders
	12 (M & W) 33.0 ± 9.8 yr	• 12 weeks • Progression from 40-65% HRR		
	12 (M & W) 31.7 ± 9.6 yr	• 12 weeks • Progression with training below VT1, between VT1 and VT2, and above VT2		

Values are reported as mean ± standard deviation unless otherwise stated.
Δ, change; BMI, body mass index; CV, coefficient of variability; HR, heart rate; HR_{max}, maximal heart rate; HRR, heart rate reserve; M, men; SD, standard deviation; SIT, sprint interval training; VO_2, aerobic capacity; VO_2max, maximal aerobic capacity; VO_2peak, highest achieved VO_2 during a test; VT1, first ventilatory threshold; VT2, second ventilatory threshold; W, watts; and W, women.

2.4.1 Changes in CRF Due to 'True' Maximal Efforts and the Use of a Verification Protocol

Ensuring that a maximal aerobic value is achieved when investigating any changes due to modifying or differing exercise doses is imperative to understand the actual changes occurring from the intervention and not owing to how aerobic capacity is measured. Historically, a plateau in VO_2max (i.e. ≤ 150 ml·min^{-1}) at the ending stages of a GXT has been the primary criterion to determine 'true VO_2max' (41). However, considerable inconsistency exists in reported the value for a plateau with the use of ≤ 150 ml·min^{-1} to ≤ 50 ml·min^{-1} (42). Furthermore, there has been an incidence in plateau ranging from 0% (43) to 100% (44) of participants in investigations which has led to the use of secondary criteria (45). However, secondary criteria used to 'confirm' VO_2max have since been highly criticised (46,47). When participants fail to reach a VO_2max based on a lack in the identification of a plateau or meeting secondary criteria, the aerobic capacity is then often reported as a peak (i.e. VO_2peak) rather than a maximal measure. Indeed, this method has been reported as a common aerobic outcome measure, especially when reporting functional capacity, fitness changes, and used to prescribe exercise interventions (4,6,7,48). For example, in a recent publication (48), VO_2peak values at 4, 8, 16, and 24 weeks were reported to identify the effects of intensity on interindividual CRF responses. However, since the values reported were based on a 'peak', conclusive evidence cannot be provided as to whether CRF was maintained, declined, or improved since only a relationship of a 'peak' to a 'peak' value were reported. Furthermore, participants tend to exhibit greater maximal effort following a training intervention due to the expectation of improvements (49). Indeed, it could be noted that a change in VO_2peak could be due to a greater increase in effort if there is minimal consideration to the testing methodology. This methodological flaw further adds inconsistency of results to the literature and aids in continuing our lack of understanding of individual variability rather than helping to shed light on the concept.

The use of a supramaximal test following a GXT was first reported by Niemala and colleagues (50) and has since evolved into what is commonly considered a 'verification protocol' (43,51–54). Recently, while there is still debate on the overall topic (55), the use of a verification protocol to confirm VO_2max has been identified as a practical and sensitive measure to identify that a 'true' maximal aerobic value has been achieved (42). The efficacy of a verification protocol has been confirmed in sedentary men and women

(56), middle-aged and older adults (57), sedentary adults with obesity (58), and altitude-residing endurance runners (59). Therefore, the use of a verification protocol would help limit the amount of overestimated CRF changes seen due to reporting of VO_2peak values and ensuring all measurements are a 'true VO_2max' and representative of training adaptations (47,57).

2.4.2 Exercise Intensity as an Integral Component to Training Responsiveness

The use of relative percent methods to establish exercise intensity (i.e. %HRmax, %HRR, and %VO_2max) have shown large inter-individual variability in VO_2max responsiveness (3,5,48,60,61) and may be due to failing to take into consideration individual metabolic characteristics (14,20,21). For example, when undergoing 60 min of cycling at work rates of 60% and 75% of VO_2max in healthy male participants, there was considerable variability in lactate responses with a reported CV of 52.4% and 41.3%, respectively (21). Similarly, it has been shown that when intensity is calculated as a percentage of the individual anaerobic threshold, ranges of 86 to 118% and 87 to 116% have been identified when exercising at 75% of VO_2max and 85% of HRmax, respectively (22). Therefore, heterogeneity in training responsiveness will ultimately result from differences in the overall homeostatic stress during the exercise intervention.

Katch and colleagues (20) suggested the use of thresholds as markers of exercise intensity to create consistency in the metabolic stimulus in a heterogeneous population. When investigating differences in training responsiveness between an individualised threshold method and standardised procedures of intensity prescription (i.e. HRR), Wolpern and colleagues (11) first demonstrated that an individualised approach elicited greater training responsiveness compared to the HRR method when exercising for 30 $min \cdot d^{-1}$ on 5 $d \cdot wk^{-1}$ for 12 weeks. These findings were again shown in a more recent publication utilizing the similar exercise prescription performed 60-75 $min \cdot d^{-1}$ on 3 $d \cdot wk^{-1}$ for 13 weeks, but also incorporating resistance and functional training (12). Interestingly, even though both interventions had different training volumes and frequencies, the individualised groups had a 100% response rate to the intervention. However, even though all participants in the individualised groups in these previous (11,12) investigations were considered to be responders, there is still variability in overall responsiveness. This variability may be due to other factors not generally accounted for (i.e. genetics, sedentary behaviour outside of the exercise training, frequency of interrupting sedentary behaviour, nutrition, etc.).

Recently, Montero and Lunby (40) found that exercise dose is the key to mitigating non-responders and not exercise intensity. Following an initial 6-week intervention where participants exercised for 60 min on 1, 2, 3, 4, or 5 days·wk^{-1}, the exercise non-responders were asked to complete a second 6-week intervention with 2 extra days a week of exercise. Indeed, they found that all participants that were previously non-responder, became responders after the second 6-week intervention with the addition 2 days a week of training. To their commend, they utilised a site- and cohort-specific TE used to establish the training responsiveness. However, they utilised W_{max} rather than VO_2max as their criteria. Interestingly, after the first 6-week intervention, participants exercising 4 days a week were all considered training responders based on their increases in W_{max}. However, if this group was evaluated based on VO_2max with the use of the commonly reported TE of 5% for VO_2max (62), 3 of the 17 participants would have been categorised as training non-responders. Furthermore, had VO_2max been used at the criteria following the second 6-week intervention, similar findings would have been noted and not all participants would have been considered 'responders.' Therefore, regarding VO_2max, it appears that an increase in exercise dose may not directly attenuate training non-responders.

2.5 Incidence of Response: Cardiometabolic Factors

There are two main investigations (Table 2.2) evaluating the incidence of response for cardiometabolic factors. Both of these studies reported adverse responses (changes in an unfavourable direction of ≥ TE) to aerobic exercise training rather than responders and non-responders. Bouchard and colleagues (13) retrospectively analysed the incidence of adverse response of six larger exercise based studies and found an overall incidence of an adverse response of one cardiometabolic risk factor was 8.3% to 13.3%. Moreover, 7% of participants had an adverse response in two or more cardiometabolic measurements. In contrast, a lower incidence of adverse cardiometabolic response to exercise were reported in an evidence-based, community wellness program of 3.6% to 6.0% (4.9% overall) for adverse response (32). However, fasting insulin was not analysed even though this cardiometabolic risk factor was associated with the highest percentage of adverse response by Bouchard et al. (13). Another factor for the lower reported findings by Dalleck and colleagues (32) could be associated with the higher individualization of exercise prescription in which weekly energy expenditure was individualised (kcal·kg^{-1}·wk^{-1}) and intensity based on percentages of VO_2R. Within the retrospective analysis of the 6 larger studies (13), 4 of the 6 studies (16,63–65) utilised VO_2max to prescribe

exercise intensity which has been shown to elicit considerable individual variability in the training responses (Mann et al., 2013), 1 of 6 used HRR (66), and one used aerobic and anaerobic threshold as markers for exercise intensity (6). Since both the Dalleck et al. (32) and Bouchard et al. (13) studies reported adverse cardiometabolic responses, it is plausible that cardiometabolic non-response is even higher.

More recently, Dalleck and colleagues (12) investigated the effects of cardiometabolic non-response when exercise intensity was prescribed based on HRR or threshold measurements (i.e. VT). Participants exercised for 13 weeks starting at 25 $min \cdot d^{-1}$ working up to 50 $min \cdot d^{-1}$ on 3 $days \cdot wk^{-1}$. Furthermore, at week 4, resistance training was added which followed a prescription based on the ACSM guidelines (25) or the American Council on Exercise integrated fitness model (67). Participants were categorised as a responder if they had a $\Delta > 0$ in a favourable direction when calculating post-program minus baseline value divided by the baseline value. The more individualised group (prescription based on VT) had more favourable responses in cardiometabolic measures with SBP (100%), HDL (100%), TG (85.7%), and BG (92.9%). The HRR group has responder rates of SBP (42.9%), HDL (50.0%), TG (85.7%), and BG (42.9%). Interestingly, there was no significant difference in influencing factors such as age, baseline cardiometabolic risk factor value, exercise adherence, and sex. Similar to findings related to VO_2max, when exercise is tailored to the participant and takes into consideration individual metabolic characteristics, there appears to be a more favourable cardiometabolic response.

Table 2.2 Evaluation of incidence of response (adverse response) of cardiometabolic measurements after cardiorespiratory fitness raining

Authors, year	Sample size	Age years	Training Variables/Methodology	Criteria for Adverse Response Rate	Adverse Response Rate
Bouchard et al., 2012 (13)	473 European HERITAGE (16)	35.8 ± 14.5	• 20 weeks • 60 training sessions • Workload up to 75% VO_2max for 50 min	• ↑ SBP of ≥ 10 mmHg • ↑ TG of > 37.0 mg/dL • ↑ ≥ 24 pmol·L^{-1} • ↓ HDL cholesterol of >4.0 mg/dL	• FI = 55 • HDL = 47 • TG = 56 • SBP = 44
	250 African American HERITAGE (16)	33.6 ± 11.5			
	326 DREW (63)	57.9 ± 6.5	• 6 months • 3-4 days·wk^{-1} • HR associated to 50% VO_2max • 4 kcal·kg^{-1}·wk^{-1}		• FI = 16 • HDL = 35 • TG = 19 • SBP = 32
			• 6 months • 3-4 days·wk^{-1} • HR associated to 50% VO_2max • 8 kcal·kg^{-1}·wk^{-1}		• FI = 9 • HDL = 21 • TG = 14 • SBP = 14
			• 6 months • 3-4 days·wk^{-1} • HR associated to 50% VO_2max • 12 kcal·kg^{-1}·wk^{-1}		• FI = 11 • HDL = 31 • TG = 18 • SBP = 12
	70 INFLAME (64)	51.2 ± 10	• 4 months • 3-5 days·wk^{-1} • 60-80% of VO_2max		• FI = 12 • HDL = 21 • TG = 9 • SBP = 11
	303 STRRIDE (65)	51.0 ± 7.7	• 6 months • Low dose/moderate intensity, low dose/ vigorous intensity, and high dose/vigorous intensity had intensities of 40-55%, 65-80%, and 65-80%, respectively, of VO_2max		• FI = 17 • HDL = 32 • TG = 34 • SBP = NA
	160 MARYLAND (66)	58.0 ± 5.8	• 6 months • 3 days·wk^{-1} • 20 min at 50% HRR working up to 40 min at 70% HRR		• FI = 4 • HDL = 8 • TG = 11 • SBP = 43
	105 JYVASKYLA (6)	53.5 ± 7.6	• 21 weeks • Strength training, endurance training, or combined training 4 days·$week^{-1}$		• FI = 2 • HDL = 27 • TG = 11 • SBP = 10
Dalleck et al., 2015 (32)	124 M 190 W		• 14-week community wellness program • 3 days·wk^{-1} • EE goal of 14-23 kcal·kg^{-1}·wk^{-1} • 40-60% of VO_2R	• ↑ SBP ≥ 10 mmHg • ↑ TG > 37.0 mg/dL • ↓ HDL > 4.0 mg/dL	Prevalence of AR was 4.9% overall (49/996) • SBP = 6.0% (20/332) • TG = 3.6% (12/332) • HDL = 5.1% (17/332) Incidence of multiple AR was 1.2% (4/332)

Values are reported as mean ± standard deviation.

Δ, change; AR, adverse response; BMI, body mass index; BG, blood glucose; BP, blood pressure; DBP, diastolic blood pressure; EE, energy expenditure; FI, fasting insulin; HRR, heart rate reserve; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; M, men; SBP, systolic blood pressure; TC, total cholesterol; TE, technical error; TG, triglycerides; VO_2, aerobic capacity; VO_2max, maximal aerobic capacity; VO_2R, VO_2 reserve; and W, women.

2.5.1 Metabolic Syndrome

MetS is the simultaneous occurrence of three or more CVD risk factors including central obesity, hyperglycaemia, hypertriglyceridemia, low HDL, and hypertension, which elevates the risk of cardiovascular events (68). Moreover, MetS confers a 5-fold increase in the risk of type 2 diabetes and a 2-fold risk of developing CVD within the next 5 to 10 years (68). Furthermore, individuals with MetS are at a higher risk of stroke, myocardial infarction, and all-cause mortality (69) and this is regardless of previous cardiovascular issues (70). Reducing the severity of this syndrome may therefore serve as a target to improve global health. Indeed, an exercise-induced increase in CRF has been well established as a protective factor against individual risk factors constituting the MetS (71), with high fit MetS individuals reported to have lower risk of cardiovascular mortality relative to less fit counterparts (72).

Due to a complex interplay of genetic and environmental factors, MetS is essentially a state of chronic low-grade inflammation. There are several factors that lead to metabolic syndrome including insulin resistance, visceral adiposity, dyslipidaemia, endothelial dysfunction, genetics, high BP, and chronic stress (73). Treatment for MetS generally consists of comprehensive lifestyle changes through modifications in diet and exercise with accompanying weight loss and the use of pharmacological agents when risk factors cannot be reduced through a lifestyle intervention (74).

2.5.2 Metabolic Syndrome z-Score

In conjunction with the difficulty in titrating available intervention dosages to optimally treat or manage MetS, there is also a dilemma in determining the change in MetS severity to better account for the clinical significance of a particular intervention. The established categorical criteria of MetS proposed by different organizations (i.e. International Diabetes Federation [IDF]) (68) are often criticised due their incapacity to account for improvement in a certain MetS component if the magnitude of change is not large enough to deviate from a qualifying category. For example, a SBP reduction from 142 to 131 mmHg following an intervention would still classify as a MetS risk factor according to the IDF criteria (SBP≥130 mmHg), regardless of achieving a clinically significant reduction (75). For this reason, a continuous risk score assessment known as the MetS z-score was introduced to better acknowledge MetS risk factor changes and thus MetS severity, following clinical interventions (76).

The MetS z-score, in summary, is the individual components of MetS statistically normalised and expressed as a z-score and is then calculated as the mean of these z-scores (76). The MetS severity has been presented as sex-specific MetS z-score calculated using the following equation (77) where FG = fasting glucose; HDL = high-density lipoprotein cholesterol; MAP = mean arterial pressure; TG = triglycerides; and WC = waist circumference:

$$Men = [(40 - HDL) \div 8.9] + [(TG - 150 \div 69) + [(FG - 100) \div 17.8] + [(WC - 102) \div 11.5] + [(MAP - 100) \div 10.1]$$

$$Women = [(50 - HDL) \div 14.5] + [(TG - 150 \div 69) + [(FG - 100) \div 17.8] + [(WC - 88) \div 12.5] + [(MAP - 100) \div 10.1]$$

With the use of a MetS z-score calculation, there is a more comprehensive understanding of changes occurring to MetS severity rather than identifying each individual factor. As of now, this method has not been used to identify training responders and non-responders, however, the methodology is very appealing due to the comprehensive nature. A similar approach to the development of the TE for VO_2max could be implemented in which more than 1 baseline measure is used to identify a CV and used at the TE to quantify training responsiveness.

2.6 Genetic and Other Factors Associated with Incidence of Response

Within the largest comprehensive exercise intervention, the HERITAGE Family Study (16), considerable insight was gained regarding the genetic factors associated with exercise training and response. It was found that baseline level of VO_2max, age, sex, and ethnic differences did not have or had minimal influence in the individual variability in response to training (33) and much of the heterogeneity in response rates were linked to a strong familial aggregation of CRF abilities. Maximal heritability for the response in VO_2max was estimated at 47% (18).

While initial CRF was not a factor for the response rate in the HERITAGE family study, Lortie and colleagues (2) found pretraining CRF accounted for 25-35% of the variation in response. Similar findings were later reported in which baseline levels played a role in the individual response to exercise training (4,5,7). Even though there is evidence that CRF training responses may be linked heavily to a genetic component, there is discrepancy within the literature whether baseline CRF levels have an influence on training adaptations.

For submaximal exercise outcome measurements within HERTAGE, familial and genetic factors accounted for 23% to 57% for the VO_2 and power output associated with 60% and 80% of maximal values with a significant contribution of maternal inheritance (78). It was also found that baseline fitness level, age, and familial heritability accounted for 30% to 50% of the variability in HR and SBP (79). These results suggest that not only can variability in submaximal HR and SBP exist due to baseline levels, but also due to a genetic component. A further analysis of submaximal exercise HR and SBP were found to be moderately heritable (20-30% of the training responses) when analysing the results of just the white participants in HERITAGE (80).

Based on evidence from the HERITAGE family study (18) and an investigation of the heritability of running performance in rats (81), less than half of the trainability in humans can be explained by genetic factors with heritability of training found at 47% and 43%, respectively. Sarzynski and colleagues (82) recently proposed that individual variability is a normal biological phenomenon reflecting genetic diversity. Consequently, there is continuing investigation into the effect genetics have on the incidence of response to CRF training.

The 2006-2007 update of the human gene map for performance and fitness phenotypes provides further insight related to genetics, performance, and VO_2max changes (83). Within this update, 11 candidate genes and 12 quantitative trait loci were identified and associated to the response of CRF related phenotypes to response of VO_2max changes. However, many of these genes were often based on few studies (many based only on one) and the gene accounting for a small percentage of the total variability in response. The most frequently studied genes were ACE, APOE, and ACTN3. Unfortunately, due to differences in population, sample size, and exercise prescription, the results varied and considered to be inconclusive (17).

In 2011, a further analysis of the HERITAGE Family Study data of 473 white subjects was completed in which 324,000 single nucleotide polymorphisms (SNP) were examined to understand the relationship to CRF training changes (84). While genome-wide significance was not reached for any of the SNPs, 39 SNPs were related to VO_2max training response and 21 SNPs accounting for nearly 49% of the variance in the trainability of VO_2max – very similar to the values stated above. However, based on the evaluation of SNPs, there was no single gene that could be identified that significantly explained the genetic variability with CRF training responsiveness. These data were later

evaluated by Ghosh and colleagues (85) with the use of a biology systems approach to better understand the underlying factors associated with variability in VO_2max trainability. Further analysis found 31 genes were associated with VO_2max changes and related to pathways of calcium signalling, nitric oxide signalling, and protein kinase A signalling. Similarly, many of these pathways have been identified in other studies (86).

Based on the genetic evidence to date, there are many pathways that are associated with VO_2max trainability and nearly an unlimited combination of signalling events that may influence the VO_2max responsiveness (82,86). With genetics proposed to account for less than 50% of the variance in responsiveness, the other 50% is still not well understood.

2.7 Statistical Insights and Ethical Considerations to Training Responsiveness

A review on interindividual differences following an exercise intervention have addressed many methodological and statistical considerations and urged caution with how many investigations have reported the topic (87). Of considerable interest, it has been highlighted that within-subject random variation is inevitable and, in some instances, can account for all of the individual variability in training responsiveness. However, in Chapter 4, it is demonstrated that different training responsiveness criteria elicit varying percentages of responders and non-responders to changes in VO_2max and this topic has been recently evaluated in more depth (88). These findings challenge the notion that observed response variability is the result of random variation in the measured parameters. Therefore, the criteria to establish responsiveness must be specific to the cohort being studied and take into consideration biological fluctuations and measurement error of employed testing procedures. Atkinson and Batterham (87) also highlight the importance of having a comparator arm (i.e. a control group) to quantify true interindividual differences in training response. While these methods are appropriate statistical methods, there are moral and ethical considerations to be addressed with the use of a control group in an exercise intervention in which there is a removal of a known positive physiological factor to improve health. For example, Hecksteden and colleagues (88) evaluated the effects of endurance training with repeated testing on individual responsiveness over a 1 yr period, but used a control group for only 6 months with reported ‘ethical constraints’ as the rationale for not having a control for the intervention duration.

While the statistical methodology previously outlined by Atkinson and Batterham (87) makes sense from a numbers perspective, it does not make sense regarding moral and ethical considerations. Recently, Montero and Lundby (40) utilised a similar approach to quantifying training responsiveness as outlined in this PhD thesis but with the use of W_{max} rather than VO_2max. They received criticism in a letter to the editor related to their investigation with the main concern of not including a control arm. In their reply (89), the authors identify some key critical points related to not using a control group. They address the cost-benefit of testing control participants and the ethical considerations of the control participants undergoing the same extensive testing as the experimental participants and receiving no perceived benefit other than the information from the testing alone. The authors end the reply stating that these types of comments on physiological investigations "contribute to the burden of tangential wordiness in our field." Indeed, there will continue to remain debate on the best statistical approaches to analyse individual training responsiveness.

The methods outlined in this thesis, and in consistency with those implemented by Montero and Lundby (40), of performing 2 to 3 measurements in all participants at baseline to establish a site- and cohort-specific TE could minimise or, in some instances, eliminate the need of a control group. Furthermore, continued work with the use of a TE as a threshold for training responsiveness is warranted and future research should explore the use of an individually based TE in comparison to group TE.

2.8 Time Course Changes of VO_2max

Over 35 years ago, Hickson et al. (90) first reported time course changes of VO_2max with participants engaging in 3 days a week of running (continuously at as strenuous of a work rate they could maintain) and 3 days a week of cycling (6 intervals for 5 minutes at 90-100% of VO_2max) for a total of 9 weeks. They concluded that a daily high intensity exercise program will no longer improve VO_2max after 3 weeks. Gaesser and Rich (91) found that increases in VO_2max were similar between healthy young men partaking in 18 weeks of high intensity (80-85% VO_2max) or low intensity (45% VO_2max) training, but data indicated more substantial improvements in the first 6 weeks compared to the last 12 weeks of training for the high intensity group. Scharhag-Rosenberger and colleagues (92) found that after 1 year of a walking or jogging program 3 days a week, 45 minutes a session, and at an intensity of 60% HRR, there was an overall improvement in VO_2max of 0.4 ± 0.3 $L \cdot min^{-1}$ and resting and submaximal heart rate decreased by 10 ± 7 bpm.

However, they found most of these changes occurred within the first 3-6 months with minimal adaptations occurring thereafter. When investigating the time course changes in VO_2max with 12 weeks of 2 varying interval training groups (high and low interval training at 80-90% and 60-70% of maximal watts, respectively) of 6-10 x 60 second bouts with 60-70 seconds of active recovery between bouts it was found that both methods significantly improved pre- to post-VO_2max (29). However, it was also reported that the high group had more than double the percentile improvement in VO_2max after 3 weeks when compared to the low group, while the low group had further improvements from weeks 3-6 and these improvements were not seen in the high group. Based on the literature, it appears there is a consistent 3- to 6-month initial window in which adaptations to VO_2max occur. Beyond this point, if the exercise training load is not increased, there are minimal improvements in VO_2max.

Many of the studies prospectively investigating time course changes in VO_2max have only evaluated one population within the study design. However, Murias et al. (93) investigated men that were old (68 ± 7 years) and young (23 ± 5 years) during a 12 week intervention. Participants cycled 3 days a week for 45 minutes at a power output that occurred at 70% of VO_2max for the first 10 weeks. After this period, participants were assigned to either continue this same protocol or complete the final two weeks with interval training (10-12 bouts of 1-min cycling at 90-100% of their peak power output). Results indicate that despite having differing start VO_2max values, the time course changes between the old and young men were very similar with improvements occurring as early as 3 weeks, but the percentage increases in VO_2max were significantly larger for the older men. They also found no difference in the changes to VO_2max between those that participated in the interval training compared to continuing the protocol. These data suggest that the while the mechanisms may be different, the time course changes in VO_2max between older and young men are comparable.

With the emerging concept of 'exercise is medicine' and being able to prescribe exercise to combat adverse effects of disease, the time course changes for VO_2max and cardiometabolic risk factor measures need to be better understood to properly determine exercise doses (i.e., intensity, volume) that will elicit an adequate response. However, much of the literature on time course changes utilises standardised methods of exercise prescription rather than individualised approaches. To the best of my knowledge, there is no literature in time course changes of VO_2max *and* cardiometabolic risk factor outcomes with the use of a threshold-based protocol and exercise volume individualised based on

kilocalories of expenditure per week with relation to body mass. Similarly, results of time course changes have traditionally been reported as only group means and standard deviations with individual time course changes not being reported. Based on a review of the literature, there has only been one study to identify individual participant time course changes after one year of a walking or jogging program (92). Reporting of individual time course for VO_2max and cardiometabolic risk factor measurements will help to further understand the individual variability in training responsiveness.

2.9 Conclusion

It is well recognised that regular steady-state aerobic exercise confers numerous health benefits – decreased CVD, decreased mortality, improved CRF, and enhanced cardiometabolic function – yet, heterogeneity in training responsiveness has been well-documented. Individual variability in training responsiveness is a nuanced and complicated area of study due to the multifaceted nature of a training 'response.' Indeed, training responsiveness has been linked to genetic components (~50% of the variability) and to the specific exercise prescription. Methodological considerations may also account for some of the variability in VO_2max responsiveness with some studies reporting a peak rather than a max value. In these situations, a true change and, therefore, a classification of responder or non-responder cannot be concluded.

When investigating responsiveness of cardiometabolic factors, historically, a focus has been placed on only one variable rather than a comprehensive method to analyse all factors. Similarly, there has also been a trend related to only highlighting important changes when values go from an unhealthy to healthy range. However, even when cardiometabolic values improve, but do not change enough to be categorised as 'healthy' or 'normal,' this is usually reported as a non-response. It has now been recognised that changes toward a healthy range have significant impact on the overall health of the participant. Recently, the use of a MetS z-score has been implemented to increase the sensitivity of changes in MetS severity which highlights these aforementioned changes that fail to reach a 'healthy' range and allows for a more comprehensive mechanism to analyse cardiometabolic factor changes as a whole. Further research is needed and warranted on differing exercise intensity in comparison to change in both VO_2max and cardiometabolic factors.

Chapter 3 - The Incidence of Training Responsiveness to Cardiorespiratory Fitness and Cardiometabolic Measurements Following Individualised and Standardised Exercise Prescription: Study Protocol for a Randomised Controlled Trial

3.1 Prelude

This chapter comprises the following paper accepted for publication: Weatherwax, R.M., Harris, N., Kilding, A., Dalleck, L.C. (2016). The incidence of training responsiveness to CRF and cardiometabolic measurements following individualized and standardized exercise prescription: study protocol for a randomized control trial. *Trials*, 17(1).

This chapter focuses on the overall methodology of the PhD thesis with the consideration of information found in the narrative literature review (Chapter 2) to help fill some of the gaps in research. Since the publication of this chapter, there were some changes in the overall experimental methodology that needed to be addressed. Therefore, this chapter is a modified version of the publication with the removal of a second 12-week exercise intervention, the addition of MetS z-score comparisons, and modifications to the testing schedule of the control group due to high drop-out rates.

3.2 Abstract

There is considerable individual variability to CRF training, but the underlying cause is not well understood. Traditionally, a standardised approach to exercise prescription has utilised relative percentages of maximal heart rate, heart rate reserve HRR, VO_2max, or VO_2 reserve to establish exercise intensity. However, this model fails to take into consideration individual metabolic responses to exercise and may attribute to the variability in training responses. It has been proposed that an individualised approach would take into consideration metabolic responses to exercises to increase responsiveness to training. In this randomised control trial, participants will undergo a 12-week exercise intervention using individualised (VT1 and VT2) and standardised (HRR) methods to prescribe CRF training intensity. Following the intervention, participants will be categorised as responders or non-responders based on changes in maximal aerobic

abilities. There are 4 main research outcomes: 1) determine the cohort specific technical error to use in the categorization of response rate; 2) investigate the time-course changes throughout 12 weeks of CRF training between the two intervention groups; 3) identify if the individualised group reduces the severity of MetS factors greater than the standardised group; and 4) determine if an individualised exercise intensity prescription is superior to a standardised approach in regards to VO_2max training responsiveness. The findings from this research will provide evidence on the effectiveness of individualised exercise prescription related to training responsiveness of VO_2max and cardiometabolic risk factors compared to a standardised approach and further our understanding of individual exercise responses. If the individualised approach proposed is deemed effective, it may change the way exercise specialists prescribe exercise intensity to enhance training responsiveness.

3.3 Introduction

Heterogeneity in the response to exercise training first received attention in the 1980's (1) with a series of standardised studies investigating trainability of sedentary adults. Among these studies was an investigation into responses of maximal aerobic power in which it was reported that interindividual differences ranged from 5% to 88% (2). Even though these original findings were reported over 30 years ago, substantial individual variability in response to prescribed exercise regimes remains a poorly understood phenomenon. Indeed, it has been purported that a more individualised approach to the exercise prescription may enhance training efficacy and limit training unresponsiveness. For instance, it has been acknowledged as far back as the late 1970s that utilizing a relative percent method (i.e., %HRR) to establish exercise intensity fails to account for individual metabolic responses to exercise (20). Nevertheless, the relative percent method remains the gold standard recommendation for exercise intensity (25). It is both plausible and practical to think that an intensity set based on an individual's threshold measurement (i.e. VT) will not only encourage more positive physiological adaptations but may account for some of the variability in training responsiveness by taking into consideration individual metabolic differences. Based on an extensive search of the literature, to our knowledge, there is only one investigation that set out to determine the incidence of response based on exercise prescription using standard methods (%HRR) compared to individualised methods (threshold based) in which they found 100% of the individualised group responded in a positive manner (11). However, this investigation had several

limitations including a modest intervention duration, only reported VO_2max changes, and sourced measurements for biological variability to use as criteria for response rate rather than testing for biological variability within the lab where data were collected.

A notable factor that confounds current understanding of training response variability is the absence of a set definition in the literature of how to interpret a response (i.e. the criteria that classifies someone as a responder or non-responder). Indeed, criteria to determine incidence of response for changes in VO_2max have included classifying a fixed proportion of the lowest training response (8), absolute changes in pre- to post-intervention values (5,7), and a change of more than one standard deviation (9). More recently, it has been proposed that technical error (TE), the combination of day-to-day biological variability and measurement error, should be applied to categorise response rate (13). If these values are considered for each research cohort to report incidence of response, there would be greater consistency of reporting results within the literature to provide further insight on individual variability. Moreover, interpretation of the individual variability in training responsiveness is limited due in part to the standard practice of past studies only reporting group means and standard deviations. With reporting of only the mean and standard deviation, results of the intervention may not be applicable to all since there is a lack of understanding related to the individual variability of the investigation.

This trial will be the first investigation to address the incidence of response of VO_2max and cardiometabolic risk factors following individualised and standardise CRF training using a site and cohort-specific TE as the criteria for response.

3.3.1 Research Aims

The objective of this research is to determine the incidence of response to VO_2max after implementation of a standardised (%HRR) and individualised (VT1 and VT2) approach to exercise prescription in a community wellness program for 12 weeks. The primary measurement outcome will be VO_2max with secondary outcomes of TC, HDL, LDL, TG, BG, and resting HR and BP. Thus, the main research aim is to determine whether an individualised exercise prescription decreases the incidence of non-response to CRF and cardiometabolic measurements compared to the standardised approach. A key secondary aim of this research is to establish whether there are differences in the time course changes of VO_2max between the experimental groups every 4^{th} week during the 12-week intervention.

3.4 Methods/Design

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (94) have been taken into consideration for the planning of this trial. The overall study (Figure 3.1) is a randomised control trial with participants completing a CRF training study 3 days a week for a duration of 12 weeks using a standardised (%HRR) and an individualised (based on VT1 and VT2) approach. The protocol has been approved by the Auckland University of Technology Ethics Committee (16/264) and the Human Research Committee of the Institutional Review Board at Western State Colorado University (HRC2016-01-90R6) with data collection occurring only at Western State Colorado University.

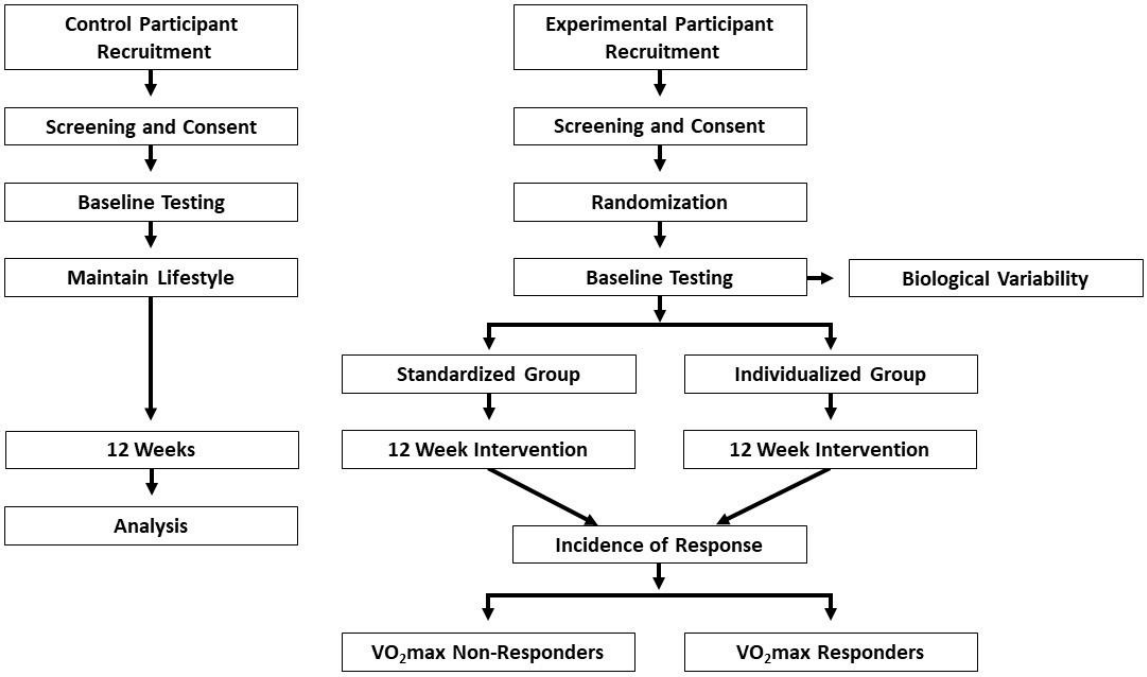

Figure 3.1 Schematic illustration of the research design

3.4.1 Sample – Experimental Groups

For the experimental groups, participants will be recruited from a community-based wellness program serving the local area. The wellness program participants are either referred by local medical professionals or seek entrance into the program from peer referrals. In order for participants to be included in the study, they must meet the following inclusion criteria:

- 30 to 75 years of age
- Considered low to moderate risk for CVD (25)

- Currently sedentary (participating in less than 30 minutes of moderate intensity physical activity on at least three days a week)
- Resided at an altitude near 2300 m for at least the last 6 months

Participants will be excluded from the study if they have any signs, symptoms, or diagnosed cardiovascular, pulmonary, or metabolic disease. During the trial, participants will be asked to maintain their normal lifestyle to ensure any adaptations were due to the intervention.

3.4.2 Sample – Control Group

The control group was recruited as a convenience sample separate from the experimental participants due to the moral and ethical considerations of withholding a known physiological and psychological benefit (i.e. an exercise intervention), similar to previous research (28,29). The control participants were recruited by advertising and word-of-mouth looking for individuals that were interested in the various health indices from the laboratory testing, but not interested in increasing regular exercise or physical activity. Control participants had to meet the same inclusion/exclusion criteria previously mentioned.

3.4.3 Sample Size Calculation

Sample size was projected with change in VO_2max as the main outcome variable. The means and standard deviations of a previous study (11) were examined and the effect size for this research study was calculated. Assuming a power of 0.80 was needed and the calculated effect size for change in VO_2max was 0.30, it was determined that approximately 16 participants would be needed for each group (27). It is assumed there would be an approximate 20% dropout rate, so the aim will be to achieve 20 participants per group.

3.5 Intervention

3.5.1 Testing

Testing sessions for both the experimental will be conducted at baseline and every 4th week whereas the control group will complete testing at baseline and post-program. Testing sessions every 4th week for the experimental group will help to establish the current physiological levels to develop the exercise prescription for the experimental groups (i.e. exercise prescription will be based on the most current laboratory testing data).

Testing will be conducted in a university-based performance laboratory under the supervision of two exercise physiologists. Prior to completing the testing sessions, participants will be asked to refrain from food and drink (other than water) for 12 hours prior to the testing session, be well hydrated, avoid the use of alcohol, caffeine, and tobacco within 24 hours of testing, be well rested, avoid significant exertion or exercise the day of testing, and report any medication use prior to testing. Testing will occur as close to the same time of day as possible with the above directions prior to each testing session. The testing will be conducted as follows:

Dietary Analysis: Participants will be instructed to not change their usual diets throughout the study and asked to complete a 3-day dietary intake recall including 2 weekdays and 1 weekend day to evaluate energy intake and the proportion of kilocalories from carbohydrates, protein, and fat.

Anthropometric Measurements: Participants will be weighed on a calibrated, medical grade scale to the nearest 0.01 kg and height will be measured using a stadiometer to the nearest 0.5 cm. Waist circumference will be measured by the narrowest horizontal circumference above the umbilicus and below the xiphoid process to the nearest 0.5 cm (25).

Resting Heart Rate and BP Measurements: Procedures for RHR and BP will follow standard guidelines (25). In summary, participants will be required to sit for 5 min with sufficient back support, feet on the ground, and arms supported at heart level. Resting heart rate will be recorded by using a medical grade pulse oximeter after the 5 min of seated rest. Blood pressure will be measured using a stethoscope and sphygmomanometer to determine left arm brachial artery BP on consecutive measure separated by 1 min. The mean of the systolic and diastolic measures will be considered the resting BP.

Fasting Blood Glucose and Lipid Measurements: All fasting lipid and blood glucose measurements will be analysed using the Cholestech LDX system which has been shown to have excellent reproducibility (95,96). An optics check of the Cholestech LDX system will be completed at the beginning of each testing session. Participants will be asked to thoroughly wash hands with soap and rinse with warm water. The skin will then be wiped with an alcohol swab and allowed to dry. Using a lancet, the distal end of the third digit of the right hand will be punctured and a finger stick sample will be collected using a 40 µl capillary tube with blood flowing freely into the tube without milking the finger. The

blood sample will then be extracted into a commercially available test cassette for analysis. Measurements of TC, HDL, LDL, TG, and blood glucose will be obtained. Upon completion of the blood profile testing and data collection, blood samples will be disposed of based on standard biohazard procedures.

VO_2max and Verification Bout: Participants will complete a modified-Balke, pseudo-ramp graded exercise test (GXT) on a power treadmill. Participants will walk or jog at a self-selected pace with an increase in incline of 1% every minute until volitional fatigue. Heart rate and expired gas will be measured continuously using a heart rate monitor and a calibrated metabolic analyser, respectively. Data will be analysed following guidelines previously reported (11). In summary, gas exchange data will be time averaged for every 15 seconds, VO_2max will be determined by averaging the last two 15 second samples, and maximal HR will be the highest achieved HR during the GXT.

Since a verification procedure has been found to be effective in middle-aged and older adults to confirm VO_2max (57), this procedure will be used to ensure participants have reached maximal capacity. The verification trial will be performed 20 min after the GXT as recommended elsewhere (97) and has been confirmed to be an effective procedure at altitude (59). The verification bout will consist of a workload that is 105% of the maximal workload during the GXT (last fully completed stage) as this workload has been shown to be sufficient to elicit verification test durations of 2-3 min (57,98) and will continue until volitional fatigue. Analysis of the verification bout will follow the same protocol as the GXT. 'True' VO_2max will be considered to be attained if the GXT and verification bout are within ± 3% (57), which is the measurement error of the gas analysis equipment. If participants are unable to reach VO_2max, they will be asked to repeat the trial no sooner than 24 h later.

The control group will complete all of the same laboratory procedures as the experimental participants and asked to maintain their normal lifestyle activity habits.

3.5.2 Biological Variability and Technical Error

To establish criteria to categorise participants as VO_2max responders or non-responders, the biological variability and measurement error will be established to determine the TE. Therefore, from the pool of experimental research participants, 15 participants will be randomly selected based on when the referral or inquiry into the wellness program is received (i.e. participants 1, 3, 5, 7, etc. until 15 confirmed participants have been

reached. If there are not 15 participants after the first round, then participants 2, 4, 6, etc. will be asked until the desired total of 15 participants is met). Participants will be asked to complete the baseline testing assessments twice within a 2-week period to determine the day-to-day biological variability. The biological variability will be combined with the measurement error of the equipment utilised (sourced from the literature and company of the equipment) to determine the TE. More details related to the statistical approaches are located in the statistical analysis section.

3.5.3 Exercise Intervention

After the completion of the baseline testing, participants will be randomly allocated to either the individualised or standardised arms at a 1:1 ratio using a computerised stratified minimization sequence. One of the primary investigators will have knowledge of the treatment groups to which participants have been allocated in order to interpret test results and prescribe target exercise intensities. However, this same investigator will not be involved in the implementation of the exercise training programs (to be completed by research assistants) in order to mitigate researcher bias. Participants will then be asked to come to the laboratory on Monday, Wednesday, and Friday to take part in the community wellness program and subsequent research. Upon arrival each day, participants will be asked to rest comfortably for 5 minutes in the seated position. Then, their resting BP and HR will be recorded. Following the resting measurements, participants will complete a 5-min warm-up starting at a low and progressively increasing intensity until they are ready to begin their CRF exercise session. At this point, participants will be asked to stay within the designated HR (described in further detail below) outlined on their exercise log as determined based on their experimental group and week of experimental trial. At approximately 1/3 and 2/3 the total session time, an exercise physiologist or research assistant will record their current HR, rating of perceived exertion (Scale 1-10), intensity of aerobic equipment, and any other pertinent notes. At the end of the CRF exercise session, the participant will be asked to complete a cool-down in which the exercise intensity is gradually reduced. While resistance training is not part of this proposed experiment, it is an integral part of the community wellness program and could be a confounding factor to the overall incidence of response. Therefore, all participants will be asked to complete the resistance training after the CRF training session is completed in order to have consistency among all participants. During the first 4 weeks, there will be no resistance training. During the next 4 weeks (week 4-8), there will be a learning and anatomical adaptation phase to resistance training in which proper technique and

range of motion will be emphasised and participants will be acclimated to the resistance training machines. During the last 4 weeks (week 8-12) participants will complete 1 set of 8-12 repetitions on 8 machine-based resistance training exercises and progress to 2 sets by the end of the 12th week (38).

3.5.4 Determination of Workload

For the standardised group, the workload will be determined based on %HRR and completed based on the following calculation:

HRR = [(Maximal HR – Resting HR) x Desired Percentage] + Resting HR

For the individualised group, the workload will be determined based on VT values as previously described (11,99) to determine VT1 and VT2. The criteria used for determining VT1 and VT2 will be a visual analysis of figures of time plotted against the relative respiratory variable – ventilatory equivalents of oxygen (VE/VO_2) and ventilatory equivalents of carbon dioxide (VE/VCO_2). Determination of VT1 will be an increase in VE/VO_2 with no increase in VE/VCO_2 and moving away from linearity of VE, whereas VT2 will be a simultaneous increase in both VE/VO_2 and VE/VCO_2. Calculations of HR values associated with VT values will be calculated prior to exercise sessions and with following HR ranges:

- Target HR > VT1 = HR range of 10 bpm below VT1 to the HR at VT1
- Target HR ≥ VT1 to <VT2 = HR range of 15 bpm above VT1 and below VT2
- Target HR ≥ VT2 = HR range of 10 bpm above VT2

Exercise volume will be prescribed based on EE per kg of body weight a week ($kcal \cdot kg^{-1} \cdot week^{-1}$) to implement an isocaloric exercise volume (i.e. in terms of kilocalories per kg a week) across individuals and groups. Previous research has found that EE ranging from 4 $kcal \cdot kg^{-1} \cdot week^{-1}$ (100) to 23 $kcal \cdot kg^{-1} \cdot week^{-1}$ (32,65,101,102) have positive effects on CRF and cardiometabolic responses to exercise. Therefore, this study will utilise a similar 12 week exercise protocol as previously described (11), while implementing a standardised isocaloric volume ($kcal \cdot kg^{-1} \cdot week^{-1}$) instead of a designated time for each exercise session. Exercise progression will follow standard guidelines that have been previously established (25). Figure 3.2 illustrates the exercise progression following baseline testing for the duration of the 12-week intervention for both experimental groups while Table 3.1 and Table 3.2 show the SPIRIT study schedule for experimental and control participants, respectively.

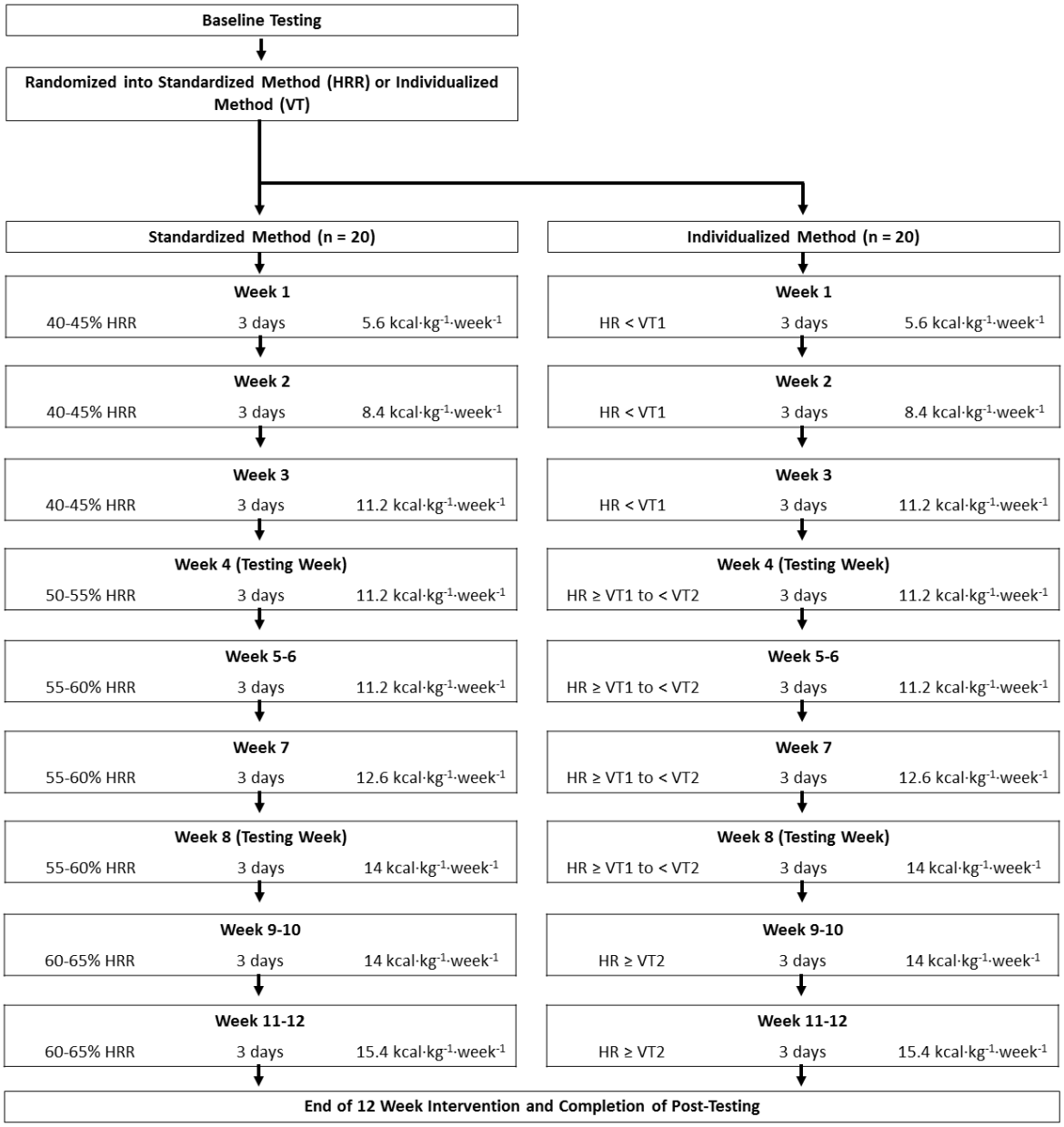

Figure 3.2 A detailed flow schematic of the exercise prescription for the experimental groups. HRR, heart rate reserve; kcal, kilocalories; VT1, first ventilatory threshold; VT2, second ventilatory threshold

Table 3.1 SPIRIT study calendar for the experimental group for the 12-week intervention

			Exercise Intervention				
Point of time:	Pre-intervention	Baseline	Time 0	Week 4	Week 8	Week 12	12 Week Analysis
Recruitment	x						
Medical history	x						
Inclusion criteria	x						
Randomization			x				
Height		x		x	x	x	
Weight		x		x	x	x	
Resting heart rate		x		x	x	x	
Resting blood pressure		x		x	x	x	
Waist circumference		x		x	x	x	
Low-density lipoprotein		x		x	x	x	
High-density lipoprotein		x		x	x	x	
Triglycerides		x		x	x	x	
Blood glucose		x		x	x	x	
Maximal exercise test		x		x	x	x	
Verification test		x		x	x	x	
3-day nutrition recall		x				x	
Biological variability			x				
Time course changes							x
Incidence of response							x

SPIRIT Standard Protocol Items: Recommendations for Interventional Trials

Table 3.2 SPIRIT study calendar for the control group for the 12-week intervention

Point of time:	Pre-intervention	Baseline	Time 0	Week 4	Week 8	Week 12	12 Week Analysis
Recruitment	x						
Medical history	x						
Inclusion criteria	x						
Height		x		x	x	x	
Weight		x		x	x	x	
Resting heart rate		x		x	x	x	
Resting blood pressure		x		x	x	x	
Waist circumference		x		x	x	x	
Low-density lipoprotein		x		x	x	x	
High-density lipoprotein		x		x	x	x	
Triglycerides		x		x	x	x	
Blood glucose		x		x	x	x	
Maximal exercise test		x		x	x	x	
Verification test		x		x	x	x	
3-day dietary recall		x				x	
IPAQ		x		x	x	x	
12-week changes							x

SPIRIT Standard Protocol Items: Recommendations for Interventional Trials, IPAQ International Physical Activity Questionnaire

3.5.5 Time Course Changes

Currently, there is no literature investigating the time course changes of VO_2max between a standardised and individualised CRF exercise program. Therefore, since testing will occur every 4th week, the time course changes over the 12 weeks of the CRF training intervention will be highlighted and addressed. These data will be used to further analyse the incidence of response during 12 weeks of structured CRF training and gain insight into the time course changes associated with CRF training for each individual and based on the CRF training intensity (standardised or individualised).

3.5.6 MetS Z-Score

Since training responsiveness is a comprehensive topic, it is generally understood that participants can be responders to 1 variable and not others. Therefore, a preliminary investigation on the feasibility of using a MetS z-score will be analysed. These data will be used to provide insight on the overall changes that occur in cardiometabolic factors following a standardised and individualised exercise intensity prescription.

3.5.7 Categorizing Responders and Non-Responders

Following the 12-week intervention, the participants will be categorised as responders and non-responders (see statistical analysis section for further details) for each testing measurement. While each testing measurement will be evaluated, the overreaching categorization of responder and non-responder will be based on VO_2max due to the profound health and performance implications of this measurement.

3.6 Data and Confidentiality Management

Electronic data will be coded, entered, and stored into a secure (password protected) database on Western State Colorado University's campus. All paper data, including consent forms, medical history documents, and daily exercise logs, will be stored in a secured locked cabinet in the Western State Colorado University Human Subject's office. Only the primary investigators will have access to the data.

Due to the nature of the study, participants will be exercising in an environment with other members from the study. Therefore, anonymity of identity cannot be guarantee throughout the study. However, no research participant will be able to see or access any personal information – medical documents, exercise log, medications, etc. To ensure participant safety when exercising, researcher assistants delivering the exercise will be informed of relevant information that may influence how the participant responds to exercise. Any data collected and displayed in results of scientific manuscripts will be displayed in a way which does not disclose individual identity.

3.7 Ethics Approval and Consent to Participate

The protocol has been approved by the Auckland University of Technology Ethics Committee (16/264) and the Human Research Committee of the Institutional Review Board at Western State Colorado University (HRC2016-01-90R6). It should be noted that even though two academic institutions reviewed and approved the protocol, data

collection will only be occurring on the campus of Western State Colorado University. Prior to any data collection and after all questions participants have about the study protocol, time commitment, and expectations have been answered, an informed consent document will be signed. If the informed consent is not signed, the participant will be excluded from the data collection.

3.8 Statistical analysis

All analyses will be performed using SPSS Version 22.0 (Chicago, IL) and GraphPad Prism 6.0 (San Diego, CA).

3.8.1 Biological Variability

Intra-class correlation (ICC) of variation, typical error and CV for VO_2max, resting HR, resting BP, and fasting blood glucose, TC, HDL, and LDL will be calculated as described previously (103). Since the CV accounts for both biological variability and measurement error, the CV will be used as the TE for the investigations. TE will be used to categorise responders and non-responders. In summary, for all criteria tested the changes in pre- to post- intervention will be analysed with responders having a change > TE and non-responders having a change that is ≤ TE.

3.8.2 Time Course Changes

Baseline group differences were determined based on an independent-samples *t*-test with $p \leq 0.05$. All measures were analysed by a GLM two-way ANOVA for repeated measures (baseline, wk 4, wk 8, and wk 12) with intensity as the between subject variable. When appropriate, a subsequent *post hoc* comparisons using a Bonferroni correction was completed. A one-way ANOVA was used to understand the changes in time point and VO_2max. The assumption of normality was tested by examining normal plots of the residuals in ANOVA models and regarded as normally distributed if Shapiro-Wilk tests are not significant (27). Effect sizes were calculated using means and pooled SD. The probability of making a type I error was set at $p \leq 0.05$ for all statistical analyses. In order to be included in the data analysis, participants needed an adherence level ≥70% with strict adherence to the targeted day-to-day exercise intensity and duration.

3.8.3 MetS Z-Score Response

All statistical analyses were performed using SPSS Version 25.0 (Chicago, IL, USA). Data were reported as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) testing was used to compare groups at baseline and Tukey *post hoc* test when

appropriate. The assumption of normality was confirmed by examination of normal plots of the residuals in ANOVA models and Shapiro-Wilk tests (27). Analysis of within-group differences in continuous variables was completed using paired sample t-tests. ANCOVA was used to analyse between-group difference of the change in main dependent variables (i.e. SBP, DBP, MAP, HDL, TG, fasting BG, and WC) continuous variables from baseline to 12 weeks, with the week 12 values as the dependent variables and the baseline value as a covariate. A subsequent *post hoc* analysis with a comparison of main effects and a Bonferroni adjustment was completed when appropriate. Analysis of within-group differences in continuous variables was completed using paired sample t-tests.

3.8.4 Incidence of Response

One-way analysis of variance (ANOVA) testing was used to compare groups at baseline and, where appropriate, Tukey *post hoc* test. The assumption of normality was confirmed by examination of normal plots of the residuals in ANOVA models and Shapiro-Wilk tests (27). Paired sample t-tests were used to analyse within-group differences in continuous variables. Between-group difference of the change in continuous variables from baseline to 12 weeks was assessed through analysis of covariance (ANCOVA), with the week 12 values as the dependent variables and the baseline value as a covariate and, where appropriate, a *post hoc* analysis with a comparison of main effects and a Bonferroni adjustment. Subsequent ANCOVA analyses were performed with the percent change in VO_2max, absolute change in VO_2max, and relative change in VO_2max as dependent variables and age, sex, height, weight, BMI, and baseline VO_2max (relative and absolute) as covariates.

Delta values (Δ) are expressed as percent change (post-testing minus baseline value divided by baseline value, multiplied by 100) for relative VO_2max for experimental groups with participants categorised as: '1' = responder (% $\Delta > 4.7\%$) or '0' = non-responder (% $\Delta \leq 4.7\%$). Chi-squared ($\chi 2$) tests were subsequently used to analyse the point prevalence of responders and non-responders to exercise training separated by exercise intensity group (individualised and standardised) between baseline and 12 weeks and a Cramer's V test to determine effect size.

3.9 Discussion

There has been a considerable amount of individual variability reported in the literature related to the response of CRF measurements (specifically, VO_2max and VO_2peak).

However, there is still an overall lack of understanding as to why this variability occurs. Unfortunately, there is minimal consistency in methodology and the criteria for determining incidence of response leading to the overall findings indicating there are changes in training responsiveness of -33 to +76% (5). However, some of the data associated with individual responses may be misleading as measurements were recorded as peak values (4,7,39) and may not be a direct representation of the maximal efforts for participants and, therefore, not an accurate representation of true physiological adaptations.

In order to have an all-inclusive definition for incidence of response the TE must be taken into account (13). Therefore, it would be important to know biological variability and measurement error for each outcome to determine whether responses are beyond that of the TE. Two recent investigations (10,11) utilised TE to determine response rate by defining a responder as an individual with improvements from pre- to post-training by > TE in a positive direction and, in contrast, an individual who improves by ≤ TE as a non-responder. Nevertheless, for the two aforementioned studies, values for day-to-day biological variability were used from previously published work and may not be directly applicable to the population being studied or the environmental conditions in which data collection takes place.

Conventionally, results of exercise-based studies are reported as the mean and standard deviation (14) and only illustrate the main effects and group differences of training responsiveness (15). Overall, there is a lack in attention to individual differences with these conventional methods of reporting data since nearly 32% of measurements (distributed normally) fall outside of 1 standard deviation. Recent literature proposes reporting not only the mean, standard deviation, and group differences, but also individual responses to the training program (14,15) or at least ranges of endurance changes (10). This approach will strengthen study findings and provide further insight into the phenomenon of individual variability and training responsiveness.

From the HERITAGE Family Study (16), a large, well-controlled, 20-week standardised endurance training program, insight was gained on the incidence of response. It was reported that genetics may play a critical role in the incidence of response (17) with trainability of VO_2max linked to familial aggregation (18). However, a potentially overlooked factor in the individual variability may be linked to suboptimal methodology of exercise prescription. Indeed, due to the theoretical and physiological mechanisms of

exercise prescription, utilization of a threshold based measurement for exercise prescription has been suggested to decrease the incidence of non-response and improve CRF and cardiometabolic factors compared to the traditional approach using intensities set relative to VO_2max, maximal heart rate (HRmax), aerobic ability reserve (VO_2R), or heart rate reserve (HRR) (19). However, there have been few studies that have reported individual responses following training relative to a threshold measurement (14). To the best of our knowledge, there is currently only one study reporting individual responses to training comparing set intensities based on the VT1 and VT2 measurements and percentage of HRR (11). During incremental exercise, VT1 is the point at which increases in ventilation become non-linear (an increase in the ventilatory equivalents of oxygen [VE/VO_2] with no increase in the ventilatory equivalents of carbon dioxide [VE/VCO_2]) and VT2 is the point at which there is an accumulation of blood lactate due to the inability to buffer the amount of lactate produced (simultaneous increase in both VE/VO_2 and VE/VCO_2) (104).

Traditionally, exercise intensity has been prescribed based on a relative percent concept – based on a percentage of HRmax, VO_2max, VO_2R, or HRR. However, caution has been advised for utilization of the relative percent method, specifically HRmax and VO_2max, as criteria to determine workload as they may not be sufficient to elicit the desired metabolic response (20,21). Furthermore, percentages for both HRmax and VO_2max correspond to a wide range of exercise intensities relative to threshold measurements (22). For example, with exercise intensities between 58% and 75% of VO_2max, some participants were found to be above while others were reported to be below their individual anaerobic threshold (23). Similar findings were noted when investigating a 12-month jogging/walking program (21). In order to make the prescription of exercise intensity more individualised, many researchers have used percentages of HRR as this takes into consideration not only HRmax, but also resting HR. However, aerobic thresholds were found to be at 70% ± 10% of HRR (24) indicating large variability in the metabolic stress across individuals at a set percentage of HRR.

Indeed, genetics have gained a lot of attention to understand the specific roles of genes and response rates. However, based on the genetic evidence to date, there are many pathways that are associated with VO_2max trainability and nearly an unlimited combination of signalling events that may influence the VO_2max responsiveness (82,86). With genetics proposed to account for less than 50% of the variance in responsiveness, the other 50% is still not well understood.

One of the major areas in which the literature is lacking in the understanding of training responsiveness is the investigation of an individualised approach to exercise prescription and the time course changes. With the emerging concept of 'exercise is medicine' and the capacity to prescribe exercise to combat adverse effects of disease, the time course changes for VO_2max and cardiometabolic risk factor measures need to be better understood to properly identify efficacious exercise doses (i.e., intensity, volume) that will elicit an adequate response. However, much of the literature on time course changes utilises standardised methods of exercise prescription rather than individualised approaches. To the best of our knowledge, there is no literature investigating time course changes of VO_2max outcomes with the use of a threshold-based protocol and exercise volume individualised based on kilocalories of expenditure per week with relation to body mass. Similarly, results of time course changes have traditionally been reported as only group means and standard deviations with individual time course changes not being reported. Based on a review of the literature, there have only been two studies to identify individual time course changes (48,92). Reporting of individual time course changes for VO_2max and cardiometabolic risk factor measurements will help to further understand the individual variability in training responsiveness.

3.9.1 Limitations

There are several limitations that merit discussion. It is possible there may be heterogeneity in training responses due to age alone given the large age range (30 to 75 years) that will be recruited for the current trial. However, the age range for the target sample will be comparable to previous studies (16,32,65) and also reflect the likely age range found in community exercise programs (105). Another possible limitation is external validity given data collection will take place at moderate altitude. Nevertheless, to the best of our knowledge, there is no evidence to suggest differences in training responsiveness (i.e. responders and non-responders) between altitude-residing individuals and sea level counterparts. A third potential limitation is the inability to anticipate how many participants will be categorised as non-responders following the first 12-week intervention.

3.10 Conclusion

In summary, this original randomised controlled trial aims to 1) investigate the efficacy of an individualised exercise prescription at improving training responsiveness and, 2) to better understand the time course changes of training adaptations to both individualised

and standardised exercise intensity prescription methods. It is anticipated that findings from this novel trial will add to our knowledge of how personalised exercise can enhance training efficacy and limit training unresponsiveness.

Chapter 4 - Using a Site-Specific Technical Error to Establish Training Responsiveness: A Preliminary Explorative Study

4.1 Prelude

This chapter comprises the following paper accepted for publication: Weatherwax, R.M., Harris, N., Kilding, A., Dalleck, L.C. (2018). Using a Site-Specific Technical Error to Establish Training Responsiveness: A Preliminary Explorative Study. *Open Access Journal of Sports Medicine,* 9.

In this chapter, the first experimental chapter, a TE is determined for the specific site and cohort being analysed. Due to the lack of a set definition of training responsiveness in the literature, I sought to understand how much biological variability and measurement error existed for repeated VO_2max tests with a verification protocol. Without a set definition in the literature regarding responsiveness, the main objective of this chapter was to highlight how different methods of quantifying responsiveness can lead to very different interpretations of the training effectiveness. The TE found specifically for this cohort being analysed will be subsequently used to address the main aim of the PhD thesis with the quantification of training responders and non-responder. Within this chapter, the technical error was calculated based on the CV with the addition of the measurement error of the metabolic analyser (i.e. ±3.0%). After the publication of this chapter and further examination into TE concepts, it is believed the measurement error was added twice in this calculation since measurement error is embedded within the CV. Therefore, in Chapter 7, this issue was addressed and the measurement error was not included twice in the TE calculation to quantify training responsiveness.

4.2 Abstract

Even though CRF training elicits numerous health benefits, not all individuals have positive training responses following a structured CRF intervention. It has been suggested that the TE, a combination of biological variability and measurement error, should be used to establish specific training responsiveness criteria (i.e. a threshold) to gain further insight on the effectiveness of the training program. To date, most training interventions use an absolute change or a TE from previous findings, which do not take into consideration the specific population, training site, equipment used to establish training

outcomes, or the specific cohort being evaluated. Therefore, the purpose of this investigation was to retrospectively analyse training responsiveness of two CRF training interventions using two common criteria and a site-specific TE. 16 men and women completed two maximal GXT and verification bouts to identify VO_2max and establish a site-specific TE. The TE was then used to retrospectively analyse training responsiveness in comparison to commonly used criteria (percent change of > 0% and > +5.6% in VO_2max) for two recent publications. The TE was found to be 7.7% for relative VO_2max. Chi squared testing showed significant differences in all training criteria for each intervention and pooled data from both interventions, except between % $\Delta > 0$ and % $\Delta > +7.7\%$ in one of the investigations. Training non-responsiveness ranged from 11.5% to 34.6%. Findings from the present study support the utility of site-specific TE criterion to quantify training responsiveness. Similar methodology of establishing a site-specific and even cohort specific TE should be considered to establish when true cardiorespiratory training adaptations occur.

4.3 Introduction

It is well established that regular physical activity and CRF training confers numerous health benefits (31,34) and that a low level of CRF is a risk factor for coronary heart disease and CVD mortality (30,35–37). It is generally accepted that CRF can be improved with the implementation of a regular aerobic exercise training program following standardised guidelines (38). However, it has also been shown that not all individuals respond positively to such exercise and evidence of considerable individual variability in training adaptations has been found, including so-termed 'non-responders' (2,5,10–12,61) and, in some instances, 'adverse responders' (13) in regard to changes in VO_2max and cardiometabolic factors (TC, HDL, LDL, TG, fasting BG, and resting BP). Training non-response is often defined as a response that does not exceed a set criteria in a favourable direction (usually a percent change greater than 0) whereas an adverse response is a change in an opposite and unfavourable direction compared to the expected positive adaptations. This variability in training responsiveness is not well understood and may be attributable to various factors including genetics, socio-cultural aspects, and a lack of a set definition in the literature for incidence of response. It has been common practice to quantify training responsiveness based on absolute changes, but this method fails to take into consideration biological variability (normal day-to-day biological fluctuations) and measurement error of the equipment (10,13,14). Consequently,

currently there is not a clear consensus on best practice to prescribe a customised exercise intervention that takes into consideration individual characteristics and diagnostic information.

Identification of different training responsiveness categories requires specific criteria. For instance, in recent years, various investigators have used TE to distinguish training responsiveness (11–13) which is comprised of measurement error and biological variability. Interindividual differences in daily environment, disease, genetics, and lifestyle are all possible modulators of biological variability. Nevertheless, it is not uncommon in the literature for a uniform biological variability metric to be incorporated into the TE definition for categorizing training responsiveness. For example, two recent investigations of exercise training in untrained participants (10,11) sourced technical error data for VO_2max from an early 1980s investigation of aerobic power (106). Such application of identical group TE criteria (i.e., one based on a uniform biological variability metric) for the categorization of responders and non-responders disregards individuality. Recently, it has been identified that a more nuanced, individualised and evidence-based approach to exercise prescription is needed to enhance training efficacy and limit training unresponsiveness (11). Therefore, we propose a more personalised approach is also required to more accurately identify 'true' individual responders and non-responders to regular exercise training. Accordingly, the purpose of the present study was to establish a site-specific TE and retrospectively analyse previously published CRF training interventions specifically addressing training responsiveness to investigate differences in sourced (i.e., from the literature and what was previously used) compared to site-specific responsiveness criteria and to highlight the possibility of reporting false-positive CRF training adaptations.

4.4 Methods

The current investigation involved the development of a site-specific TE. It also retrospectively analysed the training responsiveness of two previously published investigations (11,12). All of the investigations were conducted in the same laboratory and with a similar population.

4.4.1 Development of Site-Specific Technical Error

Sixteen men and women were sampled from a randomised control trial being conducted in a community exercise program (26) and were included if they were currently sedentary

(participating in no more than 30 min/day of physical activity on 3 days a week), between the ages of 30 and 75, and no medical contraindications as per the exclusion criteria. Exclusion criteria included signs or symptoms suggestive of pulmonary, cardiovascular, or metabolic conditions as determined by a standard medical history questionnaire. The local Human Research Committee approved this study (HRC2016-01-90R6). Each participant signed an informed consent prior to participation.

Participants were asked to complete two testing sessions (no sooner than 24 hours from each other, but within a 1-week period) while maintaining their regular daily habits and prior to starting an exercise intervention. During each testing session, participants were weighed to the nearest 0.1 kg and height was measured to the nearest 0.5 cm on a medical grade scale and stadiometer (Tanita Corporation WB-3000, Tokyo, Japan), respectively. Following basic anthropometric measurements, a GXT and verification bout were completed.

The GXT and verification testing to confirm attainment of VO_2max were completed using protocols previously published (26). In summary, participants completed a modified-Balke, pseudo-ramp protocol on a motorised treadmill (Powerjog, GX200, Maine, USA) until volitional fatigue. Following a 4 min warm-up, participants walked or ran at a self-selected pace and grade increased by 1% each minute. Expired air and gas exchange data were monitored continuously with a metabolic analyser (Parvo Medics TrueOne 2.0, Salt Lake City, UT, USA). Twenty minutes following the GXT, a verification bout was performed at a workload 5% higher than the last completed state of the GXT. Participants were encouraged to maintain the verification bout workload until volitional fatigue. Gas exchange data was averaged for every 15 seconds and VO_2max for the GXT and verification bout were determined by averaging the last two 15 second samples. VO_2max was confirmed if the GXT and verification bout were within ±3.0%, based on previous methods (57,59).

4.4.2 Retrospective Analyses of Training Responsiveness

Data on 52 adults from two studies were available for analysis. These studies are briefly described and were chosen due to the uniqueness of taking place in a laboratory that resides at ~2,350 m and the same laboratory in which the site-specific TE was developed as well as a similar training methodology. The basic descriptive, baseline, and post-training data are highlighted in Table 4.1. For each investigation, baseline and post-training VO_2max was determined based on the same aforementioned protocol using a

modified-Balke, pseudo ramp GXT on a motorised treadmill. The two final 15 second time intervals were averaged for the two ending data points during the GXT. These two processed data points were then averaged to establish VO_2max. Participants did not complete a verification protocol at baseline or post-training.

4.4.3 Western State Colorado University Threshold Study (WESTERN2015)

In summary, sedentary men and women between the ages of 18 and 54 were randomised to a non-exercise control group or one of two exercise interventions (11). For those participants randomised to the exercise groups, they performed 30 min, 5 days a week for 12 weeks of exercise training with a progressive increase of intensity based on percentage of HRR or a threshold based model using VT1 and VT2.

4.4.4 Western State Colorado University ACE IFT Study (WESTERN2016)

Non-smoking men and women between the ages of 44 and 83 were randomised to a personalised or standardised training group and completed both CRF and resistance training throughout a 13 week intervention (12). The CRF training occurred 3 days a week with a progressive increase in intensity and duration. Resistance training commenced at week 4 and consisted of 3 days a week with progressive increases throughout the intervention.

Table 4.1 Descriptive, baseline, and response to training data for two cohorts with CRF training interventions

	Age (Years)	**Height (cm)**	**Weight (kg)**	**Baseline VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)**	**Baseline VO_2max ($L \cdot min^{-1}$)**	**Post VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)**	**Post VO_2max ($L \cdot min^{-1}$)**	**VO_2max Response (% change)**
WESTERN2015 (11)	32.3 ± 9.5[a]	169.8 ± 10.1	73.1 ± 13.8	34.6 ± 7.2	2.5 ± .8	37.4 ± 7.5	2.7 ± 0.8	8.6 ± 6.7
	28.3 - 36.4[b]	165.6 - 174.1	67.2 - 78.9	31.6 - 37.7	2.2 - 2.8	34.3 - 40.6	2.4 - 3.1	5.8 - 11.4
WESTERN2016 (12)	64.9 ± 8.5	168.0 ± 9.4	83.1 ± 18.0	24.3 ± 7.7	1.9 ± 0.9	25.9 ± 7.9	2.1 ± 0.9	8.2 ± 11.6
	62.3 - 67.6	164.3 - 171.6	76.1 - 90.1	21.8 - 26.7	1.6 - 2.2	23.4 - 28.4	1.8 - 2.5	4.6 - 11.8

Descriptive statistics are reported as [a]mean ± SD and [b]95% Confidence interval. CRF, cardiorespiratory fitness; VO_2max, maximal oxygen consumption.

4.4.5 Statistical Analysis

4.4.5.1 Site-Specific Technical Error

All statistical analyses were performed using SPSS Version 22.0 (Chicago, IL). Sex differences were determined based on an independent samples T test with $p \leq 0.05$. Intra-class correlation (ICC) of variation, typical error and co-efficient of variation (CV) for VO_2max were calculated as previously described (103). The calculated CV was used in combination with the measurement error of the metabolic analyser, as previously established (107), to determine the TE. Therefore, any participant with a VO_2max training response in a positive direction that exceeds the TE (CV + measurement error) value was considered a 'responder' to the training intervention.

4.4.5.2 Training Responsiveness

To determine the individual training responsiveness from WESTERN2015 and WESTERN2016, the absolute and percentage change in VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) from baseline to post testing were calculated. Delta values (Δ) were calculated (post-program minus baseline value divided by baseline value) to establish the percent change in VO_2max. The change in VO_2max were compared using three methods of establishing training responsiveness: 1) whether or not participants had a training response greater than 0.0 (i.e., % $\Delta > 0$), since this has been commonly reported in the literature (4,5,7); 2) whether or not they exceeded a positive change greater than 5.6% (i.e., % $\Delta > +5.6\%$) which was established by Katch and colleagues (106) in the early 1980s and has been a method, more recently, to establish responsiveness (10–12); and 3) based on the calculated site-specific TE (i.e., % $\Delta >$ CV + measurement error). For each of the methods, participants were categorised as '1' = responder if their % Δ was greater than the specified criteria or '0' = non-responder if the % Δ failed to exceed the criteria.

Pearson's chi-square (χ^2) were used to stratify the incidence of response separated by the responsiveness criteria following the training intervention with a subsequent Cramer's V test to determine effect size. The probability of making a Type I error was set at $p < 0.05$ for all statistical analyses. Where significance was shown in the 3x2 χ^2 testing, a subsequent *post hoc* analysis was performed to compare between responsiveness criteria using a Bonferroni adjustment to protect against type 1 error with an established p-value of $p < 0.05/3$ or 0.017.

4.5 Results

4.5.1 Establishment of Site-Specific Technical Error

Table 4.2 shows the individual sex and group demographics, mean ± standard deviation of the averaged samples for each participant, and confidence intervals from an independent samples T-test. Only height and relative VO_2max values were significantly different ($p \leq 0.05$) between men and women.

The typical error, ICC, and CV for relative VO_2max were 1.12 $ml \cdot kg^{-1} \cdot min^{-1}$, 0.99, and 4.7%, respectively. The measurement error was 3.0% based on the manufacturer specifications (Parvo Medics) and a previous investigation comparing the aforementioned metabolic cart compared to the gold standard (107). Technical error was subsequently calculated by summing measurement error and biological variability:

$$\text{TE} = \text{measurement error (3.0\%)} + \text{biological variability (4.7\%)}$$

$$\text{TE} = 7.7\%$$

A summary of the retrospective analysis of training responsiveness findings based on % $\Delta > 0$, % $\Delta > +5.6\%$, and the laboratory specific TE (% $\Delta > +7.7\%$) can be found in Figure 4.1.

Table 4.2 Participant demographics for anthropometric and CRF measurements for the development of a site-specific technical error

			Testing Session 1			Testing Session 2		
	Age (Years)	**Height (cm)**	**Weight (kg)**	**VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)**	**VO_2max ($L \cdot min^{-1}$)**	**Weight (kg)**	**VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)**	**VO_2max ($L \cdot min^{-1}$)**
Men	53.6 ± 12.8[a]	177.9 ± 2.6*	101.4 ± 27.5	32.1 ± 14.9*	2.9 ± 0.6	100.9 ± 28.0	32.3 ± 14.5*	2.9 ± 0.6
n = 5	37.7 - 69.5[b]	174.7 - 181.1	67.3 - 135.6	13.7 - 50.6	2.1 - 3.7	66.1 - 135.7	14.3 - 50.4	2.2 - 3.7
Women	52.2 ± 14.4	166.9 ± 6.9	81.9 ± 17.6	24.8 ± 6.9	2.0 ± 0.5	81.6 ± 17.8	24.6 ± 6.3	2.0 ± 0.5
n = 11	42.5 - 61.8	162.3 - 171.5	70.0 - 93.7	20.2 - 29.4	1.6 - 2.4	69.6 - 93.5	20.4 - 28.9	1.6 - 2.3
Group	52.6 ± 13.5	170.3 ± 7.8	87.6 ± 22.3	27.1 ± 10.2	2.3 ± 0.7	87.6 ± 22.5	27.0 ± 9.8	2.3 ± 0.7
n = 16	45.4 - 59.8	166.2 - 174.5	76.1 – 99.9	21.7 – 32.5	1.9 - 2.7	75.6 - 99.6	21.8 - 32.3	1.9 - 2.7

Descriptive statistics are reported as [a]mean ± SD and [b]95% Confidence interval. CRF, cardiorespiratory fitness; VO_2max, maximal oxygen consumption.
*$p \leq 0.05$, significantly higher in men when compared to women.

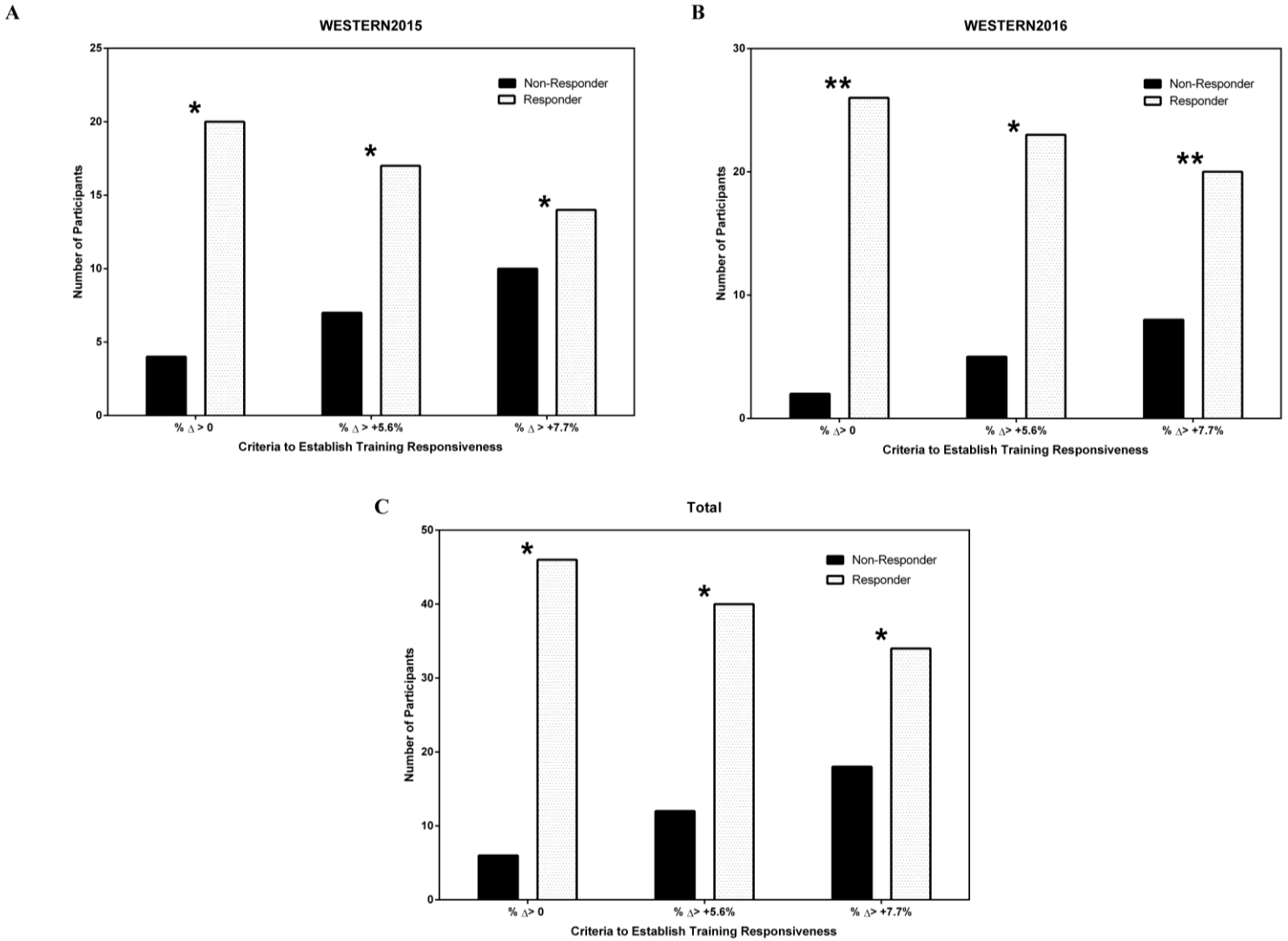

Figure 4.1 Training responsiveness for two retrospectively analysed interventions and combined analysis of interventions based on two commonly used criteria and a site-specific criteria (% Δ > +7.7%) where **A** and **B** show retrospective data analysis of Wolpern et al (11) and Dalleck et al (12), respectively, and **C** highlights the combined data pool from both investigations. Significant differences ($p < 0.017$) were observed in all groups with an * representing significant difference between all criteria and ** indicating only a significant difference between % Δ > +5.6% criteria, but not statistically different from % Δ > 0% or % Δ > +7.7%

4.5.2 WESTERN2015 and WESTERN2016

The incidence of non-response for WESTERN2015 ranged from 16.7% to 41.7% depending on the criteria used. For each criterion, there was a non-response rate of 16.7%, 29.2% and 41.7% for % $\Delta > 0$, % $\Delta > +5.6\%$, and % $\Delta > +7.7\%$, respectively. There was a significant interaction based on training responsiveness and the criteria used based on χ^2 difference testing ($p < 0.05$) with an effect size of 0.70. Based on the *post hoc* analysis, statistical significance ($p < 0.017$) was shown between all groups: % $\Delta > 0$ and % $\Delta > +5.6\%$ ($p = 0.001$); % $\Delta > 0$ and % $\Delta > +7.7\%$ ($p = 0.010$); and % $\Delta > +5.6\%$ and % $\Delta > +7.7\%$ ($p = 2.0 \times 10^{-4}$).

Similar results were found in the WESTERN2016 group with a range of non-response of 7.1% to 28.6% and a significant interaction based on the χ^2 difference testing ($p < 0.05$) and an effect size of 0.60. Specifically, there was a non-response rate of 7.1%, 17.9% and 28.6% for % $\Delta > 0$, % $\Delta > +5.6\%$, and % $\Delta > +7.7\%$, respectively. The *post hoc* analysis showed statistical significance ($p < 0.017$) between two of three groups: % $\Delta > 0$ and % $\Delta > +5.6\%$ ($p = 0.002$); and % $\Delta > +5.6\%$ and % $\Delta > +7.7\%$ ($p = 9.6 \times 10^{-5}$). There was not a statistical significant difference between % $\Delta > 0$ and % $\Delta > +7.7\%$ ($p = 0.020$).

4.5.3 Total

When evaluating responders and non-responders of the combined interventions retrospectively analysed according to the specific responsiveness criteria using χ^2 difference testing, there were significant differences ($p < 0.05$) in all responsiveness criteria with a large effect size of 0.66. The overall non-response rate of the combined interventions was 11.5%, 23.1% and 34.6% for % $\Delta > 0$, % $\Delta > +5.6\%$, and % $\Delta > +7.7\%$, respectively. Statistical significance ($p < 0.017$) was shown in the matched *post hoc* analyses between all groups: % $\Delta > 0$ and % $\Delta > +5.6\%$ ($p = 0.001$); % $\Delta > 0$ and % $\Delta > +7.7\%$ ($p = 0.001$); and % $\Delta > +5.6\%$ and % $\Delta > +7.7\%$ ($p = 0.001$).

4.6 Discussion

The main purpose of this investigation was to establish a site-specific TE to identify training responsiveness and retrospectively analyse two previous investigations that used a sourced measurement to determine training responders and non-responders and compare the results with the site-specific TE. Indeed, there were statistically significant differences between the percentage of training responders and non-responders of two previously reported interventions depending on the responsiveness criteria used. This

information provides further evidence of the need to establish guidelines for understanding the individual variability in training responsiveness. Our findings are also testimony to our conjecture on the importance of site-specific responsiveness criteria determination for greater sensitivity and specificity of the quantification of training induced adaptations. Such detail will provide better discriminative data and attenuate false positive reporting.

We determined a site-specific TE for VO_2max to establish the positive percent change needed to consider an exercise intervention as meaningful, or exceeding the biological variability and measurement error, which has recently become a method for reporting responsiveness (10,11). In the current investigation, there was a CV of 4.7% and a TE of 7.7% for VO_2max between the two assessment occasions. Previously, Katch et al (106) found a ± 5.6% variance with 90% of the variation due to biological variability and 10% due to technological error. Similarly, Shephard and colleagues (62) found a 2 day CV for VO_2max of 4.3% and a CV of 5.5% when measurement error was included from the HERITAGE study. Thus, the CV we found for VO_2max was comparable to those previously reported. However, it is important to note that if the CV is used to establish criteria for responders and non-responders in a training study, even a small difference might account for meaningfully different training responsiveness rates (i.e., 4.7% compared to 4.3%). Therefore, we believe it is critical to establish a site-specific CV and TE whenever categorizing response rate in a training study rather than sourcing information from previous studies that may not directly reflect the specific environment of training and testing. Furthermore, this was the first investigation of biological variability, measurement error, and quantifying a TE for VO_2max with the use of a verification protocol to confirm the attainment of VO_2max. Verification testing is critical in establishing a 'true' VO_2max since the most commonly used criteria has been a plateau in VO_2 with increasing intensity, but there is not a universally accepted criteria for a plateau (56). Therefore, the use of a verification bout confirms VO_2max, which can then be used to determine true exercise intervention induced adaptations.

A recent investigation has implemented the use of TE to quantify response rate (40). However, the authors used the maximal W_{max} gained in a cycling test to volitional fatigue at baseline rather than VO_2max to determine a TE threshold for responsiveness criteria. They ultimately found that CRF non-response could be mitigated if the exercise dose is increased. However, it should be noted that if they were to use VO_2max and the associated TE rather than the TE of the W_{max}, the results might have been interpreted differently.

For example, they found that one group who exercised 4 days a week were all responders based on the TE of W_{max}, but when analysing the data based on the standard TE of 5% previously reported (62), 3 of the 17 participants would have been categorised as a non-responder which is comparable to previous rates of non-response (108). Furthermore, had Montero and Lundby (40) calculated the specific cohort TE for VO_2max, this value may have been higher than previous findings, similar to the results of the current investigation. Consequently, the incidence of non-response may have been even higher and included participants in the higher dose group, suggesting that in addition to exercise dose, responsiveness may also be partially influenced by the TE criterion.

In a recent review on the topic (87), a theoretical framework has been established to evaluate training responsiveness, but the methodology must include a comparator arm (i.e., control group). With regular exercise having numerous health benefits, the use of a control group where exercise is either limited or prevented, may raise moral and ethical considerations. Therefore, the current study may provide a standard protocol to follow for future investigations that would be easy to administer and remove any ethical considerations of a control group being withheld from a known positive stimulus. Similarly, we believe that two baseline measurements are sufficient to calculate a TE and address the phenomenon of regression to the mean, which has been of high concern when calculating TEs, since the first two measurements (i.e., two baseline measurements) have been shown to have the greatest effect in reducing the regression to the mean (109). Future research should investigate the efficacy of the current proposed development of the individualised TE compared to those outlined by Atkinson and Batterham (87).

4.6.1 Limitations and Strengths

The current study involved participants with a large age range (30 to 70 years) and may have possible heterogeneity due to age alone. However, the data may be more representative to a 'real world' scenario. Furthermore, *a priori* power calculation was not performed to ensure a sufficient number of participants were included due to the preliminary and explorative nature of the study and the limited amount of previous research on the topic. The concept involved in the development of the TE may have double counted the measurement error due to adding measurement error to the CV since the CV should already include the measurement error. Furthermore, the use of a ±3.0% measurement error was based on previous literature and not tested within this lab or based on the specific metabolic analyser used in the study. Next, the population used to calculate

the site-specific TE was not the same population in WESTERN2015 and WESTERN2016. However, all three of the groups were close in individual characteristics and all participants completed the exercise testing/interventions in the same laboratory. Lastly, this investigation assumes that the site-specific TE is the same at baseline as it is at post-testing. Future research should aim to investigate whether or not TE remains consistent throughout the entirety of a training intervention.

4.6.2 Conclusion

The current study is the first to calculate a TE for VO_2max with a verification bout and establish a site-specific TE to use as a metric to quantify training responsiveness. The methods of this study are both novel and timely to implement at baseline of an exercise intervention. Therefore, we recommend future investigations incorporate two or more baseline measurements to develop a site-specific TE to use when quantifying training responsiveness. Similar to an exercise prescription, methods to quantify training response must be individualised based on the cohort and laboratory and not follow a 'one-size fits all' model. Furthermore, future research should investigate the use of a truly individualised TE to establish responsiveness (i.e., each participant would have a unique TE based on their multiple baseline testing measurements).

Chapter 5 - Time Course Changes in 'True' VO_2max Following Individualised and Standardised Exercise Training

5.1 Prelude

In Chapter 4, the TE error was determined to help quantify the overall training responsiveness following the 12-week intervention. However, little is known on when changes occur to elicit a 'response' in VO_2max following a standardised and individualised exercise prescription. Therefore, this chapter explores the changes in VO_2max every 4th week during the 12-week intervention. An understanding of the time course changes is critical to identifying when meaningful changes in CRF measures occur. Data from the time course analysis can help provide insight as to when favourable changes should be anticipated and allow practitioners working in the field the opportunity to modify protocols if desired changes in CRF measures are not being seen at designed time-points in clients or patients (i.e. exercise is medicine).

5.2 Abstract

This study sought to examine time course changes in VO_2max confirmed with verification testing following 12-weeks of standardised vs. individualised exercise training. Participants (N=39) were randomly allocated to differing exercise intensity prescription groups: ventilatory threshold (individualised) or % heart rate reserve (standardised). At baseline, 4, 8, and 12 weeks, participants completed maximal exercise testing with a verification protocol to confirm 'true VO_2max.' VO_2max in the standardised group changed from 24.3±4.6 ml·kg-1·min-1 at baseline to 24.7±4.6, 25.9±4.7, and 26.0±4.2 ml·kg-1·min-1 at week 4, 8, and 12, respectively, with a significant difference ($p<0.05$) in VO_2max at week 8 and 12 compared to baseline. The individualised group had increases in VO_2max from 29.5±7.5 ml·kg-1·min-1 at baseline to 30.6±8.4, 31.4±8.4, and 32.8±8.6 ml·kg-1·min-1 at week 4, 8, and 12, respectively. In the individualised group, there were significant differences ($p<0.05$) in VO_2max from baseline to week 8 and 12 and a significant increase in VO_2max from week 8 to 12. Although not statistically significant, we provide preliminary data demonstrating a more rapid and potent improvement in VO_2max when exercise intensity is individualised. This is the first investigation to employ use of the verification procedure to confirm 'true VO_2max' changes following exercise training using ventilatory thresholds.

5.3 Introduction

Low CRF is a well-established predictor of cardiovascular disease and mortality (30,35,36). It has generally been accepted that CRF can be improved following a regular aerobic exercise training program (38). Furthermore, with the emerging concept of 'Exercise is Medicine' and using individualised exercise as medicine (15), the time course changes in CRF and, specifically, VO_2max need to be better understood to properly determine exercise doses (i.e., intensity, volume). An understanding of the time course changes in CRF is imperative to properly prescribe and adjust training regimens to enhance adaptations (15).

Much of the literature on time course changes investigates a standardised methodology of exercise prescription using HRR (92), percent VO_2peak (48), and percent VO_2max (93). Recently, there has been evidence that a more individualised exercise prescription using metabolic threshold (i.e. ventilatory thresholds) enhances training adaptations and overall responsiveness to VO_2max (11,12). Therefore, it is important to understand the differences in time course outcomes following a standardised compared to an individualised exercise prescription. To the best of our knowledge, this has yet to be reported in the literature.

Our knowledge on interindividual differences and time course changes has been confounded based on methodological weaknesses of accepted primary and secondary criteria used to determine VO_2max (42,46,47). There is often a discrepancy in how maximal values are reported and it has become common that the highest achieved VO_2 (i.e. VO_2peak) during a maximal test is used to prescribe intensity and evaluate effectiveness of a training intervention, but a peak value may not directly represent a true maximal value of aerobic capacity. For example, Ross and colleagues (48) reported VO_2peak at 4, 8, 16, and 24 weeks to identify the effects of intensity on interindividual responses to CRF. However, since only peak values were reported, we cannot conclusively determine that CRF was maintained, declined, or improved since a true maximal value is not reported. The use of a supramaximal test following a GXT was first reported by Niemala and colleagues (50) and has since evolved into what is commonly considered a 'verification protocol' to confirm a 'true VO_2max' (43,51–54). Indeed, the efficacy of a verification protocol has been confirmed in sedentary men and women (56), middle-aged and older adults (57), sedentary adults with obesity (58), and altitude-residing endurance runners (59). However, to our knowledge, a verification protocol to

confirm VO_2max has not been used to examine time course changes due to steady-state CRF training with exercise intensity determined by ventilatory threshold measurements.

The main purpose of the current investigation was to examine the effects of standardised and individualised exercise prescription on VO_2max confirmed by a verification bout at 4-week increments over a 12-week CRF training intervention. It was hypothesised that an individualised method of exercise intensity prescription would provide a more rapid and potent increase in VO_2max compared to a standardised technique.

5.4 Materials and Methods

The current investigation involved repeated measurements (every fourth week) to understand the differences in time course changes of VO_2max with individualised and standardised exercise prescription. A detailed description of the study and participant flow diagram has been previously published (26). This study was carried out in accordance with and approved by the Auckland University of Technology Ethics Committee (16/264) and the Western State Colorado University Institutional Review Board (HRC2016-01-90R6). All participants provided written informed consent in accordance with the Declaration of Helsinki.

5.4.1 Participants

Sedentary men and women were recruited from a local community-based wellness program and the general community via advertisement at the university, local newspaper, and word-of-mouth. Participants were eligible for inclusion if they were between the ages of 30 and 75, considered low to moderate risk based on the American College of Sports Medicine Standards (25), and participated in less than 30 min of moderate intensity physical activity on 3 days a week or less for the last 3 months. Participants were excluded from the investigation if they reported signs or symptoms suggestive of pulmonary, cardiovascular, or metabolic conditions determined from a standard medical history questionnaire.

5.4.2 Experimental Testing

Outcome variables, other than dietary recall and physical activity questionnaire, were obtained at baseline, week 4, week 8, and week 12 following the completion of the exercise intervention. To the best of our ability, we maintained consistency with day of the week and time of day between repeated testing sessions for each participant with

repeated testing occurring within a day and ±3 hours of the original day of the week and time of day. All participants were instructed to refrain from any strenuous exertion for the 12 hours prior to testing.

5.4.2.1 Resting and Anthropometric Measurements

RHR was analysed following standardised procedures (25). In summary, when participants arrived at the laboratory, they sat for 5 min with sufficient back support, feet on the ground, and arms supported near heart level. Following the 5 min of seated rest, a medical-grade pulse oximeter (Nonin Medical Inc., Plymouth, MN, USA) was used to establish resting heart rate.

Participants were weighed to the nearest 0.1 kg and height measured to the nearest 0.5 cm on a calibrated, medical-grade scale and a stadiometer (Tanita Corporation WB-3000, Tokyo, Japan), respectively.

5.4.2.2 Dietary Analysis

Throughout the 12-week intervention, participants were asked to maintain their regular nutritional habits. At baseline and post-intervention, a 3-day dietary intake recall including two weekdays and one weekend day with the inclusion of types of food/drink, portion sizes, and any specific nutritional information they could provide was solicited. The dietary recall was used to investigate energy intake and the proportion of kilocalories from carbohydrates, protein, and fat.

5.4.2.3 Maximal Exercise Testing with Verification Protocol

Participants completed a GXT using a modified-Balke, pseudo-ramp protocol on a motorised treadmill (Powerjog GX200, Maine, USA). Following a 4-min warm-up with an increasing workload, participants walked or jogged at a self-selected pace with a starting incline of 0% and had a subsequent increase in incline of 1% every min until volitional fatigue was reached. Throughout the GXT, participant HR using a chest strap and radio-telemetric receiver (Polar Electro, Woodbury, NY, USA) and expired air and gas exchange data using a metabolic analyser (Parvo Medics TrueOne 2.0, Salt Lake City, UT, USA) were continuously monitored and recorded. Prior to each exercise test, the metabolic analyser was calibrated per manufacturer guidelines in the instructional manual with a calibration gas mixture (16.00% O_2 and 4.00% CO_2) and room air (20.93% O_2 and 0.003% CO_2). Gas exchange data were averaged for every 15-sec and VO_2max was

determined by averaging the final two 15 sec VO_2 average data during the GXT. The highest achieved HR during the GXT was considered the maximal HR (HR_{max}).

In order to confirm 'true VO_2max,' a verification protocol was performed 20 min following the completion of the GXT. The verification protocol included a 4-min warm-up followed by a volitional test to exhaustion at a constant workload that was set at 5% higher than the last completed stage of the GXT. The workload was determined by taking the final metabolic equivalent (MET) value for the GXT and increasing the speed, incline, or combination of the two to achieve a 5% higher MET value for the verification bout. Gas exchange data and HR were continuously monitored and averaged every 15 sec. VO_2max during the verification protocol was established in the same manner as the GXT, with the average of the final two 15 sec data points for VO_2. A 'true VO_2max' was confirmed if the GXT and verification protocol were within ± 3.0%, based on previously published methods (57,59). If there was a greater than ± 3.0% between the GXT and verification bout, participants repeated the maximal exercise testing with verification protocol within 24-72 hours until 'true VO_2max' was confirmed with the ± 3.0% criterion.

5.4.2.4 Determination of Ventilatory Thresholds

The VT1 and the VT2 were determined based on previously published methods (11,12,26). In summary, ventilatory thresholds were determined based on visual inspection of time plotted against the VE/VO_2 and the ventilatory equivalents of carbon dioxide VE/VCO_2. VT1 was determined to occur when VE/VO_2 increased without a concurrent increase in VE/VCO_2 and VT2 occurred at the point in which both VE/VO_2 and $VEVCO_2$ increased simultaneously. All assessments of VT1 and VT2 were completed by two experienced exercise physiologists. If there were conflicting results, the original assessments were re-evaluated, and a consensus was agreed upon.

5.4.3 Exercise Prescription

Following recruitment and prior to baseline testing, participants were randomised into one of two exercise training groups according to a computer-generated sequence of random numbers that was stratified by sex. Participants exercised on 3 days a week throughout the 12-week study with an incremental increase in HR and duration. Exercise prescription was based on individualised or standardised methods using ventilatory threshold measurements or HRR, respectively. Since exercise testing occurred every 4 weeks, values were updated based on the most current exercise testing session. The week-

to-week exercise prescription for both groups has been previously published in detail (26). In summary, the standardised group started with an exercise intensity between 40-45% of HRR and progressed to 60-65% of HRR. The individualised group used the following criteria to establish training intensity:

- Target HR < VT1 = HR range of 10 bpm below VT1 to the HR at VT1
- Target HR ≥ VT1 to < VT2 = HR range of 15 bpm directly between VT1 and VT2
- Target HR ≥ VT2 = HR range of 10 bpm above VT2

Exercise volume was prescribed based on energy expenditure per kg of body weight a week ($kcal \cdot kg^{-1} \cdot wk^{-1}$) rather than a standard time per exercise session to establish an isocaloric exercise volume across individuals and groups. The total weekly energy expenditure was then divided by 3 to get the daily exercise energy expenditures. The developed energy expenditures were then correlated to the exercise testing gas exchange values to determine a specific duration (i.e. time in min) for each exercise session. A detailed description of the development of energy expenditure criteria has been previously published (26).

5.4.4 Exercise Training

Upon arrival to the lab, participants rested for 5 min in a seated position and subsequently resting HR was recorded. After completion of resting measurements, participants warmed-up at a self-selected pace with increases in workload for 5 minutes until the prescribed exercise intensity was reached. Participants then exercised for their prescribed duration based on the calculated energy expenditure and HR was continuously monitored using a chest strap and radio-telemetric receiver (Polar Electro, Woodbury, NY, USA). At approximately 1/3 and 2/3 the total time, a research assistant ensured the participant was within the correct HR range. Following the designated time, participants completed a 5 min cool-down with decreasing workloads until HR was within 15 bpm of resting values.

5.4.5 Statistical Analysis

All statistical analyses were performed using SPSS Version 22.0 (Chicago, IL, USA). Data are reported as mean ± SD. Based on a power calculation previously published (26) and an assumption of a 20% dropout rate, 20 participants were desired for each group. Baseline group differences were determined based on an independent-samples *t*-test with

$p \leq 0.05$. All measures were analysed by a general linear model two-way ANOVA for repeated measures (baseline, wk 4, wk 8, and wk 12) with intensity as the between subject variable. When appropriate, a subsequent *post hoc* comparison using a Bonferroni correction was completed. A one-way ANOVA was used to understand the changes in time point and VO_2max. The assumption of normality was tested by examining normal plots of the residuals in ANOVA models and regarded as normally distributed if Shapiro-Wilk tests are not significant (27). Effect sizes were calculated using means and pooled SD. The probability of making a type I error was set at $p \leq 0.05$ for all statistical analyses. In order to be included in the data analysis, participants needed an adherence level ≥70% with strict adherence to the targeted day-to-day exercise intensity and duration.

5.5 Results

5.5.1 Participants

A total of 49 participants were recruited and 39 participants completed all testing sessions with an adherence rate of 82.9% ± 5.7% and 86.1% ± 4.7% for the standardised and individualised groups, respectively. The 10 participants not included in the final data were excluded due to unrelated medical issues (1 and 2 participants in the standardised and individualised groups, respectively), self-withdrawal from the study (3 participants in the standardised group) or did not achieve ≥70% adherence (1 and 4 participants in the standardised and individualised groups, respectively). Baseline and every fourth week physical and physiological characteristics are shown in Table 5.1. There was no statistical significance between pre- and post-intervention dietary intake as show in Table 5.2.

Intervention fidelity for both groups in terms of intensity and exercise duration was very high, as shown in Table 5.3. In only a single instance (standardised week 3), the actual mean time (min) completed was 3 min less than the target range for that week.

5.5.2 Time Course Changes

There was an overall change in VO_2max from baseline to week 12 of 1.7±1.9 $ml \cdot kg^{-1} \cdot min^{-1}$ and 3.4±1.5 $ml \cdot kg^{-1} \cdot min^{-1}$ for the standardised and individualised groups, respectively. A two-way repeated measures ANOVA revealed a main effect for group ($F=7.866$; $p<0.05$; Partial Eta Squared=0.175). There was a significant interaction between group and time point ($F=3.555$; $p<0.05$; Partial Eta Squared=0.88). The one-way ANOVA showed a main effect for time point on VO_2max for the standardised group ($F=8.758$; $p<0.05$; Partial Eta Squared=0.316) and individualised group ($F=29.559$;

$p<0.05$; Partial Eta Squared=0.622). *Post hoc* analysis revealed that VO_2max was significantly increased during week 8 and 12 compared to baseline for both groups and differed significantly from week 8 to week 12 for the individualised group (Figure 5.1).

Table 5.1 Physical and Physiological characteristics at baseline, week 4, week 8, and 12-weeks for standardised individualised groups

Parameter	Standardised (n=20; women=16, men=4)				Individualised (n=19; women=14, men=5)			
	Baseline	**Week 4**	**Week 8**	**Week 12**	**Baseline**	**Week 4**	**Week 8**	**Week 12**
Age (yr)	51.2 ± 12.5	-	-	-	44.9 ± 11.4	-	-	-
Height (cm)	168.3 ± 9.5	-	-	-	172.1 ± 7.1	-	-	-
Weight (kg)	83.9 ± 20.7	84.0 ± 20.3	83.9 ± 20.4	83.8 ± 20.3	80.6 ± 16.2	80.7 ± 15.8	80.2 ± 15.2	79.9 ± 15.2
BMI	29.5 ± 5.5	29.5 ± 5.3	29.5 ± 5.4	29.4 ± 5.3	27.1 ± 4.2	26.9 ± 4.0	26.9 ± 3.8	26.8 ± 3.8
Resting HR ($b \cdot min^{-1}$)	70.0 ± 8.8	69.9 ± 11.2	68.1 ± 8.4	68.2 ± 8.0	68.8 ± 9.7	72.4 ± 8.7	69.3 ± 9.4	68.1 ± 11.4
Maximal HR ($b \cdot min^{-1}$)	165.2 ± 16.1	164.5 ± 16.2	166.3 ± 16.3	164.9 ± 15.1	170.1 ± 18.4	171.7 ± 16.5	170.7 ± 14.7	169.2 ± 14.4
VO_2max ($L \cdot min^{-1}$)	2.0 ± 0.6	2.1 ± 0.6	2.2 ± 0.6†‡	2.2 ± 0.6‡	2.4 ± 0.8	2.5 ± 0.8	2.5 ± 0.8‡	2.6 ± 0.8†‡
% Diff in VO_2max (GXT and Verification)	-0.2 ± 1.8	0.0 ± 1.9	0.6 ± 1.7	-0.4 ± 1.8	0.2 ± 1.7	0.6 ± 2.1	0.7 ± 1.8	-0.7 ± 1.7
% Δ in Abs VO_2max	-	2.0 ± 6.7	6.9 ± 8.4	7.5 ± 7.7	-	3.9 ± 8.0	6.1 ± 6.5	10.6 ± 5.3

Values are mean ± SD.BMI, basal metabolic rate; GXT, graded exercise test; HR, heart rate; Δ, change; VO_2max, maximal oxygen uptake.

†Significantly difference from previous time point; ‡significantly different from baseline

Table 5.2 Alterations in dietary intake in response to 12 weeks of standardised or individualised CRF training in sedentary adults

Parameter	Baseline	Week 12
Standardised		
Calorie intake (kcal)	1520 ± 563.2	1518 ± 500
Carbohydrate (g)	160 ± 60.5	158 ± 63
Lipid (g)	61 ± 31.2	62 ± 26
Protein (g)	64 ± 16.4	63 ± 22
Carbohydrate (%)	41 ± 6.9	40 ± 7
Lipid (%)	35 ± 9.2	37 ± 8
Protein (%)	18 ± 6.3	17 ± 5
Individualised		
Calorie intake (kcal)	1539 ± 493	1555 ± 403
Carbohydrate (g)	168 ± 68	164 ± 57
Lipid (g)	68 ± 23	67 ± 13
Protein (g)	73 ± 36	64 ± 25
Carbohydrate (%)	43 ± 8	41 ± 6
Lipid (%)	40 ± 7	40 ± 8
Protein (%)	19 ± 10	16 ± 3

Values are mean ± SD

Table 5.3 Exercise prescription and progression for standardised and individualised exercise prescription based on percentage of heart rate reserve and ventilatory thresholds, respectively

	Standardised				Individualised			
Week	**Target HR**	**Actual HR**	**Target Min**	**Actual Min**	**Target HR**	**Actual HR**	**Target Min**	**Actual Min**
1	108 ± 10 to 113 ± 11	113 ± 12	27 ± 6 to 32 ± 9	32 ± 9	105 ± 14 to 115 ± 14	114 ± 14	26 ± 6 to 31 ± 9	31 ± 8
2	108 ± 10 to 113 ± 11	113 ± 11	41 ± 10 to 48 ± 13	46 ± 11	105 ± 14 to 115 ± 14	114 ± 14	39 ± 10 to 47 ± 14	44 ± 9
3	108 ± 10 to 113 ± 11	114 ± 12	54 ± 13 to 64 ± 17	51 ± 10	105 ± 14 to 115 ± 14	114 ± 13	52 ± 13 to 63 ± 18	54 ± 9
4	118 ± 11 to 123 ± 11	120 ± 12	45 ± 8 to 49 ± 8	47 ± 8	122 ± 15 to 136 ± 15	131 ± 15	38 ± 8 to 48 ± 13	42 ± 9
5	124 ± 11 to 128 ± 11	126 ± 12	42 ± 8 to 47 ± 8	45 ± 7	122 ± 15 to 136 ± 15	134 ± 17	38 ± 8 to 48 ± 13	43 ± 9
6	124 ± 11 to 128 ± 11	127 ± 12	42 ± 8 to 47 ± 8	45 ± 7	122 ± 15 to 136 ± 15	135 ± 16	38 ± 8 to 48 ± 13	44 ± 9
7	124 ± 11 to 128 ± 11	127 ± 11	48 ± 9 to 53 ± 9	49 ± 7	122 ± 15 to 136 ± 15	133 ± 17	41 ± 8 to 52 ± 11	49 ± 9
8	124 ± 11 to 128 ± 11	127 ± 12	52 ± 10 to 58 ± 10	53 ± 8	125 ± 14 to 139 ± 15	134 ± 16	45 ± 8 to 57 ± 11	50 ± 9
9	129 ± 11 to 134 ± 12	131 ± 12	48 ± 8 to 53 ± 9	51 ± 8	144 ± 15 to 154 ± 15	149 ± 17	37 ± 9 to 42 ± 10	40 ± 10
10	129 ± 11 to 134 ± 12	132 ± 12	48 ± 8 to 53 ± 9	50 ± 7	144 ± 15 to 154 ± 15	148 ± 17	37 ± 9 to 42 ± 10	40 ± 10
11	129 ± 11 to 134 ± 12	133 ± 11	53 ± 9 to 59 ± 9	53 ± 6	144 ± 15 to 154 ± 15	148 ± 17	41 ± 10 to 47 ± 11	44 ± 10
12	129 ± 11 to 134 ± 12	133 ± 13	53 ± 9 to 59 ± 9	53 ± 6	144 ± 15 to 154 ± 15	147 ± 17	41 ± 10 to 47 ± 11	45 ± 10

Values are mean ± SD. HR, heart rate; VT1, first ventilatory threshold; VT2, second ventilatory threshold.

Mean ± SD HR values represent the average of all three training days within each week with averages calculated based on the recorded measurements obtained at 1/3 and 2/3 time points during each exercise session.

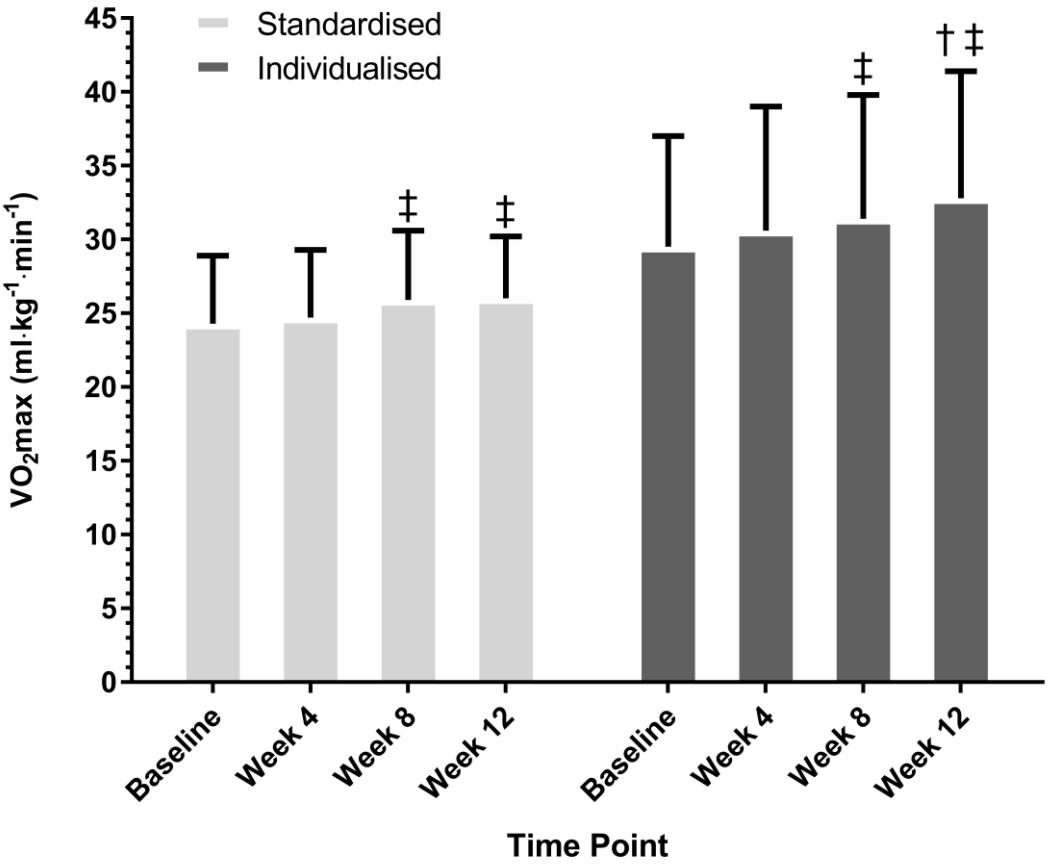

Figure 5.1 Group relative VO_2max at baseline, week 4, week 8, and week 12 for standardised and individualised exercise prescription. †Significantly different from previous time point; ‡significantly different from baseline

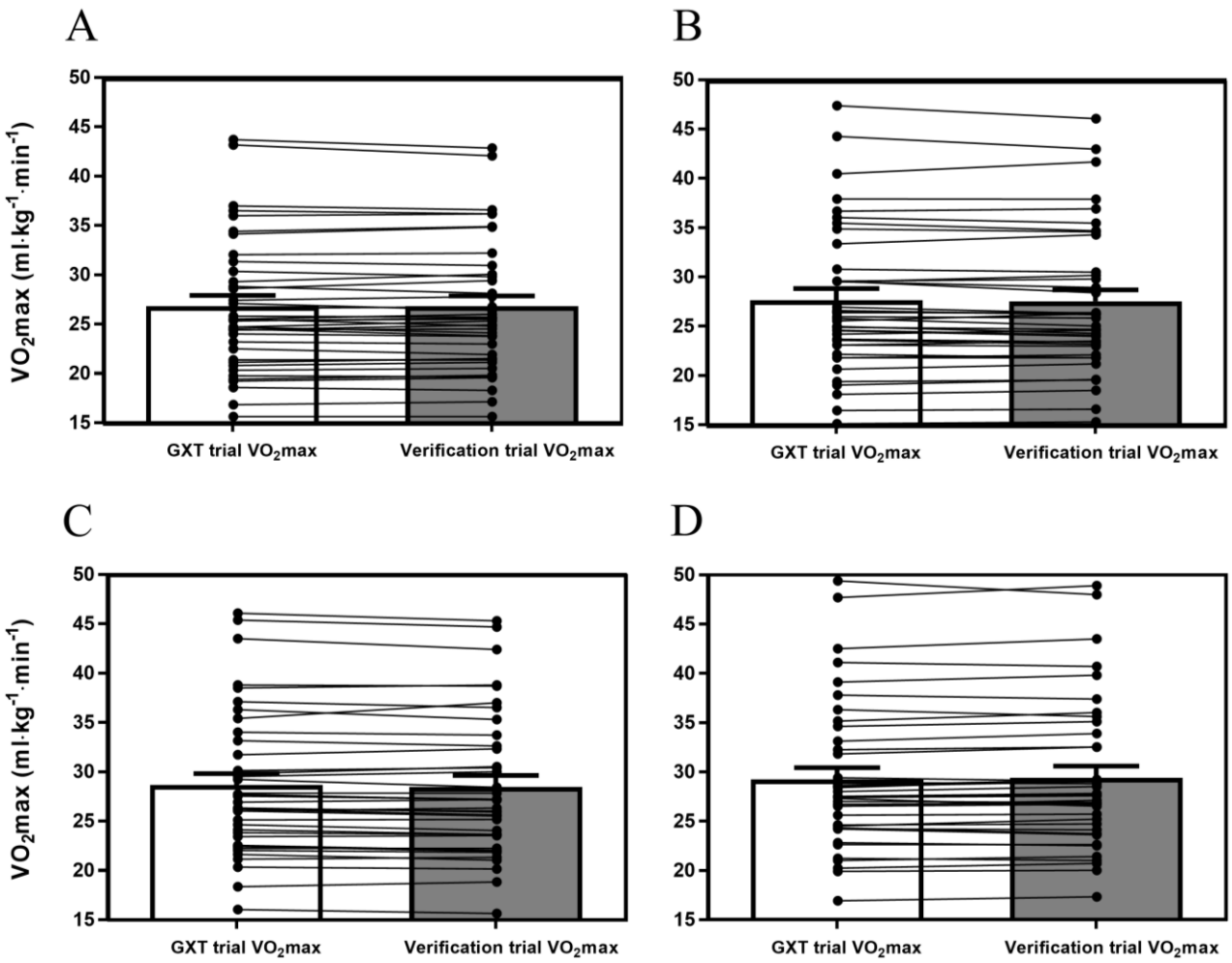

Figure 5.2 Comparison of mean GXT trial VO_2max and verification trial VO_2max and individual (39 participants) VO_2max data represented by the line graphs at baseline (A), week 4 (B), week 8 (C), and week 12 (D)

5.5.3 GXT and Verification Testing

Only 4 participants (2 participants at baseline and 2 participants at week 4) had greater than a ±3.0% difference between the GXT and verification bout, but 3 of these tests were rescheduled, subsequently the verification protocol was confirmed. On one occasion during the week 4 testing, one participant had a 4.0% difference between GXT and verification and a subsequent testing session to confirm VO_2max was not completed. However, VO_2max was confirmed for all of the other testing sessions. The individual differences and group mean for VO_2max in the GXT and verification bout can be seen in Figure 5.2.

5.6 Discussion

This study sought to compare the VO_2max time course changes at 4 week increments between a standardised and individualised 12-week CRF training program with exercise intensity established based on %HRR or ventilatory thresholds. The main finding from the present study was that, although not statistically significant, we provide preliminary data demonstrating an individualised approach to method of exercise intensity prescription elicits more rapid and potent improvement in VO_2max relative to a standardised paradigm. Indeed, at week 4, there was nearly a two-fold greater improvement for the individualised group compared to the standardised group. Furthermore, even though both training approaches elicited a statistically significant improvement in VO_2max at week 12 compared to baseline, there was a 41% higher improvement in the individualised group compared to the standardised group based on mean percent changes. Moreover, these changes in CRF are due to 'true' adaptation based on the use of a verification bout to confirm that VO_2max was achieved and results were not reported as simply peak values. Overall, these novel findings add to the growing body of evidence (11,12,15) that an individualised exercise prescription for steady state aerobic exercise enhances training adaptations.

Our findings that VO_2max increased 1.7±1.9 $ml \cdot kg^{-1} \cdot min^{-1}$ and 3.4±1.5 $ml \cdot kg^{-1} \cdot min^{-1}$ for the standardised and individualised groups, respectively, following the 12 week intervention were consistent with previous findings using similar exercise prescription protocols for 12 weeks (11) and 13 weeks (12). However, results from this study are the first to demonstrate the difference in time course changes between a standardised and individualised exercise prescription. Based on our findings, it was shown that after 8 weeks, there is a statistically significant improvement in VO_2max compared to baseline.

These results are consistent with previous findings (48,91). Following the first 9 weeks of training at either a high (80-85% VO_2max) or low intensity (45% VO_2max) during an 18 week training intervention, 74% and 90% of the overall changes were demonstrated in the high and low intensity respectively (91). When comparing these results with those seen in the current 12-week intervention, 90% of the overall change in VO_2max was seen by week 8 for the standardised group. However, for the individualised group, only 55% of the overall change in VO_2max at week 8 was seen. This is lower than previously reported for the same time point (i.e. week 8) and indicating there was a greater magnitude of change from week 8 to 12 in the current investigation compared to week 8 to 18 previously (91). This is also noteworthy since the change in VO_2max between week 8 and 12 for the individualised group was the only time in which there was a statistically significant change compared to the preceding time points.

The current study was the first, to our knowledge to use a verification protocol to confirm VO_2max when investigating time course changes when comparing exercise intensity prescription using HRR or ventilatory thresholds. Ensuring that a maximal aerobic value is achieved when investigating any changes due to modifying or differing exercise doses is imperative to understand true changes occurring from the intervention and not owing to how aerobic capacity is measured. Historically, a plateau in VO_2max (i.e. $\leq$ 150 $ml \cdot min^{-1}$) at the ending stages of a GXT has been the primary criterion to determine 'true VO_2max' (41). However, there has been inconsistency regarding the value for a plateau with the use of $\leq$ 150 $ml \cdot min^{-1}$ to $\leq$ 50 $ml \cdot min^{-1}$ (42) and there has been an incidence in plateau ranging from 0% (43) to 100% (44). Therefore, the use of secondary criteria were proposed (45), but have since been highly criticised (46,47). Based on these considerations, VO_2peak rather than VO_2max has been recorded as a common aerobic outcome measure, especially when reporting functional capacity, fitness changes, and used to prescribe exercise interventions (4,6,7,48). Unfortunately, VO_2peak does not directly indicate that aerobic adaptations have occurred due to the lack of sensitivity of this measurement (47). Recently, while there is still debate on the overall topic (55), the use of a verification protocol to confirm VO_2max has been identified as a practical and sensitive measure to ensure that a 'true' maximal aerobic value has been achieved (42). Furthermore, participants tend to exhibit greater maximal effort following a training intervention due to expecting improvements (49). Indeed, it could be noted that a change in VO_2peak could be due to a greater increase in effort if there is minimal consideration to the testing methodology. With the use of a verification protocol, this overestimation of

training adaptations is mitigated by ensuring all measurements are a 'true VO_2max' and representative of training adaptations (47,57).

The relative percent method (i.e. using percentages of HR_{max}, HRR, VO_2max, and VO_2R) has been a common practice for prescribing exercise intensity. However, these values may not be sensitive enough to provide a workload that elicits the desired metabolic response (8,20). For example, participants exercising at a workload at 75% of VO_2max was 86-118% of the individual lactate threshold (22). Similarly, 22% and 78% of participants exceeded the individual lactate threshold at 60% and 75% of VO_2max, respectively, and some participants were above and others below lactate threshold at a workload associated with 70±1% of VO_2R (21). Furthermore, Azevedo et al. (24) found the ventilatory threshold occurred at 78±7% HR_{max} and 70±10% HRR. Based on these findings, it can be implied that workloads established with the use of the relative percent method increases variability in the metabolic response to exercise. Based on our current findings, we found that when steady state aerobic exercise is prescribed on an individual basis using VT1 and VT2 as points to base exercise intensity and progression, there was a superior interaction between VO_2max and time point compared to the standardised group. We believe this is due to taking into consideration individual metabolic characteristics with the exercise prescription and the relative percent intensity providing variation in metabolic demands due to the exercise intensity prescription (19).

From a practical standpoint, it could be suggested that either the use of an isocaloric dose of steady state aerobic exercise using HRR or threshold measures can increase VO_2max following 12 weeks of CRF training. However, it should be noted the individualised training group with the use of the ventilatory thresholds provided more rapid and greater change in VO_2max, hence might underpin its potential relatively greater efficacy for prescription purposes by taking into account individual metabolic characteristics that are not considered when using relative percent methods. Therefore, it is recommended that steady state aerobic exercise prescription for sedentary individuals should be completed based on threshold measurements to take into consideration individual metabolic characteristics and enhance training adaptations. Furthermore, based on our data, if aerobic training adaptations are not observed after 8 weeks of steady-state aerobic training, modifying the exercise prescription intensity or method of intensity prescription (i.e. changing from a relative percent method to an individualised method) should be considered to achieve the desired results.

5.6.1 Limitations

A potential risk for selection bias exists in the present study as the principle investigator was aware of which treatment group to which participants were allocated and also performed all GXT and verification protocol testing. However, the application of the verification protocol likely minimised any potential selection bias due to its robustness for verifying 'true VO_2max.' Even though the participants included in the study represent a standard exercise clinic demographic, there was a large age range and, therefore, not a homogenous group to study. There may be heterogeneity in results due to age alone. Furthermore, men were underrepresented, accounting for only 23% of the participants. At baseline, there was a significant difference in VO_2max values with the individualised group having higher values. However, while not statistically significant, based on the results of the study, the individualised group improved greater than the standardised group when, in theory, they had a lower capacity to improve. Lastly, the issue of training responsiveness is nuanced area of study with multiple outcomes to assess, but the current investigation only identified CRF (i.e. VO_2max) changes. Future studies should take into consideration these limitations to further address the time course changes in exercise intensity prescription methods. Similarly, further research is warranted to investigate a more comprehensive approach to understanding time course changes with the development of a composite score to explore all training responsiveness factors (i.e. aerobic and cardiometabolic measurements).

5.7 Conclusion

In conclusion, an individualised exercise prescription based on metabolic characteristics elicits a more rapid and effective improvement in CRF. On a practical level, and based on our data, exercise specialists may consider a re-evaluation of the CRF training program for previously sedentary individuals if improvements in VO_2max are not observed after 8 weeks of training. Lastly, for the first time, we have demonstrated that the verification procedure can be successfully employed to confirm 'true' changes in VO_2max following exercise training comparing exercise intensity prescription differences using HRR and ventilatory threshold methods.

Chapter 6 - Changes in Metabolic Syndrome Severity Following Individualised Versus Standardised Exercise Prescription: A Feasibility Study

6.1 Prelude

This chapter comprises the following paper accepted for publication: Weatherwax, R.M., Ramos, J.S., Harris, N., Kilding, A., Dalleck, L.C. (2018). Changes in Metabolic Syndrome Severity Following Individualized and Standardized Exercise Prescription: A Feasibility Study. *International Journal of Environmental Research and Public Health*, 15(11).

As outlined in Chapter 2, it is understood that training responsiveness is comprehensive and complex. For example, a participant can be classified as a responder for one variable but may not respond for others. With this in mind, the use of a MetS z-score was incorporated to determine if there are differences in changes of MetS severity following a standardised and individualised exercise intensity prescription. Furthermore, much of the literature only focuses on VO_2max responsiveness, therefore, this chapter highlights important changes that occur in cardiometabolic factors.

6.2 Abstract

This study sought to investigate the efficacy of standardised versus individualised exercise intensity prescription on MetS severity following a 12-week exercise intervention. A total of 38 experimental participants (47.8±12.2 yr, 170.7±8.0 cm, 82.6±18.7 kg, 26.9±6.7 $ml \cdot kg^{-1} \cdot min^{-1}$) were randomised to one of two exercise interventions (exercise intensity prescribed using heart rate reserve or ventilatory threshold). Following the 12-week intervention, MetS z-score was significantly improved for the standardised (-2.0±3.1 to -2.8±2.8 [p=0.01]) and individualised (-3.3±2.3 to -3.9±2.2 [p=0.04]) groups. When separating participants based on prevalence of MetS at baseline and MetS z-score responsiveness, there were 6 and 3 participants in the standardised and individualised groups, respectively, with 3+ MetS risk factors. Of the 6 participants in the standardised group, 83% (5/6) of the participants were considered responders whereas 100% (3/3) of the individualised participants were responders. Furthermore, only 17% (1/6) of the participants with MetS at baseline in the standardised

group no longer had symptoms of MetS following the intervention. In the individualised group, 67% (2/3) of participants with baseline MetS were not considered to have MetS at week 12. These findings suggest that an individualised approach to the exercise intensity prescription may ameliorate the severity of MetS.

6.3 Introduction

Metabolic syndrome (MetS) is the simultaneous occurrence of three or more cardiovascular disease risk factors including central obesity, hyperglycaemia, hypertriglyceridemia, low HDL, and hypertension, which elevates the risk of cardiovascular events (68). Reducing the severity of this syndrome may therefore serve as a target to improve global health. Indeed, an exercise-induced increase in cardiorespiratory fitness has been well established as a protective factor against individual risk factors constituting the MetS (71), with high fit MetS individuals reported to have lower risk of cardiovascular mortality relative to less fit counterparts (72). However, the results of previous studies have shown considerable individual variability in responses to a specific dose of standardised exercise, including the so-termed 'responders', 'non-responders', and, in some cases, 'adverse responders' (13,110). This variability in response to exercise has been purported among others (110,111), to be attributed to the lack of a personalised approach to the exercise prescription (14).

It is believed that a more individualised approach to exercise prescription may better optimise training efficacy and thus limit training unresponsiveness (14). Specifically, it has been reported that when exercise intensity is titrated according to a threshold-based model (i.e. ventilatory threshold), 100% of individuals showed favourable change in $\dot{V}O_2$max compared to only 41.7% when the exercise intensity was 'standardised' or prescribed according to a relative percent method (i.e. %HRR) (11). It has been suggested that the variability in response to a standardised exercise prescription may be due to the incapacity of this method to account for individual metabolic differences (20). Furthermore, it should be noted that investigations thus far have only concentrated on the impact of different 'short-term' standardised exercise doses on the inter-individual $\dot{V}O_2$max (110) and individual cardiometabolic responses (13). Indeed, the specific inter-individual 'MetS severity' changes in response to 'individualised training' have yet to be explored.

Moreover, in conjunction with the difficulty in titrating available intervention dosages to optimally treat or manage MetS, there is also a dilemma in determining the change in MetS severity to better account for the clinical significance of a particular intervention. The established categorical criteria of MetS proposed by different organizations (i.e. IDF) (68) are often criticised due their incapacity to account for improvement in a certain MetS component if the magnitude of change is not large enough to deviate from a qualifying category. For example, a systolic blood pressure reduction from 142 to 131 mmHg following an intervention would still classify as a MetS risk factor according to the IDF criteria (SBP≥130 mmHg), regardless of achieving a clinically significant reduction (75). For this reason, a continuous risk score assessment known as the MetS z-score was introduced to better acknowledge MetS risk factor changes and thus MetS severity, following clinical interventions (76). Interestingly, similar to previous findings (112), Earnest et al. (76) reported highly fit individuals to have lower MetS severity, depicted as reduced MetS z-score relative to less fit counterparts.

The aim of this study was to investigate the efficacy of standardised versus individualised exercise prescription on MetS severity over a 12-week program. We hypothesised that individualised exercise intensity prescription would induce a greater proportion of individuals reducing the severity of MetS more than the standardised intervention.

6.4 Materials and Methods

A total of 49 sedentary men and women interested in starting an exercise intervention and improving their health and well-being were recruited as experimental participants from a community wellness program and surrounding community through advertisement at the local university, newspaper, and word-of-mouth. In order to be considered for the investigation, the participants needed the following inclusion criteria: low to moderate risk based on the American College of Sports Medicine Standards (25), participation in less than 30 min of moderate intensity physical activity on 3 days a week or less, and between the ages of 30 and 75 years. Participants were excluded from the investigation if they showed signs or symptoms suggestive of pulmonary, cardiovascular, or metabolic conditions determined from a standard medical history questionnaire and intake interview. Similar to previous research (28,29), a convenience sample (20 control participants) separate from the experimental participants was used to take into consideration the moral and ethical considerations of withholding a known physiological and psychological benefit of an exercise intervention. Therefore, control participants

were recruited by finding individuals that were interested in the various health measurements from the baseline and 12-week laboratory testing and met the same inclusionary criteria, but not interested in increasing physical activity. Control participants were encouraged to maintain their current dietary intake and physical activity habits following the baseline laboratory testing.

Written informed consent was obtained from all participants prior to initiation of the study. The current investigation is a secondary analysis of a larger randomised control trial. A description of the study methodology and rationale has been previously published in detail (26). The Auckland University of Technology Ethics Committee (16/264) and the Western State Colorado University Institutional Review Board (HRC2016-01-90R6) have approved the methodology for this study.

6.4.1 Experimental Testing

At baseline and week 12, all primary outcome variables were obtained. In order to mitigate possible changes due to the time of day testing took place, baseline and post-program testing occurred on the same day of the week and time of day, to the best of our ability. Participants were instructed to refrain from consumption of food or drink, other than water, and partaking in strenuous exertion for the 12 hours leading up to the laboratory testing. All post-program testing took place within approximately 2-3 days of the last exercise training session.

6.4.2 Analysis of Dietary and Physical Activity Habits

Participants verbally agreed to not change their regular nutritional intake habits and at baseline and post-program they completed a 3-day dietary recall (2 weekdays and 1 weekend day). Either prior to the baseline testing when initial contact and interest in the study was provided or at the first baseline testing appointment, participants were provided a nutritional log with columns identifying day of the week/time eaten, a prompt to provide as much detail about the food or beverage as possible (type, brand, restaurant eaten at, etc.), the amount eaten, how the food was prepared, and whether they added fat, salt, or sugar to the food or drink. Participants were encouraged to complete the dietary recall throughout the day as they ate and drank food to increase the accuracy of the information received. If they were actively logging food with all of the desired information, the participant was allowed time during the initial baseline assessment to record the last two weekdays and the closest weekend day to the food log. In order to establish energy intake,

percentages of macronutrients and grams of macronutrients, participants recorded as much detail about the food and drink consumed on each of the 3 days.

Also at baseline and post-intervention, participants completed the IPAQ to identify physical activity levels (MET-min·wk^{-1}) and sedentary behaviour per day (i.e. time spent sitting). The researcher completing the baseline testing went through each of the prompts to explain what was being asked and helped the participants identify the time and associated intensity level of the activity. In some instances, further discussion was needed with participants to identify whether sedentary behaviour inclusionary criteria at baseline were met for experimental participants at baseline and post-program for control participants.

6.4.3 Anthropometric and Resting Measurements

Participants were weighed to the nearest 0.1 kg on a medical grade scale and measured height to the nearest 0.5 cm using a stadiometer (Tanita Corporation WB-3000, Tokyo, Japan). Waist circumference was measured at the narrowest horizontal circumference above the umbilicus and below the xiphoid process to the nearest 0.5 cm (25). Resting HR followed standardised procedures (25). Participants sat with back support for 5 min with their feet on the ground and arms supported near heart level. A medical-grade pulse oximeter (Nonin Medical Inc., Plymouth, MN, USA) was used to establish resting HR following the 5 min of rest. Following assessment of resting HR and while still in the same seated position, blood pressure was assessed using a standard stethoscope and sphygmomanometer (American Diagnostic Corporation Diagnostic 700 Series, Hauppauge, NY, USA) to determine left arm BP. The average of two consecutive resting measurements separated by 1 min were used.

6.4.4 Blood Profile Measurements

The Cholestech LDX system (Alere Inc., Waltham, MA, USA), which has been shown to have excellent reproducibility (95,96), was used to analyse all fasting lipid and blood glucose measurements. All analyses were performed based on manufacturer guidelines. In summary, an optics check was completed prior to all blood analyses. Participants washed their hands thoroughly with soap and rinsed with warm water and the skin was subsequently wiped with an alcohol swab and allowed to dry. On the distal end of the third digit of the right hand, a lancet was used to puncture the finger and the free-flowing blood sample was collected using a 40 µl capillary tube without milking the finger. The blood sample was then transferred from the capillary tube into the commercially available

test cassette for analysis. Measurements of TC, HDL, TG, and BG were obtained. Blood samples were disposed of based on standard biohazard procedures.

6.4.5 Maximal Exercise Test and Verification Protocol

A GXT using a modified-Balke pseudo-ramp protocol on a motorised treadmill (Powerjog GX200, Maine, USA) was completed to determine VO_2max and threshold measurements using a participant chosen self-selected pace. Following a 4-min warm-up with the workload gradually increasing to the starting self-selected speed and an incline of 0%, the incline was then increased by 1% each min until volitional fatigue was reached. During the GXT, HR was monitored using a chest strap and radio-telemetric device (Polar Electro, Woodbury, NT, USA) and expired air and gas exchange data using a metabolic analyser (Parvo Medics TrueOne 2.0, Salt Lake City, UT, USA) were continuously recorded and monitored. Before the GXT, the metabolic analyser was calibrated with a calibration gas mixture (16.00% O_2 and 4.00% CO_2) and room air (20.93% O_2 and 0.03% CO_2) in accordance to manufacturer guidelines and instructional manual. Following the GXT, the last 15 sec of gas analysis data were averaged and considered to be the final data point. Subsequently, the 15 sec gas exchange data occurring before the final data point were also averaged. The mean of the two processed data points represented VO_2max for the GXT. The highest HR reached during the GXT was considered to be the maximal HR and HRR was calculated by taking the difference between maximal and resting HR.

A supramaximal verification protocol was used to confirm a 'true' VO_2max was achieved using methods previously published (57,59). In summary, 20 min following the completion of the GXT, participants were asked to complete a 4 min warm-up followed by a volitional test to fatigue at a constant workload that was 5% higher than the last completed stage of the GXT. During the verification protocol, HR and gas exchange data were monitored and VO_2max was determined based on the same protocols as the GXT. A 'true' VO_2max was confirmed if the two calculated VO_2max values from the GXT and verification protocol were within ±3.0%, the measurement error of the metabolic analyser. If a participant had a difference in VO_2max values > 3.0%, they were asked to repeat the GXT and verification bout protocol within 24-72 hours until a difference less than ±3.0% was achieved to confirm 'true' VO_2max reached.

The determination of VT1 and VT2 were performed based on previously published methods (11,12,26). In summary, a visual inspection of the gas exchange data from the GXT were analysed to determine VT1 and VT2 using time, VE/VO_2 and VE/VCO_2. VT1

occurred when VE/VO_2 increased without a concurrent increase in VE/VCO_2 whereas VT2 was the point that both VE/VO_2 and VE/VCO_2 simultaneously increased.

6.4.6 Exercise Prescription and Training

Prior to baseline testing, participants were randomised into one of the two experimental groups according to a computer-generated sequence of random numbers stratified by sex. Participants exercised on 3 days a week for 12 weeks following detailed descriptions published elsewhere (26). Exercise intensity was established based on percentages of HRR or based on the heart rates at VT1 and VT2 occurring during the GXT. Exercise volume was equated for each group based on energy expenditure per kg of body weight per week ($kcal \cdot kg^{-1} \cdot wk^{-1}$) to ensure an isocaloric volume among groups. The prescribed HR was correlated with a VO_2 from the GXT to establish a low and high exercise volume and converted to a min range per exercise session.

During the exercise intervention, participants rested in a seated position for 5 minutes when they arrived at the laboratory. Subsequently, resting heart rate and blood pressure were recorded following methods outlined before in section 6.4.3 to ensure drastic changes in these measures were not noted. Following the resting measurements, participants warmed-up at a self-selected pace with increase in the exercise workload for 5 minutes at which point the prescribed exercise intensity was reached. Participants then exercised for the prescribed duration (i.e. time) based on the calculated energy expenditure derived from values obtained during the GXT with continuous monitoring of heart rate using a chest strap and radio-telemetric receiver (Polar Electro, Woodbury, NY, USA). Furthermore, exercise heart rate was checked by a research assistant at approximately 1/3 and 2/3 the total time to ensure the intensity prescription was adhered. At the end of the exercise session, participants completed a 5 min cool-down with decreasing workloads until heart rate was within 15 bpm of resting values.

6.4.7 Establishment of Metabolic Syndrome z-Score

A continuous risk score assessment scale (MetS z-score) has been previously used to identify changes in MetS risk factors following an exercise intervention (113). The MetS severity was presented as sex-specific MetS z-score, previously validated to evaluate cardiometabolic risk in middle-aged men and women (114). MetS z-score was calculated using the following equations (77) where FG = fasting glucose; HDL = high-density lipoprotein cholesterol; MAP = mean arterial pressure; TG = triglycerides; and WC = waist circumference:

$$Men = [(40 - HDL) \div 8.9] + [(TG - 150 \div 69) + [(FG - 100) \div 17.8] + [(WC - 102) \div 11.5] + [(MAP - 100) \div 10.1]$$

$$Women = [(50 - HDL) \div 14.5] + [(TG - 150 \div 69) + [(FG - 100) \div 17.8] + [(WC - 88) \div 12.5] + [(MAP - 100) \div 10.1]$$

6.4.8 Establishment of Metabolic Syndrome Responsiveness Criteria

A coefficient of variability for the MetS z-score was developed as a sub-group from the current investigation. At baseline, 15 participants completed the two baseline testing sessions, as described previously, no sooner than 24 hours and no more than 7 days later while maintaining their current lifestyle. The MetS z-score was determined for both testing sessions and were subsequently used to determine a CV based on previously published protocols (113). In order for a participant to be considered a responder to improvements in MetS variables, they would need to have a MetS z-score change greater than the established MetS z-score CV in a favourable direction.

6.4.9 Statistical Analysis

All statistical analyses were performed using SPSS Version 25.0 (Chicago, IL, USA). Data were reported as mean ± SD. One-way analysis of variance (ANOVA) testing was used to compare groups at baseline and Tukey *post hoc* test when appropriate. The assumption of normality was confirmed by examination of normal plots of the residuals in ANOVA models and Shapiro-Wilk tests (27). A two-way ANCOVA was used to analyse between-group difference of the change in main dependent variables (i.e. SBP, DBP, MAP, HDL, TG, fasting BG, and WC) from baseline to 12 weeks, with the week 12 values as the dependent variables and the baseline value as a covariate. A subsequent *post hoc* analysis with a comparison of main effects and a Bonferroni adjustment was completed when appropriate. Analysis of within-group differences in continuous variables was completed using paired sample t-tests.

Delta values (Δ) for MetS z-score were expressed as 12-week value minus baseline value to establish the change (Δ) in Mets z-score. The calculated laboratory-specific biological variability value (0.6) was compared to the Δ in MetS to determine MetS responsiveness. Subsequently, participants were categorised as '1' = responder ($\Delta > 0.6$) or '0' = non-responder ($\Delta \leq 0.6$). Chi-square (χ^2) tests were used to analyse the incidence of responders and non-responders for MetS z-score following the intervention separated by

experimental group (standardised and individualised) and a Cramer's V test to determine effect size.

6.5 Results

A total of 38 experimental participants who completed all testing sessions and had an exercise adherence of 82.9% ± 5.9% and 86.1% ± 4.7% for the standardised and individualised groups, respectively, were analysed. Eleven experimental participants were not included in the final data analyses due to unrelated medical issues (n = 3), falling below the 70% adherence (n = 4), self-withdrawal (n = 3), and insufficient blood profile data (n = 1). There was considerable attrition for the control group with only 8 of the 20 recruited participants completing all exercise testing sessions due to increased physical activity and exercise habits following the baseline testing session. The reasons for not including the 12 participants in the control group in the final data analyses were due to unrelated medical issues (n = 2) and self-withdrawal (n = 10).

Physical and physiological characteristics at baseline and post-program (12 week) are presented in Table 6.1. At baseline, there was a significant difference in SBP (mmHg) [$F(2,43) = 3.85$, $p = 0.29$] and VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) [$F(2,44) = 3.64$, $p = .035$]. *Post hoc* analysis indicated the mean SBP for the individualised group (119.7±7.2 mmHg) was significantly lower than the standardised group (126.7±9.9 mmHg) and VO_2max for the standardised group (24.4±4.7 $ml \cdot kg^{-1} \cdot min^{-1}$) was significantly lower than the individualised group (29.5±7.5 $ml \cdot kg^{-1} \cdot min^{-1}$). However, there were no other significant between-group differences at baseline across experimental and control groups for all other variables. Adherence to the prescribed exercise intensity and duration for both experimental groups was excellent. In only one instance (week 3 for exercise duration in the standardised group) did the actual exercise performed differ from what was prescribed for that week.

Table 6.1 Physical and physiological characteristics and dietary intake at baseline and 12-weeks for standardised, individualised, and control groups

Parameter	Control (n=8; women=6, men=2)		Standardised (n=19; women=15, men=4)		Individualised (n=19; women=14, men=5)	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Age (yr)	45.6 ± 7.9	-	51.2 ± 12.5	-	44.9 ± 11.4	-
Height (cm)	171.7 ± 6.4	-	169.2 ± 8.8	-	172.1 ± 7.1	-
Weight (kg)	75.3 ± 15.1	75.1 ± 14.6	84.5 ± 21.1	84.4 ± 20.7	80.6 ± 16.2	79.9 ± 15.2
BMI	25.5 ± 4.5	25.5 ± 4.6	29.3 ± 5.7	29.3 ± 5.4	27.1 ± 4.2	26.8 ± 3.8
WC (cm)	86.8 ± 10.8	86.2 ± 10.6	94.1 ± 15.8	90.9 ± 15.1*	88.0 ± 12.1	84.5 ± 11.0*†
Systolic BP (mmHg)	119.8 ± 7.8	121.5 ± 11.0	126.7 ± 9.9	120.6 ± 6.5*	119.7 ± 7.2‡	115.6 ± 8.9*
Diastolic BP (mmHg)	82.0 ± 7.0	81.0 ± 10.8	80.3 ± 11.1	74.7 ± 7.9*	76.1 ± 8.4	77.4 ± 6.8
MAP (mmHg)	94.6 ± 6.2	94.5 ± 9.8	95.8 ± 9.9	90.0 ± 6.6*	90.6 ± 7.7	90.1 ± 6.8
TG (mmol·L^{-1})	1.9 ± 1.4	1.9 ± 1.6	1.4 ± 0.5	1.4 ± 0.6	1.3 ± 0.6	1.2 ± 0.6
Fasting BG (mmol·L^{-1})	5.1 ± 0.5	5.4 ± 0.5	5.2 ± 0.6	5.1 ± 0.7	5.1 ± 0.4	5.0 ± 0.5
HDL (mmol·L^{-1})	1.3 ± 0.4	1.4 ± 0.3	1.6 ± 0.6	1.6 ± 0.6	1.5 ± 0.5	1.6 ± 0.5
MetS z-Score	-1.4 ± 3.8	-1.3 ± 4.0	-2.0 ± 3.1	-2.8 ± 2.8*	-3.3 ± 2.3	-3.9 ± 2.2*
Caloric intake (kcal)	1327 ± 418	1265 ± 317	1520 ± 563	1518 ± 500	1539 ± 493	1555 ± 403
Carbohydrate (g)	136.5 ± 55.0	121.1 ± 41.8	160.4 ± 60.5	158.8 ± 63.9	168.2 ± 68.6	164.5 ± 57.2
Lipid (g)	56.0 ± 18.1	54.0 ± 11.9	61.1 ± 31.2	62.8 ± 26.4	68.6 ± 23.4	67.5 ± 13.6
Protein (g)	71.7 ± 43.6	55.0 ± 7.6	64.1 ± 16.4	63.8 ± 22.0	73.6 ± 36.6	64.8 ± 25.2
Carbohydrate (%)	40.6 ± 5.8	37.9 ± 5.6	41.7 ± 6.9	40.9 ± 7.8	43.1 ± 8.2	41.9 ± 6.7
Lipid (%)	38.7 ±7.5	39.2 ± 7.0	35.9 ± 9.2	37.1 ± 8.4	40.7 ± 7.9	40.6 ± 8.1
Protein (%)	22.1 ± 13.4	17.9 ± 3.1	18.2 ± 6.3	17.8 ± 5.1	19.6 ± 10.6	16.5 ± 3.8
PA (MET·min^{-1}·wk^{-1})	1354 ± 1018	1176 ± 1109	838 ± 979	3680 ± 1671*†	937 ± 587	3855 ± 2261*†
Time Sitting (hours·d^{-1})	6.5 ± 1.2	6.9 ± 2.5	5.6 ± 2.7	4.5 ± 2.3*†	6.3 ± 2.4	5.4 ± 2.4*
Resting HR (b·min^{-1})	74.1 ± 7.8	69.5 ± 7.5	70.4 ± 8.9	68.8 ± 7.7	68.8 ± 9.7	68.1 ± 11.4
Maximal HR (b·min^{-1})	173.9 ± 12.4	170.1 ± 11.1*	166.4 ± 15.7	167.6 ± 15.5	170.1 ± 18.4	169.2 ± 14.4
VO_2max (ml·kg^{-1}·min^{-1})	28.4 ± 4.5	27.7 ± 4.6	24.4 ± 4.7	26.2 ± 4.2*†	29.5 ± 7.5‡	32.8 ± 8.6*†
VO_2max (L·min^{-1})	2.2 ± 0.7	2.1 ± 0.7	2.0 ± 0.6	2.2 ± 0.6*†	2.4 ± 0.8	2.6 ± 0.9*†
% Diff in VO_2max (GXT and Verification)	0.6 ± 1.5	0.0 ± 2.1	-0.2 ± 1.8	-0.4 ± 1.8	0.2 ± 1.7	-0.7 ± 1.7
% Δ in VO_2max	-	-2.3 ± 8.5	-	7.7 ± 8.3†	-	11.4 ± 3.7†

Values are mean ± SD. BG, blood glucose; BMI, body mass index; BP, blood pressure; GXT, graded exercise test; HDL, high density lipoprotein; HR, heart rate; MAP, mean arterial pressure; MET, metabolic equivalents; PA, physical activity; TG, triglycerides; WC, waist circumference; Δ, change.

$^{*}p \leq 0.05$ pre- to post-change within-group difference; †Significant difference from control group; ‡Significantly different from standardised group

6.5.1 Changes in MetS z-Score and MetS Variables

Following the 12-week intervention, MetS z-score was significantly improved for both experimental groups with improvements of -2.0±3.1 to -2.8±2.8 [$t(18) = 3.01$, $p = 0.01$] and -3.3±2.3 to -3.9±2.2 [$t(18) = 2.28$, $p = 0.04$] for the standardised and individualised groups, respectively. When analysing the individual components of the MetS z-score for the standardised group, there were significant reductions in SBP of 126.7±9.9 to 120.6±6.5 mmHg [$t(18) = 4.06$, $p = 0.001$], DBP [$t(18) = 2.31$, $p = 0.03$] of 80.3±11.1 to 74.7±7.9 mmHg, MAP [$t(18) = 3.07$, $p = 0.01$] of 95.8±9.9 to 90.0±6.6 mmHg, and waist circumference [$t(18) = 6.95$, $p = 1.7 \times 10^{-6}$] 94.1±15.8 to 90.9±15.1 cm. For the individualised group, there were significant reductions in SBP [$t(18) = 2.18$, $p = 0.04$] of 119.7±7.2 to 115.6±8.9 mmHg and waist circumference [$t(18) = 5.63$, $p = 2.4 \times 10^{-5}$] of 88.0±12.1 and 84.5±11.0 cm. When investigating mean scores for components of the

MetS z-score at baseline in the standardised group, it was found that fasting BG, HDL, and TG each were in a healthy category. In the individualised group, the mean scores for the following components of the MetS z-score were within a healthy category at baseline: DBP, MAP, TG, fasting BG, and HDL.

6.5.2 Incidence of MetS z-Score Responders and Non-Responders

The incidence of MetS z-score responders and non-responders in both standardised and individualised groups are shown in Figure 6.1. In the standardised group, 63% (12/19) of participants were considered responders with a favourable change in MetS z-score ($\Delta >$ 0.6) and 37% (7/19) were considered non-responders with an undesirable change in MetS z-score. Similarly, in the individualised group, 58% (11/19) of participants were responders and 42% (8/19) were considered non-responders for changes in MetS z-score. Based on the χ^2 analysis, there was not a significant difference in incidence of response ($p = 0.74$; Cramer's $V = 0.54$) of exercise training strategy on MetS z-score responsiveness.

When separating participants based on prevalence of MetS at baseline and MetS z-score responsiveness, there were 6 and 3 participants in the standardised and individualised groups, respectively, considered to have MetS. Of the 6 participants in the standardised group, 83% (5/6) of the participants were considered responders, whereas 100% (3/3) of participants in the individualised group were considered to be responders. Furthermore, only 17% (1/6) of the participants with MetS at baseline in the standardised group no longer had symptoms of MetS following the intervention. In the individualised group, 67% (2/3) of participants with baseline MetS were not considered to have MetS at week 12. In the control group, only 13% (1/8) of participant at baseline had 3 or more factors associated with MetS. However, at 12 weeks, 28% (3/8) participants had MetS. The specific changes that occurred on an individual level in MetS z-score components for non-responders in both experimental groups are presented in Table 6.2. This table highlights how participants can be labelled as non-responders, with unfavourable changes occurring in components of the MetS z-score, even though that measure remained in a healthy category.

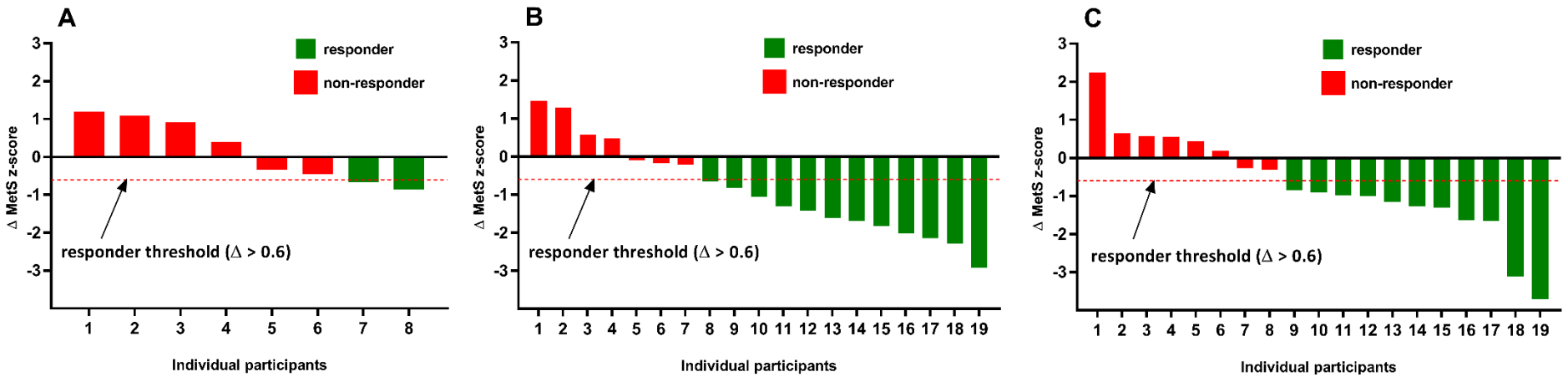

Figure 6.1 Metabolic syndrome (MetS) z-score responsiveness (Δ) for the control (A), standardised (B), and individualised (C) groups following 12 weeks exercise training. The dashed line indicates the threshold of minimum change (Δ > 0.6) in a favourable direction required to be considered a responder

Table 6.2 A breakdown of all the individual change in MetS z-score components for non-responders in both the standardised and individualised experimental groups

Change in MetS z-score component	Number of Participants	
	Standardised	Individualised
SBP increased, but remained healthy	1	4
DBP increased, but remained healthy	1	4
TG increased, but remained healthy	5	4
BG increased, but remained healthy	2	3
HDL decreased, but remained healthy	3	4
WC increased, but remained healthy	1	0
DBP increased to an unhealthy range	1	2
TG increased to an unhealthy range	1	1
BG increased to an unhealthy range	1	1
HDL started unhealthy and decreased in an unhealthy range	1	0

BG, fasting blood glucose; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference

6.5.3 Changes to Other Parameters

Changes in BMI, weight, resting HR, and maximal HR were not significantly different within or between either experimental group following the 12-week exercise intervention. Furthermore, there was not a significant difference in dietary intake and for each macronutrient at baseline and 12 weeks in any of the groups. There was a significant increase in physical activity from 836±975 to 3680±1671 $MET \cdot min^{-1} \cdot wk^{-1}$ [$t(18) = -5.68$, $p = 2.2 \times 10^{-5}$] and 937±587 to 3855±2261 $MET \cdot min^{-1} \cdot wk^{-1}$ [$t(18) = -5.28$, $p = 5.1 \times 10^{-5}$] for the standardised and individualised groups, respectively. However, this increase in activity was expected since the final prescribed exercise duration was 1847±442 $MET \cdot min^{-1} \cdot wk^{-1}$ and 2647± 892 $MET \cdot min^{-1} \cdot wk^{-1}$ for the standardised and individualised groups, respectively. Furthermore, time spent sitting significantly decreased 5.6±2.7 to 4.5±2.3 $hours \cdot d^{-1}$ [$t(18) = 2.11$, $p = 0.05$] and 6.3±2.4 to 5.4±2.4 $hours \cdot d^{-1}$ [$t(18) = 2.40$, $p = .03$].

The verification procedure following the GXT confirmed VO_2max at baseline and post-program in all participants (46/46). The individual differences between the GXT and verification procedure at baseline and 12 weeks is presented in Table 1. Both experimental groups had significant improvements in absolute and relative VO_2max in comparison to the control group. However, there was not a significant difference between the two experimental groups. Indeed, within group differences showed relative VO_2max significantly improved from 24.4±4.7 to 26.2±4.2 $ml \cdot kg^{-1} \cdot min^{-1}$ [$t(18) = -4.46$, $p = 3.1 \times 10^{-4}$] and 29.2±7.5 to 32.8±8.6 $ml \cdot kg^{-1} \cdot min^{-1}$ [$t(18) = -9.86$, $p = 1.1 \times 10^{-8}$] for the standardised and individualised groups, respectively. Absolute VO_2max in the standardised group significantly improved from 2.0±0.6 to 2.2±0.6 $L \cdot min^{-1}$ [$t(18) = -4.70$, $p = 1.8 \times 10^{-4}$] and significant improvements in the individualised group were seen with a change of 2.4±0.8 to 2.6±0.9 $L \cdot min^{-1}$ [$t(18) = -6.45$, $p = 1.0 \times 10^{-6}$]. There was a greater overall percent change for the individualised compared to the standardised group (11.4±3.7% compared to 7.7±8.3%).

6.6 Discussion

To our knowledge, this is the first study to investigate the impact of two isocaloric exercise interventions with exercise intensity prescribed either on a standardised (%HRR) or individualised basis (threshold-based model using VT1 and VT2) on the severity of MetS. As expected, both exercise interventions resulted in more responders to a positive change in MetS severity ($\Delta > 0.6$), depicted as a change in MetS z-score, compared to

control (Figure 6.1A). However, in contrast with our hypothesis, our results showed a similar percentage of individuals who significantly reduced MetS severity following both exercise interventions (standardised, 63% [12/19] vs individualised, 58% [11/19]). Interestingly, albeit based on a limited sample size, for those participants diagnosed with MetS at baseline, there was a greater number of individuals who reversed the syndrome following the individualised exercise intervention (66, 2/3) compared to the standardised (17%, 1/6) exercise prescription.

Previously, Johnson et al. (115) found exercise volume plays a critical role in ameliorating MetS severity when exercise is performed at a low amount (~19 km·wk^{-1}) with moderate intensity (40-55% VO_2peak) for ~175 min·wk^{-1} or a high amount (~32 km·wk^{-1}) with high intensity (65-80% VO_2peak) for ~175 min·wk^{-1} compared to a low amount (~19 km·wk^{-1}) with high intensity (65-80% VO_2peak) for ~115 min·wk^{-1} over an 8 month period. In the current investigation, our data support the previous volume and MetS severity findings with the standardised group increasing exercise volume to 168±27 min·wk^{-1}. However, our data is also inconsistent with these previous findings with the individualised group increasing exercise volume to only 131±32 min·wk^{-1}. Indeed, Ramos and colleagues (113) reported a reduction in MetS severity following two methods of high intensity interval training (HIIT) and continuous moderate intensity training. They found that a low-volume HIIT (51 min·wk^{-1}) was as effective as a high-volume HIIT (114 min·wk^{-1}) and moderate intensity continuous exercise (150 min·wk^{-1}) following a 16-week intervention. One of the proposed mechanisms lessening the severity of MetS in the low-volume HIIT group was a due to a similar improvement in cardiorespiratory fitness (i.e. VO_2max). Therefore, with both experimental groups significantly improving VO_2max, even though there was not a significant difference between groups, we believe this is one potential mechanism underpinning why no difference in MetS severity reduction was seen between groups. Furthermore, it has been shown that individuals with greater insulin resistance, in which individuals with diagnosed MetS are likely to have relative to those without the syndrome, are more sensitive to any dose of exercise (76). This is supported by our findings which showed no difference in the proportion of MetS individuals who responded to either an individualised or standardised exercise dose. Indeed, we found that of the 6 participants in the standardised group, 83% (5/6) of the participants were considered responders whereas 100% (3/3) of the individualised participants were responders. Thus, the difference in the number of individuals diagnosed with MetS at baseline in the standardised group (n=6) versus the individualised group

(n=3) may have caused our inability to detect a significant difference in MetS z-score change between groups.

It was not surprising that further improvements in some of the MetS z-score criteria were not seen due to the health status of each group at baseline. For example, the standardised group was in a healthy range for fasting BG, HDL, and TG and the individualised group was in a healthy range for DBP, MAP, TG, fasting BG, and HDL. Therefore, both groups had limited ability to improve MetS criteria, especially in the individualised group, due to a 'ceiling effect' (14). Moreover, as exhibited in Table 2, a non-response in various individual components of the MetS z-score may not result in an unfavourable change to cardiometabolic health. Indeed, Dalleck and colleagues (32) found that an adverse cardiometabolic response (i.e. a response in an unfavourable direction by two times the technical error) rarely resulted in increased 10-year cardiovascular disease risk. These findings are important to recognise because even if a participant has an unfavourable change in a MetS risk factor, it may not always be associated with an increased risk, overall, especially if other cardiometabolic and cardiovascular factors are improving.

An individualised exercise prescription has been shown to increase the training responsiveness of VO_2max following an exercise intensity prescription based on ventilatory thresholds compared to a standardised approach using HRR (11,12). Indeed, unpublished data from the current investigation supports these previous findings with 60% and 100% of standardised and individualised participants, respectively, considered VO_2max responders to a site- and cohort-specific technical error. Therefore, an individualised program appears to be superior to a standardised program when evaluating changes in VO_2max due to the driving force being the exercise intervention itself. Given the reported cardioprotective benefits conferred by higher levels of fitness (i.e., improved VO_2max) (72), these findings have important public health implications. However, when investigating changes in cardiometabolic risk factors (i.e. changes in MetS factors), it has been established that the exercise intervention as well as the lifestyle outside of the exercise intervention play a critical role in the changes in MetS factors. For example, dietary intake (116,117), sedentary behaviour (118), sitting for prolonged periods (119), sleep duration (120), and chronic stress (73) have all been linked to influencing components of MetS syndrome. Moreover, heightened psychological stress and inadequate sleep have been linked to a variety negative health factors including altered endocrine function, increased sympathetic and decreased parasympathetic tone, increase blood pressure, and increase insulin and glucose levels (121–123). Furthermore,

psychological stress and insufficient sleep have been linked to a reduction in post-exercise recovery (124,125). In the present study, the individualised group, while not statistically significant, had an overall increase in caloric intake from baseline to post-intervention and sedentary behaviour (time spent sitting) remained about an hour more than the standardised group. Unfortunately, we did not delineate the overall time spent sedentary compared to continuous durations of time engaged in sedentary behaviour (i.e. 5 hours of sedentary behaviour in one setting or 30 mins of sedentary behaviour 10 times throughout the day). Indeed, these two factors and those previously mentioned but not accounted for in the investigation may have been influential factors in the overall MetS z-score responsiveness at the individual level.

We believe the present study highlights the feasibility of using a MetS z-score to quantify cardiometabolic training responsiveness. However, future research should investigate a standardised and individualised approach to exercise intensity prescription in individuals with known MetS at baseline, control for sedentary behaviour and frequency of interrupting sedentary behaviour throughout the intervention, have a standardised dietary intake for participants leading up to blood analysis, and include a more comprehensive training responsiveness criterion (i.e. incorporation of MetS z-score and VO_2max responsiveness criteria).

6.6.1 Limitations

With this being a feasibility study, there are several limitations that should be noted. There was an overall lack of participants with known MetS in both groups, however, many participants in both groups had 1 or more cardiometabolic risk factors at baseline. Therefore, the present results cannot be generalised to clinical populations at this point. Further research is warranted to identify differences in the standardised and individualised exercise intensity prescription methodologies in a MetS-specific cohort. The participant pool represented a standard ‘exercise clinic demographic’, but there may be heterogeneity in results due to the large age range used. There were many lifestyle and psychological factors that were not accounted for and could have had an impact on the overall findings. Furthermore, men were underrepresented and only accounting for 24% of the participants. Additionally, while dietary intake was analysed at baseline and post-intervention, there was not a standardised dietary protocol prior to blood analysis which may have accounted for some of the changes in individual blood profiles. Moreover, survey data were used in this study to analyse dietary intake/habits and physical activity

levels at baseline and post-program. This methodology itself may have limited the overall interpretations of the findings. Both methods relied on the honesty of the participants to accurately record nutritional data and quantify their activity levels. These surveys were only conducted on two occasions. Incorporating more frequent analyses of these measures would have allowed for a better understanding of whether changes in nutrition and activity levels (outside of the prescribed exercise intervention) occurred. Lastly, hydration status during testing, exercise, and changes from pre- to post-intervention were not assessed.

6.7 Conclusions

Our findings suggest that MetS z-score significantly improved following 12 weeks of standardised and individualised exercise intensity prescription. While there was no significant difference in individual MetS z-score responsiveness, it appears that an individualised approach may ameliorate the severity of MetS in individuals with 3 or more cardiometabolic risk factors at baseline. Further research is warranted on whether an individualised exercise prescription approach further reduces MetS severity when compared to a standardised approach in individuals with known MetS.

Chapter 7 - Incidence of VO_2max Responders to Personalised vs Standardised Exercise Prescription

7.1 Prelude

This chapter comprises the following paper accepted for publication: Weatherwax, R.M., Harris, N., Kilding, A., Dalleck, L.C. (2018). Incidence of VO_2max Responder to Personalized vs Standardized Exercise Prescription. *Medicine & Science in Sport & Exercise*, 51(4).

In Chapter 4, a site- and cohort-specific TE was established to understand the minimum improvements required for a response in VO_2max to be consider beyond that of biological variability and the measurement error. In Chapter 5, the overall 4-week changes in VO_2max were highlighted to identify the overall timing of changes. Within this chapter, the final experimental chapter, the primary aim of the PhD is addressed: does an individualised exercise intensity prescription increase the overall CRF training responsiveness compared to a standardised method. Indeed, this chapter provides insightful information on the potency of an individualised method to increase VO_2max due to greater consideration of individual metabolic characteristics.

7.2 Abstract

Despite knowledge of cardiorespiratory fitness (CRF) training responders and non-responders, it is not well understood how the exercise intensity prescription impacts the incidence of response. The purpose of this study was to determine CRF training responsiveness based on cohort specific technical error (TE) following 12 weeks of standardised or individually prescribed exercise and the use of a verification protocol to confirm maximal oxygen uptake (VO_2max). Sedentary adult participants (9 men; 30 women; 48.2±12.2 yr) completed exercise training on 3 days a week for 12 weeks with exercise intensity prescribed based on standardised methods using heart rate reserve (HRR) or an individualised approach using ventilatory thresholds. A verification protocol was used at baseline and 12 weeks to confirm the identification of a true VO_2max and subsequent relative percent changes to quantify CRF training responsiveness. A cohort-specific TE (4.7%) was used as a threshold to identify incidence of response. Relative VO_2max significantly increased ($p < .05$) from 24.3±4.6 to 26.0±4.2 $ml \cdot kg^{-1} \cdot min^{-1}$ and

29.2±7.5 to 32.8±8.6 ml·kg^{-1}·min^{-1} for the standardised and individualised groups, respectively. Absolute VO_2max significantly increased ($p < .05$) from 2.0±0.6 to 2.2±0.6 L·min^{-1} and 2.4±0.8 to 2.6±0.9 L·min^{-1} for the standardised and individualised groups, respectively. A significant difference in responsiveness was found between the individualised and standardised group with 100% and 60% of participants categorised as responders, respectively. A threshold model for exercise intensity prescription had a greater effect on the incidence of CRF training response compared to a standardised approach using HRR. The use of thresholds for intensity markers accounts for individual metabolic characteristics and should be considered as a viable and practical method to prescribe exercise intensity.

7.3 Introduction

Low cardiorespiratory fitness (CRF) has been shown to be a predictor of future cardiovascular disease (CVD) incidence and mortality (30), but substantial evidence exists showing that increasing physical activity and exercise can increase CRF (i.e. maximal oxygen consumption, VO_2max) and mitigate adverse health effects (31). However, since the 1980s (1), it has been known that considerable individual variability in CRF training responsiveness occurs following a structured aerobic exercise program and, therefore, not all individuals receive the same health outcomes. Indeed, this variability in CRF adaptations has since been shown in a variety of populations including healthy, but untrained adults (8–12), post-menopausal women (5), and overweight and obese men and women (7).

Despite knowledge that individual variability in training responsiveness occurs, the causative mechanisms are not fully understood. Through HERITAGE, it was found that age, sex, race, and initial fitness do not significantly affect changes in VO_2max response to standardised exercise training (33). However, it was found that VO_2max responsiveness has a significant genetic component and yielded a maximal heritability estimate of 47% (18). More recently, 21 single nucleotide polymorphisms were found to explain 49% of the variability in VO_2max trainability (82). Since genetics do not account for all of the variability in training responsiveness, it has been proposed that the methodology of exercise prescription could play a critical role in eliciting a desired or undesirable change in VO_2max. In the late 1970's, it was shown that utilising a relative percent method (i.e. percentage of heart rate reserve, HRR) for prescribing exercise intensity fails to consider individual metabolic differences (20), yet it is still a

recommended approach (25). Recent investigations have proposed a more individualised exercise prescription using ventilatory thresholds to personalise a training regime based on individual metabolic responses (11,12) and, therefore, enhance the potential benefits of regular physical activity.

Our understanding of individual variability following standardised CRF training is confounded owing to methodological weaknesses of criteria used to determine VO_2max (42,46,47). The highest VO_2 achieved (VO_2peak) during a graded exercise test (GXT) has been commonly used to prescribe exercise intensity and evaluate training responsiveness. However, a VO_2peak value does not always indicate a 'maximal' value for aerobic fitness. When only peak values are reported, it is unclear whether post-intervention values improve, maintain, or decline. For example, if a participant has a VO_2peak of 25.0 $ml \cdot kg^{-1} \cdot min^{-1}$ and 30 $ml \cdot kg^{-1} \cdot min^{-1}$ at baseline and post-intervention, respectively, it is not easily understood what true changes occurred in CRF. If the baseline VO_2 was indeed a peak value and the post-intervention VO_2 was a true maximal value, determination of training effect on aerobic function is not possible because there is no way to retrospectively determine the true baseline maximal value. Therefore, a verification protocol (i.e. a supramaximal test following a GXT) has been proposed to confirm when a 'true' maximal effort has been achieved (51,56,57,59). Recently, two investigations have incorporated the use of a verification protocol to identify individual differences in training responsiveness following sprint (126) and high-intensity (127) interval training. To our knowledge, however, the use of a verification protocol has not been used when evaluating individual training responsiveness following individualised and standardised steady-state exercise intensity prescription.

Another fundamental issue of understanding individual variability following CRF training is a lack in accepted criteria for what is considered to be a response to quantify 'responders' and 'non-responders' or those who have a desirable change compared to an undesirable change in a specific parameter, respectively. Commonly, training responsiveness has been quantified based on absolute changes from baseline to post-intervention, but this method does not take into consideration normal day-to-day fluctuations in biological variability and the measurement error of the equipment being used (10,13,14). It has been proposed that in order to have an all-inclusive definition for incidence of response, the technical error (TE, biological variability and measurement error) must be taken into consideration (13). However, often times when TE error has been used to quantify training responsiveness, the TE has been sourced from previous

literature rather than developing one that is specific to the site and cohort being analysed (10–12). Indeed, this methodology may not be sensitive enough to truly identify CRF training responders and non-responders. Furthermore, many training investigations only report the group mean ± standard deviation which fails to address the physical adaptations seen in individual participants. Therefore, it is possible that there could be a misrepresentation of exercise prescription effectiveness on the overall training response when only group differences are reported. Collectively, these issues underpin the need for further study in order to better understand how an individualised approach to the exercise prescription can augment training responsiveness. Indeed, much needed novel data are required to advance the field of exercise programming. Accordingly, the purpose of the current investigation was to determine CRF training responsiveness (changes in VO_2max with the use of a verification protocol to confirm true VO_2max) based on a site and cohort specific TE following 12 weeks of standardised or individually prescribed exercise. Due to taking into consideration the individual metabolic characteristics, it is believed that the individualised group will have a greater overall responsiveness compared to the standardised group.

7.4 Methods

Men and women were recruited from a community wellness program and from the surrounding community via advertisement at the local university, newspaper, and word-of-mouth to be randomised to one of two experimental groups. Inclusion criteria for participation in the study included being considered low to moderate risk based on the American College of Sports Medicine Standards (25), participation in less than 30 min of moderate intensity physical activity on 3 days a week or less, and between the ages of 30 and 75 years. Exclusionary criteria included evidence of signs or symptoms suggestive of pulmonary, cardiovascular, or metabolic conditions determined from a standard medical history questionnaire and intake interview. Similar to previous research (28,29), a third group (i.e. the control group) was recruited as a convenience sample separate from experimental participants due to the moral and ethical considerations of withholding a known physiological and psychological benefit (i.e. an exercise intervention) that were interested in the various health indices from the laboratory testing, but not interested in increasing regular exercise or physical activity. Control participants had to meet the same inclusion/exclusion criteria previously mentioned and undergo all of the same laboratory testing at baseline and 12 weeks. Following the baseline testing, control participants were encouraged to maintain their current physical activity behaviour and dietary intake habits.

All participants provided written informed consent prior to initiation of the study. A detailed description of the study methodology and rationale has been previously published (26). The Auckland University of Technology Ethics Committee (16/264) and the Western State Colorado University Institutional Review Board (HRC2016-01-90R6) approved this study.

7.4.1 Experimental Testing

All primary outcome variables were obtained at baseline and week 12. To the best of our ability, baseline and post-program testing occurred on the same day of the week and time of day to ensure consistency and mitigate any possible changes due to timing of the testing. Prior to testing sessions, participants were instructed to refrain from any strenuous exertion and to not consume food or drink, other than water, for 12 hours. All post-program testing took place within 1-4 days of the last exercise training session.

7.4.2 Dietary Analysis

During the 12-week study, participants verbally agreed to not change their regular nutritional intake habits and completed a 3-day dietary recall (2 weekdays and 1 weekend day) at baseline and post-program. Participants were instructed to record as much detail about the food and drink ingested throughout the 3 days recorded. The dietary recall was used to establish energy intake, percentages of macronutrients, and grams of macronutrients.

7.4.3 Physical Activity Analysis

At baseline at post-intervention, participants completed the IPAQ to establish average physical activity levels (MET-min·wk^{-1}) and time spent sitting per day. At baseline, the results of the IPAQ survey and a subsequent discussion about weekly physical activity levels were used in combination to establish whether sedentary behaviour inclusionary criteria were met.

7.4.4 Anthropometric Measurements and Resting Heart Rate

Participants were weighed to the nearest 0.1 kg on a medical grade scale and height was measured to the nearest 0.5 cm using a stadiometer (Tanita Corporation WB-3000, Tokyo, Japan). Resting heart rate (HR) was determined using standardised procedures (25). In summary, participants were seated with back support for 5 min with their feet on the ground and arms supported near heart level. A medical-grade pulse oximeter (Nonin

Medical Inc., Plymouth, MN, USA) was used to establish resting heart rate following the 5 min of rest.

7.4.5 Maximal Exercise Test and Verification Protocol

A GXT using a modified-Balke pseudo-ramp protocol on a motorised treadmill (Powerjog GX200, Maine, USA) was completed to determine VO_2max and threshold measurements. Participants chose a self-selected pace to complete the test. After the completion of a 4-min warm-up with the workload gradually increasing to the starting self-selected speed and an incline of 0%, the incline was then increased by 1% each min until volitional fatigue was reached. During the GXT, HR was monitored using a chest strap and radio-telemetric device (Polar Electro, Woodbury, NT, USA) and expired air and gas exchange data using a metabolic analyser (Parvo Medics TrueOne 2.0, Salt Lake City, UT, USA) were continuously recorded and monitored. Before the GXT, the metabolic analyser was calibrated with a calibration gas mixture (16.00% O_2 and 4.00% CO_2) and room air (20.93% O_2 and 0.03% CO_2) in accordance to manufacturer guidelines and instructional manual. Following the GXT, the last 15 sec of gas exchange data were averaged and considered to be the final data point. Subsequently, the 15 sec gas exchange data occurring before the final data point were also averaged. The mean of the two processed data points represented VO_2max for the GXT. The highest HR reached during the GXT was considered to be the maximal HR and HRR was calculated by taking the difference between maximal and resting HR.

A verification protocol was used to confirm a 'true' VO_2max was achieved using methods previously published (57,59). In summary, 20 min following the completion of the GXT, participants were asked to complete a 4 min warm-up followed by a volitional test to fatigue at a constant workload that was 5% higher than the last completed stage of the GXT. The workload was determined by taking the final metabolic equivalent (MET) value for the GXT and increasing the speed, incline, or combination of the two to achieve a 5% higher MET value for the verification bout. During the verification protocol, HR and gas exchange data were monitored in the same manner as the GXT. The verification VO_2max was determined based on the same method as the GXT by averaging the final two 15 sec averaged data points. A 'true' VO_2max was confirmed if the two calculated VO_2max values from the GXT and verification protocol were within ±3.0%, which is the measurement error of the gas exchange measurements (107). The GXT and verification protocol VO_2max values were averaged and this value was used as the participant

VO_2max to identify training responders and non-responders. If a participant had a difference in VO_2max values > 3.0%, they were asked to repeat the GXT and verification bout protocol within 24-72 hours until a difference less than ±3.0% was achieved to confirm 'true' VO_2max reached.

7.4.6 Determination of Ventilatory Thresholds

The determination of the first ventilatory threshold (VT1) and the second ventilatory threshold (VT2) were performed based on previously published methods (11,12,26). A visual inspection of the gas exchange data were analysed to determine VT1 and VT2 using time, ventilatory equivalents of O_2 (VE/VO_2) and ventilatory equivalents of CO_2 (VE/VCO_2). VT1 occurred when VE/VO_2 increased without a concurrent increase in VE/VCO_2 whereas VT2 was the point that both VE/VO_2 and VE/VCO_2 simultaneously increased. All assessments were completed by two experienced exercise physiologists. If there were conflicting results, the original assessments were re-evaluated, and a consensus was agreed upon.

7.4.7 Exercise Prescription

Participants were randomised into one of the two experimental groups according to a computer-generated sequence of random numbers stratified by sex. Throughout the 12-week intervention, participants exercised 3 days a week in an indoor fitness facility on motorised equipment with a set HR and time established based on the GXT results. Participants exercised using a motorised treadmill, elliptical trainer, and/or stationary bike. In order to equate exercise volume, the exercise duration was based on energy expenditure per kg of body weight per week ($kcal \cdot kg^{-1} \cdot wk^{-1}$) to establish an isocaloric volume between groups. The energy expenditure was determined based on matching the prescribed exercise HR to the corresponding energy expenditure from the GXT. For the standardised group, exercise intensity was based on percentages of HRR, whereas the individualised group had an intensity that was established based on VT1 and VT2. For the HR intensity when established using VT1 and VT2, the following HR ranges were used:

- Target HR > VT1 = HR range of 10 bpm below VT1 to the HR at VT1
- Target HR ≥ VT1 to < VT2 = HR range of 15 bpm directly between VT1 and VT2
- Target HR ≥ VT2 = HR range of 10 bpm above VT2

A full summary of the week-to-week progression in exercise prescription can be seen in Table 7.1.

Table 7.1 A summary of the week-to-week exercise prescription for the standardised and individualised groups

Week	Energy Expenditure	Standardised Target Heart Rate	Individualised Target Heart Rate
	$kcal \cdot kg^{-1} \cdot wk^{-1}$	% HRR	
1	5.6	40-45	HR < VT1
2	8.4	40-45	HR < VT1
3	11.2	40-45	HR < VT1
4	11.2	50-55	HR ≥ VT1 to < VT2
5	11.2	55-60	HR ≥ VT1 to < VT2
6	11.2	55-60	HR ≥ VT1 to < VT2
7	12.6	55-60	HR ≥ VT1 to < VT2
8	14.0	55-60	HR ≥ VT1 to < VT2
9	14.0	60-65	HR ≥ VT2
10	14.0	60-65	HR ≥ VT2
11	15.4	60-65	HR ≥ VT2
12	15.4	60-65	HR ≥ VT2

HR, heart rate; HRR, heart rate reserve; kcal, kilocalories; VT1, first ventilatory threshold; VT2, second ventilatory threshold

7.4.8 Establishment of the Technical Error for Training Responsiveness

A site and cohort-specific TE (combination biological variability and measurement error) was developed from a sub-group from the current investigation. Specific details and results have been previously published (128). In summary, 16 participants completed two baseline testing sessions, as described previously, no sooner than 24 hours and no more than 7 days later while maintaining their current lifestyle. The biological variability for VO_2max was established by determining the coefficient of variability following repeat testing sessions and was found to be 4.7%. Therefore, the TE was established to be 4.7% for VO_2max and indicating that a participant in our laboratory and within this sample population needs to have a change in VO_2max greater than 4.7% in order for the training adaptations to be considered meaningful.

7.4.9 Statistical Analysis

All statistical analyses were performed using SPSS Version 25.0 (Chicago, IL, USA). Data were reported as mean ± standard deviation (SD). Based on a power calculation previously published (26) and an assumption of a 20% dropout rate, 20 participants were desired for each group. One-way analysis of variance (ANOVA) testing was used to compare groups at baseline and, where appropriate, Tukey *post hoc* test. The assumption of normality was confirmed by examination of normal plots of the residuals in ANOVA models and Shapiro-Wilk tests (27). Paired sample t-tests were used to analyse within-group differences in continuous variables. Between-group difference of the change in

continuous variables from baseline to 12 weeks was assessed through analysis of covariance (ANCOVA), with the week 12 values as the dependent variables and the baseline value as a covariate and, where appropriate, a *post hoc* analysis with a comparison of main effects and a Bonferroni adjustment. Subsequent ANCOVA analyses were performed with the percent change in VO_2max, absolute change in VO_2max, and relative change in VO_2max as dependent variables and age, sex, height, weight, BMI, and baseline VO_2max (relative and absolute) as covariates.

Delta values (Δ) are expressed as percent change (post-testing minus baseline value divided by baseline value, multiplied by 100) for relative VO_2max for experimental groups with participants categorised as: '1' = responder (% $\Delta > 4.7\%$) or '0' = non-responder (% $\Delta \leq 4.7\%$). Chi-squared (χ^2) tests were subsequently used to analyse the point prevalence of responders and non-responders to exercise training separated by exercise intensity group (individualised and standardised) between baseline and 12 weeks and a Cramer's V test to determine effect size.

Table 7.2 Number of participants recruited and rationale for exclusion of data

	Control	**Standardised**	**Individualised**
Participants Recruited	20	25	24
Participants who completed the study	8	20	19
Rationale for exclusion of participants:			
Unrelated medical issues	2	1	2
Did not achieve ≥70% adherence	-	1	3
Self-withdrawal	10	3	-

7.5 Results

A total of 49 experimental and 20 control participants were recruited for the investigation. There were 39 experimental participants that completed all of the testing sessions and an adherence of 82.9% ± 5.7% and 86.1% ± 4.7% for the standardised and individualised groups, respectively. Of the 20 control participants recruited, 8 completed all testing sessions. There was considerable attrition with the control group due to participants increasing physical activity and exercise following the baseline testing or obtaining health outcomes from testing and electing to not participate in the follow-up testing session. A summary of the number of participants and rationale for exclusion in the study for each group is highlighted in Table 7.2.

Baseline and post 12 week physical and physiological characteristics are presented in Table 7.3. At baseline, there was a significant difference in VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)

between experimental groups [F(2,44) = 3.86, p = .029] with the mean VO_2max for the standardised group (24.4 ± 4.6 ml·kg^{-1}·min^{-1}) lower than the individualised group (29.5 ± 7.5 ml·kg^{-1}·min^{-1}). However, neither experimental group differed from the control group at baseline. Dietary intake was comparable (p>0.05) at baseline across groups. Furthermore, there were no significant within or between group changes (p>0.05) in dietary intake from baseline to 12 weeks, as presented in Table 7.3.

Intensity and exercise duration fidelity for both experimental groups were very high, as shown in Figure 7.1. Only during week 3 for the standardised group the actual mean min completed was 3 min less than the target range for that week.

7.5.1 Changes in VO_2max

Following the 12-week intervention, both experimental groups significantly improved CRF. Relative VO_2max significantly increased from 24.3±4.6 to 26.0±4.2 ml·kg^{-1}·min^{-1} [t(19) = -3.93, p = .001] and 29.2±7.5 to 32.8±8.6 ml·kg^{-1}·min^{-1} [t(18) = -9.86, p < .0001] for the standardised and individualised groups, respectively. Similarly, there was a significant increase in absolute VO_2max from 2.0±0.6 to 2.2±0.6 L·min^{-1} [t(19) = -3.83, p = .001] and 2.4±0.8 to 2.6±0.9 L·min^{-1} [t(18) = -6.45, p < .0001] for the standardised and individualised groups, respectively. However, while not statistically significant, a 1.5-fold greater increase in the relative percent change in VO_2max (11.4±3.7% compared to 7.7±8.3%) was found in the individualised group compared to the standardised group.

There were significant between-group differences at post-program when adjusting for age, sex, and pre-intervention values for percent change in VO_2max [F(2,44) = 11.799, p < .0001], VO_2max (ml·kg^{-1}·min^{-1}) [F(2,44) = 13.337, p < .0001], and VO_2max (L·min^{-1}) [F(2,44) = 16.536, p < .0001]. Subsequent group differences can be seen in Table 7.3.

Table 7.3 Physical and physiological characteristics and dietary intake at baseline and 12-weeks for standardised, individualised, and control groups

Parameter	Control (n=8; women=6, men=2)		Effect size within group	Standardised (n=20; women=16, men=4)		Effect size within group	Individualised (n=19; women=14, men=5)		Effect size within group
	Baseline	Week 12	Cohen's d	Baseline	Week 12	Cohen's d	Baseline	Week 12	Cohen's d
Age (yr)	45.6 ± 7.9	-	-	51.2 ± 12.5	-	-	44.9 ± 11.4	-	-
Height (cm)	171.7 ± 6.4	-	-	168.3 ± 9.5	-	-	172.1 ± 7.1	-	-
Weight (kg)	75.3 ± 15.1	75.1 ± 14.6	0.01	83.9 ± 20.7	83.8 ± 20.3	0.00	80.6 ± 16.2	79.9 ± 15.2	0.04
BMI	25.5 ± 4.5	25.5 ± 4.6	0.00	29.4 ± 5.5	29.4 ± 5.3	0.00	27.1 ± 4.2	26.8 ± 3.8	0.07
Calorie intake (kcal)	1327 ± 418	1265 ± 317	0.17	1520 ± 563	1518 ± 500	0.00	1539 ± 493	1555 ± 403	0.04
Carbohydrate (g)	136.5 ± 55.0	121.1 ± 41.8	0.32	160.4 ± 60.5	158.8 ± 63.9	0.03	168.2 ± 68.6	164.5 ± 57.2	0.06
Lipid (g)	56.0 ± 18.1	54.0 ± 11.9	0.13	61.1 ± 31.2	62.8 ± 26.4	0.06	68.6 ± 23.4	67.5 ± 13.6	0.06
Protein (g)	71.7 ± 43.6	55.0 ± 7.6	0.53	64.1 ± 16.4	63.8 ± 22.0	0.02	73.6 ± 36.6	64.8 ± 25.2	0.28
Carbohydrate (%)	40.6 ± 5.8	37.9 ± 5.6	0.47	41.7 ± 6.9	40.9 ± 7.8	0.11	43.1 ± 8.2	41.9 ± 6.7	0.16
Lipid (%)	38.7 ±7.5	39.2 ± 7.0	0.07	35.9 ± 9.2	37.1 ± 8.4	0.14	40.7 ± 7.9	40.6 ± 8.1	0.01
Protein (%)	22.1 ± 13.4	17.9 ± 3.1	0.43	18.2 ± 6.3	17.8 ± 5.1	0.07	19.6 ± 10.6	16.5 ± 3.8	0.40
Physical Activity ($MET \cdot min^{-1} \cdot wk^{-1}$)	1354 ± 1018	1176 ± 1109	0.17	831 ± 954	3660 ± 1629†‡	2.12	937 ± 587	3855 ± 2261†‡	1.77
Time Sitting ($hours \cdot d^{-1}$)	6.5 ± 1.2	6.9 ± 2.5	0.20	5.6 ± 2.6	4.4 ± 2.3†‡	0.49	6.3 ± 2.4	5.4 ± 2.4†	0.38
Resting HR ($b \cdot min^{-1}$)	74.1 ± 7.8	69.5 ± 7.5	0.60	70.0 ± 8.8	68.2 ± 8.0	0.21	68.8 ± 9.7	68.1 ± 11.4	0.07
Maximal HR ($b \cdot min^{-1}$)	173.9 ± 12.4	170.1 ± 11.1†	0.32	165.2 ± 16.1	164.9 ± 15.1	0.02	170.1 ± 18.4	169.2 ± 14.4	0.05
VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)	28.4 ± 4.5	27.7 ± 4.6	0.15	24.3 ± 4.6*	26.0 ± 4.2†‡	0.39	29.5 ± 7.5	32.8 ± 8.6†‡	0.41
VO_2max ($L \cdot min^{-1}$)	2.2 ± 0.7	2.1 ± 0.7	0.14	2.0 ± 0.6	2.2 ± 0.6†‡	0.33	2.4 ± 0.8	2.6 ± 0.9†‡	0.23
% Diff in VO_2max (GXT and Verification)	0.6 ± 1.5	0.0 ± 2.1	-	-0.2 ± 1.8	-0.4 ± 1.8	-	0.2 ± 1.7	-0.7 ± 1.7	-
% Δ in VO_2max	-	-2.3 ± 8.5	-	-	7.7 ± 8.3‡	-	-	11.4 ± 3.7‡	-

Values are mean ± SD. BMI, body mass index; GXT, graded exercise test; HR, heart rate; MET, metabolic equivalents; VO_2max, maximal oxygen consumption averaged from the GXT and verification protocol; Δ, change.

*Significantly different at baseline from individualised group; †Pre- to post-change within-group significant ($p \leq 0.05$) difference; ‡Significantly difference ($p \leq 0.05$) from control group

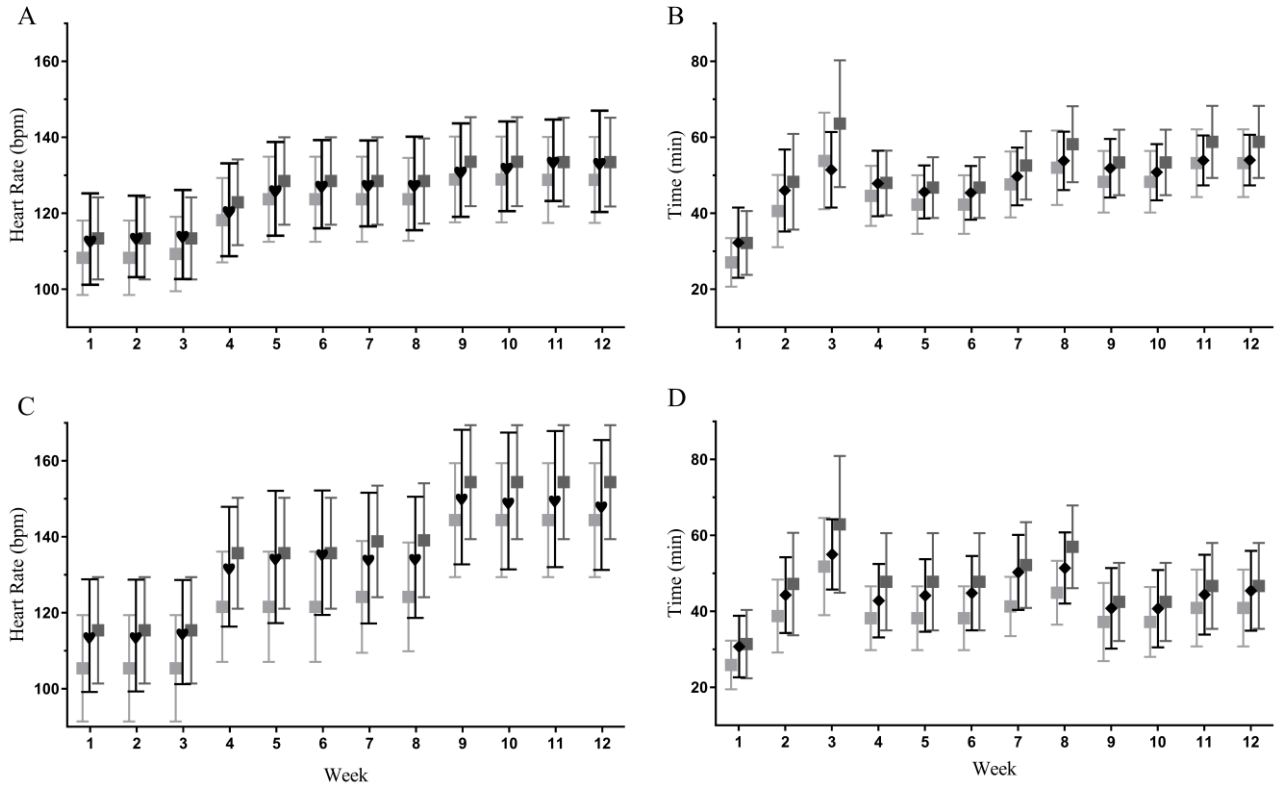

Figure 7.1 The prescribed mean and standard deviation (bars) for the lower and upper limits represented by the light grey and dark grey squares, respectively, for heart rate and time compared to the mean observed heart rate (♥) and time (♦) for the standardised (A, B) and individualised (C, D) group

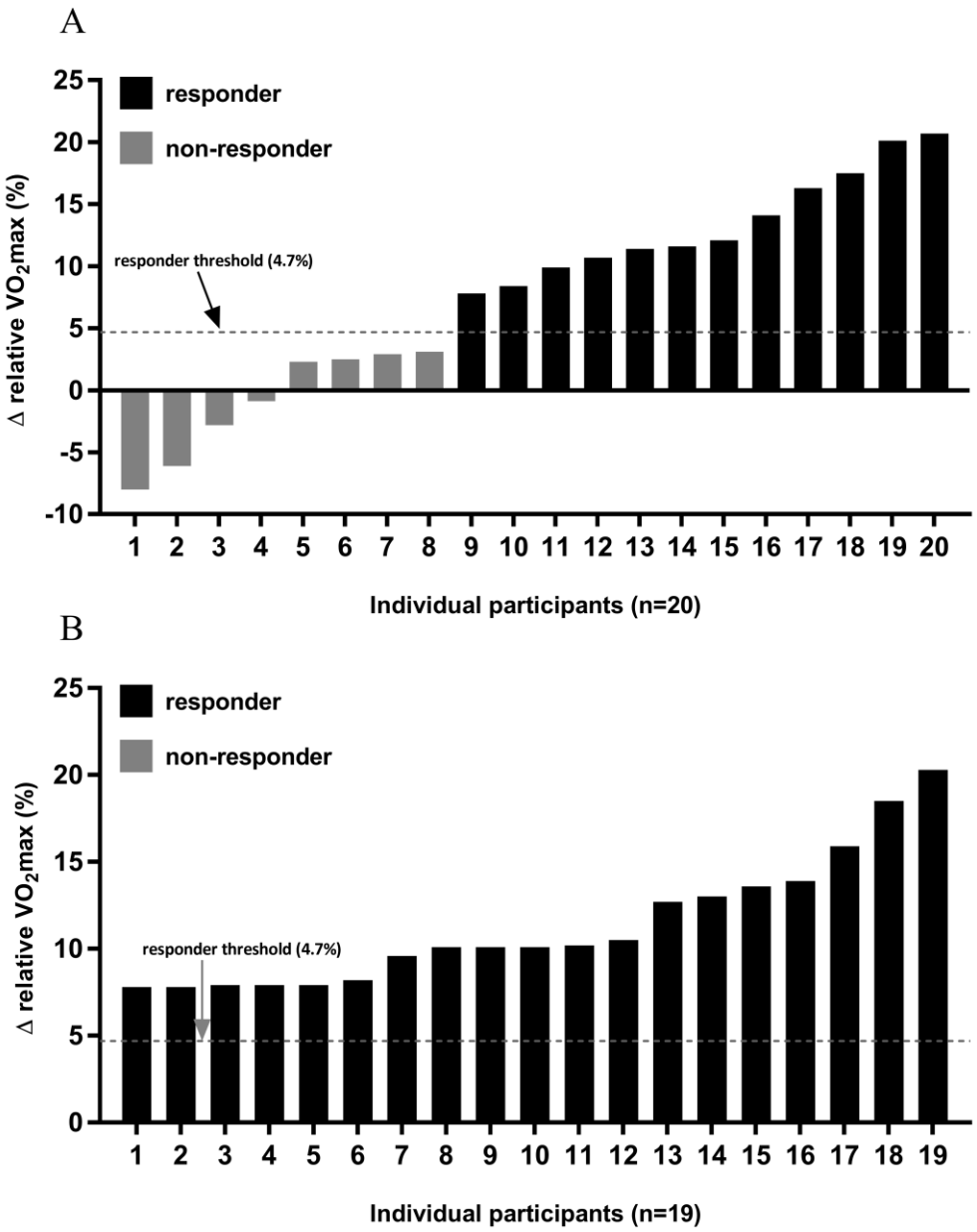

Figure 7.2 Variability in relative VO_2max responsiveness (% change) to 12 weeks of standardised (A) and individualised (B) exercise training. The dashed line indicates the minimum change (Δ > 4.7%) required to be considered a meaningful adaptation in VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$)

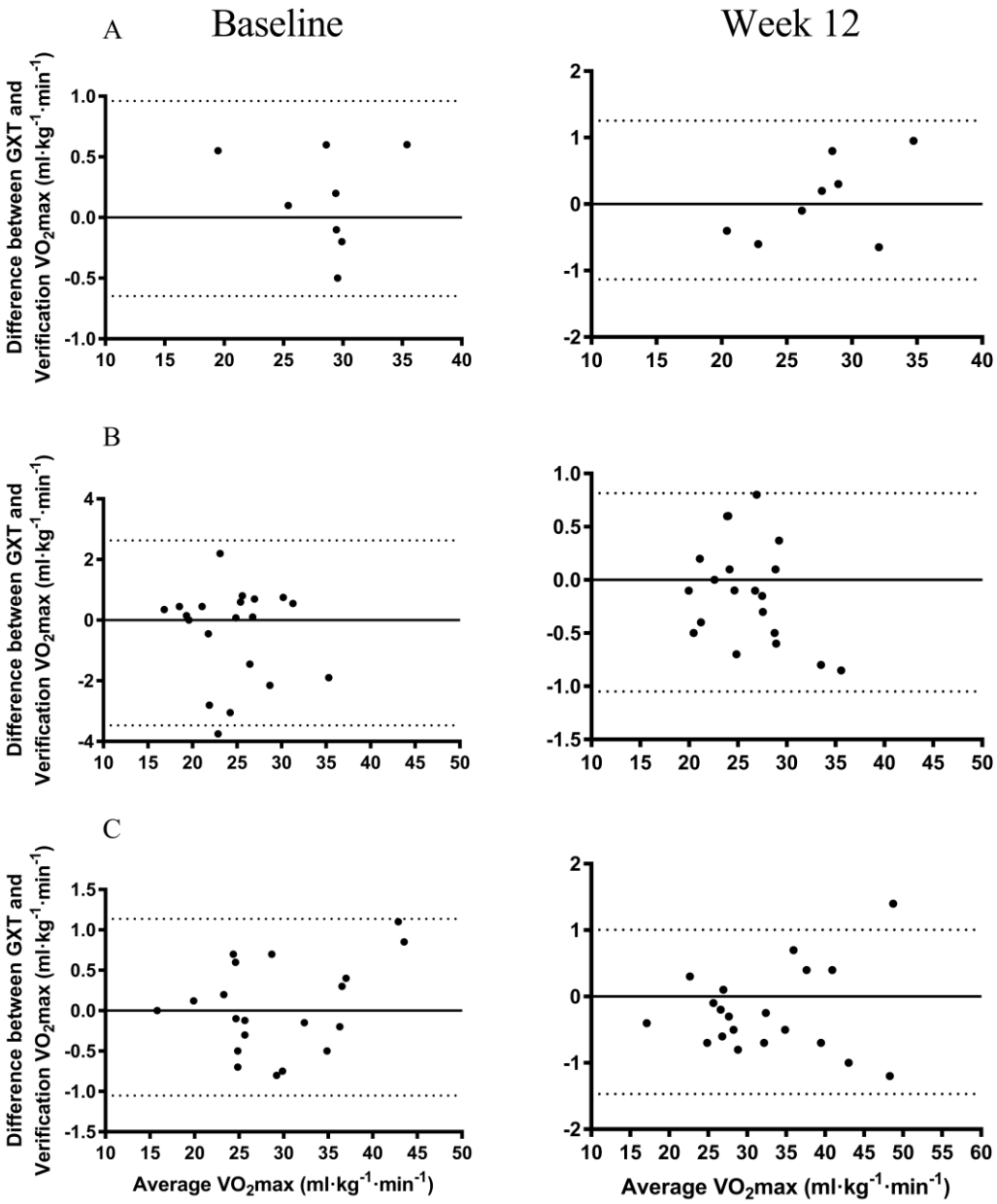

Figure 7.3 Narrowest 95% limits agreement between the GXT and verification protocols at baseline and week 12 for the control (A), standardised (B), and individualised (C) groups. All GXT and verification tests were within ±3.0% (ml·kg^{-1}·min^{-1}). GXT, graded exercise test, VO_2max, maximal oxygen consumption

7.5.2 Prevalence of VO_2max Responders and Non-Responders

The prevalence of responders and non-responders in both standardised and individualised groups are shown in Figure 7.2. In the standardised group, 60% (12/20) of participants were considered responders with a favourable change in VO_2max ($\Delta > 4.7\%$) and 40% (8/20) were considered non-responders with a non-meaningful change in VO_2max ($\Delta \leq 4.7\%$). All participants (19/19) in the individualised group had a desirable change in VO_2max ($\Delta > 4.7\%$) and were categorised as responders. Based on the χ^2 analysis, there was a significant difference in incidence of response ($p = 0.002$) and a large effect (Cramer's $V = 0.50$) of exercise training strategy on VO_2max responsiveness. Age, sex, and baseline VO_2max (absolute and relative) did not have a significant effect on VO_2max responsiveness.

7.5.3 GXT and verification testing

At baseline and 12 weeks, there were only 2 participants in the individualised group that had a greater than ±3.0% difference between the GXT and the verification test. These participants repeated GXT and verification testing on a separate day to confirm attainment of true VO_2max. Therefore, the verification procedure confirmed VO_2max at baseline and post-program in all participants (47/47). The individual differences in relation to their VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) for the GXT and verification testing at baseline and week 12 are presented in Figure 7.3.

7.5.4 Changes in Other Parameters

Following the 12 weeks, changes in BMI, weight, resting HR, and maximal HR were not significantly different within or between either experimental group. However, for the standardised group, there was a significant increase in physical activity from 831±954 to 3660±1629 $MET \cdot min^{-1} \cdot wk^{-1}$ [$t(19) = -5.95$, $p < .0001$] and time spent sitting significantly decreased from 5.6±2.6 to 4.4±2.3 $hours \cdot d^{-1}$ [$t(19) = 2.38$, $p = .028$]. Similar findings were noted for the individualised group with a significant increase in physical activity from 937±587 to 3855±2261 $MET \cdot min^{-1} \cdot wk^{-1}$ [$t(18) = -5.28$, $p < .0001$] and decreased time sitting of 6.3±2.4 to 5.4±2.4 $hours \cdot d^{-1}$ [$t(18) = 2.40$, $p = .027$]. The increase in physical activity reported on the IPAQ at post-program was expected to increase from baseline due to the prescribed exercise intervention accounting for nearly 1830±463 $MET \cdot min^{-1} \cdot wk^{-1}$ and 2647± 892 $MET \cdot min^{-1} \cdot wk^{-1}$ for the standardised and individualised groups, respectively. For the control group, there was only a significant difference in maximal HR of 173.9±12.4 to 170.1±11.1 bpm [$t(7) = 3.12$, $p = .017$]. At post-program,

there were significant between-group differences in physical activity levels [$F(2,44) = 5.583$, $p = .007$] and time spent sitting [$F(2,44) = 4.304$, $p = 0.20$].

7.6 Discussion

To our knowledge, this is the first study to report on the CRF training responses following a standardised and individualised exercise prescription with a cohort specific threshold for VO_2max responsiveness and the inclusion of a verification protocol to identify a true VO_2max. Our innovative data demonstrates that a significant effect of exercise intensity prescription method on the incidence of VO_2max responders occurred with the individualised group eliciting 100% responsiveness whereas the standardised group had a 60% incidence of response. These novel findings underscore the importance of a personalised exercise intensity prescription to enhance training efficacy. At the group level, there was a statistically significant positive change in CRF and no difference between groups. However, at the individual level all participants in the individualised group improved VO_2max greater than the established TE of 4.7% and were considered VO_2max responders, whereas 8 out of 20 participants in the standardised group failed to elicit a percent change in VO_2max greater than 4.7% and were considered to be VO_2max non-responders. These findings highlight the need to consider individual responses when trying to address best practices to identify exercise prescription methods that promote positive training adaptations rather than only reporting group mean and standard deviation. Furthermore, while not statistically significant, there was a 48% greater improvement in the percent change in VO_2max at post-program for the individualised group compared to the standardised group. These changes in cardiorespiratory fitness are indicative of true maximal changes from baseline to post-program due to the incorporation of a verification protocol to confirm a 'true' VO_2max was achieved. These findings provide further insight to the growing body of literature on the importance of personalised or individualised exercise prescription to enhance training efficacy.

Variability in training responsiveness has been linked to the specific exercise prescription and may underpin the individual variability in VO_2max responsiveness following an exercise training intervention (14). For example, in sedentary post-menopausal women, there was an incidence of non-response of 44.7%, 23.8%, and 19.3% when exercising at 50% VO_2max for 6 months at 4, 8, or 12 $kcal \cdot kg^{-1} \cdot wk^{-1}$, respectively (5). These results indicate that with an increase in exercise volume, there will be a subsequent improvement in CRF training responsiveness. However, it should be noted that 17 of 88 participants

were reported as non-responders in the highest training volume group indicating that an even higher training volume may be needed to further increase training responsiveness. Furthermore, Ross and colleagues (48) recently found that CRF non-response was eliminated following 24 weeks of exercise when the intensity was higher (i.e. 75% of VO_2peak) compared to a lower (i.e. 50% VO_2peak) where the incidence of non-response was 17.6% when exercising at a fixed amount of 300 and 600 kcals per session for women and men, respectively, in abdominally obese adults. Moreover, they reported that exercise at the recommended amount per week (i.e. 150 min·wk^{-1}) for 24 weeks at an intensity of 50% VO_2peak is not sufficient for CRF training adaptions and yielded non-response rates of 38.5% and 17.6% when participants exercised close to 30 and 60 minutes, respectively. However, at 16 weeks, there was a 10.3% non-response rate (3 of 29 participants) in the 75% VO_2peak group that showed 100% response at 24 weeks. More recently, Montero and Lundby (40), found that an extra 6 weeks of moderate exercise with an increase in training frequency of 2 days a week can mitigate training non-response. However, it should be noted that the TE for maximal wattage was used as a threshold to establish CRF training responsiveness. Indeed, at the end of the first 6 weeks of training, all participants training for 60 min on 4 days a week were considered CRF training responders based on increases in maximal wattage. However, if this group was evaluated based on VO_2max changes, there would have been 3 out of 17 participants classified as non-responders when using the commonly reported 5% TE for VO_2max (62). Furthermore, at the completion of the second 6-week training period in which 2 more days a week of training were added, all participants become responders and exceeded the TE for wattage max. However, had these participants been evaluated on the change in VO_2max, it appears some of them would not have been considered responders. While the research evidence suggests that both exercise volume and intensity have a direct effect on CRF training responsiveness, the findings of the present study further highlight that the specific prescription approach is also an influential factor in determining individual responsiveness.

Our findings provide further support on the efficacy of a threshold-based model for exercise prescription. The use of relative percent methods to establish exercise intensity (i.e. %HRmax, %HRR, and %VO_2max) have shown large inter-individual variability in VO_2max responsiveness (3,5,48,60,61) and may be due to failing to take into consideration individual metabolic characteristics (14,20,21). For example, when undergoing 60 min of cycling at work rates of 60% and 75% of VO_2max in healthy male participants, there was considerable variability in lactate responses with reported

coefficient of variations of 52.4% and 41.3%, respectively (21). Similarly, it has been shown that when intensity is calculated as a percentage of the individual anaerobic threshold, ranges of 86 to 118% and 87 to 116% have been identified when exercising at 75% of VO_2max and 85% of HRmax, respectively (22). Therefore, heterogeneity in training responsiveness will ultimately result from differences in the overall homeostatic stress during the exercise intervention. Katch and colleagues (20) suggested the use of thresholds as markers of exercise intensity to create consistency in the metabolic stimulus in a heterogeneous population. Furthermore, our findings that VO_2max training responsiveness was superior in the individualised group were consistent with previous findings. Wolpern and colleagues (11) first demonstrated that an individualised approach to exercise prescription using ventilatory threshold markers to establish training intensity elicited greater training responsiveness compared to the HRR method when exercising for 30 $min \cdot d^{-1}$ on 5 $d \cdot wk^{-1}$ for 12 weeks. These findings were again shown in a more recent publication utilising the similar exercise prescription performed 60-75 $min \cdot d^{-1}$ on 3 $d \cdot wk^{-1}$ for 13 weeks, but also incorporating resistance and functional training (12). Interestingly, even though the exercise training volumes were established with differing criteria (i.e. energy expenditure or time) for these previous and the current investigation, the individualised groups had a 100% response rate to the intervention. However, even though all participants in the individualised groups in previous (11,12) and within the current investigation were considered to be responders, there is still variability in overall responsiveness (Figure 7.2). This variability may be due to other factors not accounted for in this investigation (i.e. genetics, sedentary behaviour outside of the exercise training, frequency of interrupting sedentary behaviour, etc.). Future research should explore the relationship between these factors and the variability in CRF responsiveness in known responders.

A higher absolute intensity may be a natural by-product of the threshold-based approach to establishing exercise intensity for an individualised exercise prescription. Indeed, as shown in Figure 7.1, there is a noticeable difference in the absolute exercise intensities between groups. This discrepancy in absolute exercise heart rate intensities in the standardised (Figure 7.1A) and individualised (Figure 7.1C) groups can be directly attributable to the intensity prescription methodology and is an important issue to highlight. It has been suggested that when exercise intensity is anchored to individual ventilatory thresholds it might better normalise the metabolic stimulus for individuals with varying fitness levels (5, 14). However, these same principles are not applied when

using the HRR method. Therefore, by using the HRR method, which is currently among the gold standard methods for prescribing exercise intensity, the overall target exercise intensity may be underestimated for the majority of individuals and overestimated for some others. Nevertheless, it is also plausible that between-group differences in exercise heart rate intensities may have affected the incidence of responders within each treatment group in the present study.

In the present study, participants in the individualised group increased CRF by 1.0 ± 0.5 MET whereas participants from the standardised group experienced only a 0.5 ± 0.5 MET improvement. These findings are comparable to results from other exercise training studies involving previously sedentary adults. For instance, Bateman et al. (129) reported an improvement in METs of 0.94 and 1.05 in untrained, overweight men and women with mild-to-moderate dyslipidaemia, following eight months of aerobic or a combination of aerobic and resistance training, respectively. More recently, in an investigation using similar exercise intensity prescription methodology to the present study, improvements of 0.49 (HRR group) and 1.11 METs (threshold-based group) were observed following 13 wk of aerobic training for 5 $d \cdot wk^{-1}$ at 30 $min \cdot d^{-1}$ (11). Individual maximal CRF and the associated MET value constitutes a potent predictor of CVD prognosis (31). For example, it has been reported that a 1-MET increase in CRF corresponds to 13% and 15% decrements in all-cause mortality and CVD, respectively (130). Accordingly, the differences in CRF improvement in METs in the present study between the individualised and standardised groups represent an important clinical finding as an optimal method of exercise intensity prescription may contribute to a greater potential to mitigate future CVD events.

Methodologically, two novel factors considered in the current investigation were the use of a site- and cohort-specific TE and a verification protocol to confirm a 'true' VO_2max was achieved for all testing sessions. The TE is a conservative approach that takes into consideration the normal day-to-day biological fluctuations and the measurement or assessor error of the testing procedures. When a change in a physiological parameter exceeds the TE in a positive direction, it can be stated that a true and desired change has occurred. However, if there are factors underpinning methodological issues with the testing to establish the TE (i.e. suboptimal criteria to determine VO_2max), the TE will not be an accurate assessment of a true change. For example, Ross and colleagues (48) utilised a cohort specific TE calculated in consistency with the current investigation with a responsiveness threshold of 0.204 $L \cdot min^{-1}$. However, this TE was calculated based on

VO_2peak rather than VO_2max and may not accurately dictate when a true change in CRF occurs. The use of VO_2peak has been criticised in the literature with a change in CRF possibly due to a greater increase in effort from the expectations of improving following an exercise intervention rather than a true increase in CRF fitness (i.e. VO_2max) (49). Moreover, primary and secondary criteria used to determine achievement of VO_2max have also been criticised (46,47). For example, a plateau in VO_2 at the final stages of a GXT has been considered indicative of VO_2max; however, there is inconsistency in the literature regarding criteria for a plateau and a supramaximal verification protocol has been suggested to confirm attainment of a 'true' VO_2max (42). To our knowledge, we are the first to incorporate a verification bout to confirm VO_2max was achieved in the development of our site- and cohort-specific TE. Therefore, it is noteworthy the change in VO_2max in the individualised group exceed the TE in 100% of the participants and elicited true adaptations due to the CRF training intervention.

A review on interindividual differences following an exercise intervention have addressed many methodological and statistical considerations and urged caution with how many investigations have reported the topic (87). Of considerable interest, they highlight that within-subject random variation is inevitable and, in some instances, can account for all of the individual variability in training responsiveness. We have previously demonstrated that different training responsiveness criteria elicit varying percentages of responders and non-responders to changes in VO_2max (128) and this topic has been recently evaluated in more depth (88). These findings challenge the notion that observed response variability is the result of random variation in the measured parameters. Therefore, the criteria to establish responsiveness must be specific to the cohort being studied and take into consideration biological fluctuations and measurement error of employed testing procedures. Atkinson and Batterham (87) also highlight the importance having a comparator arm (i.e. a control group) to quantify true interindividual differences in training response. While these methods are appropriate statistical approaches, there are moral and ethical considerations to be addressed with the use of a control group in an exercise intervention in which there is a removal of a known positive physiological factor to improve health. For example, Hecksteden and colleagues (88) evaluated the effects of endurance training with repeated testing on individual responsiveness over a 1 yr period, but used a control group for only 6 months with reported 'ethical constraints' as the rationale for not having a control for the intervention duration. We believe that using the methods outlined in the current investigation or performing 2 to 3 measurements in all

participants at baseline to establish a site- and cohort-specific TE could minimise or, in some instances, eliminate the use of a control group. Furthermore, we suggest continued work with the use of a TE as the threshold for responsiveness but start to focus on individual levels (i.e. individual TE to establish responsiveness). Training responsiveness is an individual and not a group phenomenon, yet all criteria for responsiveness and training interventions have focused on group factors. Further research is warranted to create consistency and acceptance in the scientific community of methodology to accurately examine training responsiveness at the individual level.

Limitations

Due to the randomisation process, there is the possibility of selection bias with the principle investigator being aware of which treatment group participants were allocated. However, the use of a verification protocol to confirm a true VO_2max likely minimised potential selection bias. Another limitation is training responsiveness was based only on VO_2max. Training responsiveness is a multifaceted area of study and future research should focus on a more comprehensive approach to understanding individual variability with consideration of multiple health parameters. The use of a cohort-developed TE, in this instance, can only be used with the assumption that baseline and post-program TE are indeed the same. Future research should explore whether or not TE changes throughout an exercise intervention. A final limitation was the small sample size for the control group due to difficulties of recruitment and retention of these participants.

Conclusion

Overall, in previously sedentary adults, 12 weeks of aerobic exercise training based on an individualised exercise prescription using ventilatory threshold measures had a greater effect on the incidence of training response compared to a standardised approach using HRR. While the exact mechanisms are still not entirely understood, it is believed that exercise intensity prescribed with the use of ventilatory thresholds takes into consideration individual metabolic characteristics which are overlooked when using relative percent methods (i.e. %VO_2max, %VO_2R, HRR, etc.). The use of a threshold-based model for steady state aerobic exercise intensity prescription should be considered in both research and practical applications.

Chapter 8 - Discussion

8.1 Summary of Research and Practical Applications

This thesis makes a substantial contribution to the fields of exercise physiology, exercise prescription methodology, and applied exercise science regarding individual variability in training responsiveness (i.e. training responders and non-responders). This contribution to the scientific literature was completed through a series of investigations comparing a standardised and individualised exercise intensity prescription. In summary, the following were achieved: identified a practical method to establish a value (i.e. TE) to quantify training responsiveness specific to the group being studied, identified 4-week changes in VO_2max, highlighted the feasibility of using a MetS z-score to understand changes in cardiometabolic factors, and explored individual CRF training responsiveness following a 12-week exercise intervention.

The narrative review in Chapter 2 included a summary of research related to individual variability following steady-state aerobic exercise. There have been a variety of methodologies published with the use of differing criteria to identify a CRF training response, therefore, it is difficult to come to conclusions of the underlying mechanisms associated with the training variability. However, it appears there is not an impact on individual variability of CRF due to baseline age, sex, race, and initial fitness, but it appears that exercise intensity and volume may have a significant interaction with the overall CRF responsiveness. While it has been clearly established in the literature that steady-state aerobic exercise is beneficial for reducing CVD and severity of MetS, there have been minimal investigations on cardiometabolic responsiveness and severity of MetS syndrome. Much of the literature in this area has focused on cardiometabolic adverse response (response in an unfavourable direction more than 2 time the TE).

Chapter 3 presented a detailed description and rationale for the methodology for the thesis. The content within this chapter was originally published in *Trials* but has since been modified and updated to reflect unforeseen changes in the structure of the thesis data collection and statistical analyses. This chapter specifically addressed the participant randomization, exercise prescription intervention, and details related to the day-to-day operations of data collection and analysis.

Chapter 4 was the first experimental chapter and addressed the first aim of the thesis - identification of TE using a cohort and site-specific approach. Indeed, using a sub-group of the main participant population, a TE error was successfully established with repeated testing at baseline. In summary, participants completed baseline testing (anthropometric, VO_2max, and blood profile measures) on two occasions no sooner than 24 hours and within a 1-week period. Data from the averaged VO_2max values between the GXT and verification protocol were analysed, and a CV was determined. In order to have a conservative approach, the CV and measurement error were combined to get a TE of 7.7% (this was later modified in Chapter 7 based on the inclusion of measurement error twice in the original calculation). Then, to show the impact of the criteria used to dictate training responsiveness, a retrospective analysis of two previously published investigations (both of which were completed in our laboratory and, therefore, an appropriate target cohort for a site-specific approach) were completed to highlight differences in training responders and non-responders comparing two commonly reported values of $\Delta > 0$, $\Delta > 5.6\%$ for and the established TE of $\Delta > 7.7\%$, all in respect to change in VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$). Data from this chapter identifies two critical components to the topic of individual variability and CRF responsiveness following steady-state aerobic exercise: 1) the specific criteria used to establish training responsiveness can overestimate, underestimate, or accurately assess responders and non-responders and 2) the criteria used to determine training responders and non-responders must be specific to both the population being analysed and the specific location in which testing and training occurs. Moreover, these findings have provided insight on future directions of research including identifying a more individualised method to establish training responsiveness. Essentially, if training responsiveness is an individual phenomenon and training interventions are focusing more on prescriptive criteria based on individual factors (i.e. personalised medicine), then it would only make sense to have a responsiveness criterion that is specific to every individual participant rather than using group standards.

The objective of Chapter 5 was to identify and understand the overall changes in VO_2max at 4 week increments throughout the duration of the 12-week exercise training study. An understanding of the 'window of time' that is sufficient to elicit meaningful changes in CRF will provide critical insight into when changes occur. Often, research investigations or exercise programs conducted outside of research only focus on pre- and post-intervention outcomes. While these are both important, there is often a lack of oversight as to when the changes did or did not occur. For a more practical application, for example,

if a sedentary individual starts a 12-week exercise training intervention and has a 20% improvement in cardiorespiratory function at the completion of the program, there is not an understanding as to when the 20% was achieved. If the 20% improvement occurred at week 8, would that indicate the last 4 weeks of training were not prescribed accurately or with enough precision to continue to see further improvements? Conversely, if that same person would have had a lack in response at 12 weeks, having knowledge of when changes should be seen would allow for the exercise professional to modify the exercise prescription prior to the 12^{th} week to enhance the overall training responsiveness. Indeed, result from Chapter 5 provide insight into these changes. The findings indicate that, while not statistically significant, there appears to be a more rapid and potent improvement in VO_2max in the individualised group compared to the standardised with increases of 3.7±7.3% and 1.7±6.7%, respectively, at week 4. Furthermore, both groups experienced a significant improvement in VO_2max at week 12 compared to baseline, there was a 48% higher improvement in the average percent change in the individualised group compared to the standardised group. Therefore, I believe the evidence shows that an individualised exercise intensity prescription is superior in eliciting greater changes at early time points and following 12 weeks of exercise training.

It has generally been accepted that a person can be a responder to one measure, but not others. Therefore, the purpose of Chapter 6 was to identify the feasibility of using a MetS z-score to more comprehensively analyse changes in cardiometabolic risk factors. Following the 12-week exercise intervention, both groups significantly improved cardiometabolic profiles with a reduction in MetS z-score from -2.0±3.1 to -2.8±2.8 and -3.3±2.3 to -3.9±2.2 for the standardised and individualised groups, respectively. However, there was not a statistically significant difference in MetS z-score severity between the two groups. Similarly, there was also not a difference between the individual responsiveness (i.e. responders and non-responders) between groups with 63% (12/19) and 58% (11/19) of participants having a favourable change in MetS z-score ($\Delta > 0.6$) for the standardised and individualised groups, respectively. It is believed that a greater between group difference and individual difference were not seen due to the overall health status of participants at baseline. However, there were some interesting trends that should be highlighted. As shown in Table 6.2, it appears that a higher percentage of participants categorised as non-responders in the individualised group were healthy with fewer MetS risk factors at baseline and at post-program (i.e. 2 of 7 compared to 6 of 8 participants in the standardised and individualised groups, respectively, had no MetS risk factors at

baseline). Similarly, Table 6.3 shows participants can be labelled as non-responders with unfavourable changes occurring in MetS criteria, even though the measures remain in a healthy range. It is believed these two factors may have been confounding variables for the overall results of the investigation, rather than the exercise intervention itself. However, while the results did not support the original hypothesis, I believe there is merit to further investigate this topic. If I had originally recruited participants that specifically had MetS or at least 2 or more MetS factors, I believe there would have been a greater response in mitigating MetS severity for the individualised group compared to the standardised group.

Chapter 7 addressed the primary aim of this PhD thesis with the investigation of the overall CRF training responsiveness following an exercise intensity prescription based on the relative percent method (standardised approach using HRR) and a more individualised method (anchoring intensity based on VT1 and VT2). As hypothesised, the individualised method provided superior results with all participants (100%; 19/19) categorised as a CRF responder whereas only 60% (12/20) in the standardised group increased VO_2max ($ml \cdot kg^{-1} \cdot min^{-1}$) enough to break the 4.7% threshold needed to be considered a responder. Furthermore, based on percent increases in relative VO_2max, the individualised group had a much lower group standard deviation of change (i.e. 3.7% compared to 8.3%, as shown in Table 7.3). This finding points to the individualised group having a more personalised exercise prescription with more consistent increases in VO_2max for the group as a whole in comparison to the standardised group.

The findings from Chapter 7 are even more insightful since the VO_2max testing utilised a verification protocol to confirm maximal values were reached. This was a novel factor for the thesis since, to my knowledge, this has not been previously reported when analysing CRF responsiveness following steady-state aerobic exercise. Ensuring that a maximal aerobic value is achieved when identifying changes due to modifying or differing exercise prescription is imperative to understand true changes occurring from the intervention and not owing to how aerobic capacity is measured. Unfortunately, VO_2peak rather than VO_2max has been reported as a common aerobic outcome measure, for a variety of reasons (more information has been presented in Chapter 2 and Chapter 5), but may not directly indicate that aerobic adaptations have occurred due to the lack of sensitivity of this measurement (47). Therefore, with the use of a verification protocol, I am confident that all VO_2max data are representative of true maximal capacity and any changes in VO_2max are indicative true training adaptation.

While results from Chapter 7 need to be replicated and further research is warranted prior to changing the suggested guidelines for exercise intensity prescription, I believe these results highlight the importance of an individualised exercise intensity prescription and these methods can be incorporated by exercise professionals practicing in the field. The use of a metabolic cart (i.e. assessing expired air and gas exchange data during a GXT) would be considered the most accurate way to determine VTs, however, the use of the 'talk test' could be warranted when advanced laboratory techniques are not available (131). The 'talk test' would allow for the VTs to be estimated and used as anchor points for establishing the exercise intensity, similar to methods in this thesis. The 'talk test' would be low cost and available in almost all exercise settings. Furthermore, when using the VTs to establish intensity, especially when increasing VO_2max is not the main objective of the exercise program, then reaching volitional fatigue during the GXT would not be needed. Instead, the test could be stopped once the VT2 is reached. Moreover, this practice could also be used in participants in which maximal exercise testing is not warranted (i.e. clinical setting or elderly) to ensure they have an exercise intensity prescription that is established based on individual metabolic characteristics rather than relative percent concepts derived from maximal values.

8.2 Study Limitations

The studies within this PhD thesis have several limitations that have assisted to guide direction for future research. One of the original inclusionary criteria may have actually contributed to one of the main limitations of the research for this PhD thesis. The participants who were recruited for the investigations had a large age range (30 to 70 years) and, therefore, were not a homogenous group to study. However, the data may be more generalizable to a 'real world' scenario or capture the participant demographics of a community exercise program. Furthermore, men were underrepresented, accounting for only 23% of the participants. Next, a potential risk for selection bias existed in this thesis as the principle investigator (i.e. me) was aware of which treatment group to which participants were allocated. However, the application of the verification protocol likely minimised any potential selection bias due to its robustness for verifying 'true VO_2max.'

After the completion of the baseline testing, experimental participants were randomised to either the individualised or standardised groups at a 1:1 ratio using a computerised stratified minimization sequence. This method of randomization caused a considerable limitation with there being a significant difference in baseline VO_2max values. However,

the individualised group had a higher VO_2max to start, so in theory, they had decreased potential to improve CRF. In future research, participants should be randomised to increase similarity in various baseline measures (i.e. age, sex, baseline VO_2max) across treatment groups.

The use of a GXT and verification protocol to identify a 'true VO_2max' within these studies using the most current guidelines for gold-standard exercise testing. However, some limitations exist with these protocols. The criteria used to determine a 'true VO_2max (i.e. less than 3.0% difference between the GXT and verification protocol) was based on a measurement error of the metabolic analyser from previous literature. The specific metabolic analyser used for data collection was not tested for measurement validity and reliability. While it is not believed to be different from previous literature, the measurement error may not be ±3.0% for this specific analyser and, therefore, the criteria used to confirm VO_2max may be under- or over-estimated.

Within the original calculation of the TE in Chapter 4, the measurement error was counted twice. Instead of 7.7% for a cohort-specific TE, this value should have been 4.7% for changes in VO_2max. However, after completing subsequent statistical analyses using the updated TE value, there was no change in the statistical outcomes or impact of the findings in Chapter 4.

When analysing the time course changes (Chapter 5), an *a priori* power calculation was not performed to ensure a sufficient number of participants were included due to the preliminary and explorative nature of the study and the limited amount of previous research on the topic. The data used to analyse the site- and cohort-specific TE, therefore, may be underpowered. Similarly, when developing a TE at baseline to use as a threshold to quantify training responsiveness, it must also be assumed that the TE at post-program is the same. Within this thesis, I operated under this assumption and this may not actually be the case. However, to my knowledge, there has not been previous research identifying the similarities or differences in baseline versus post-program TE. Furthermore, within this same chapter, the group in which the TE was created (i.e. participants for the thesis studies) were not the same population that were retrospectively analysed. However, all three of the groups were close in individual characteristics and all participants completed the exercise testing/interventions in the same laboratory.

Within Chapter 6, there were several limitations when evaluating the feasibility of using a MetS z-score with this population and following these methods of exercise intensity interventions. Since the main aim of this thesis was not to investigate MetS, there was not an emphasis on recruiting participants with known MetS or 2 or more factors associated with MetS. Therefore, there was an overall lack of participants with known MetS in both groups, however, many participants in both groups had at least 1 or more cardiometabolic risk factors at baseline. Similarly, since this was not the main objective of the research, there were many lifestyle and psychological factors that were not accounted for and could have had an impact on the overall findings (i.e. diet, sleep quality, psychological stress, and duration of sedentary behaviour). Lastly, while dietary intake was analysed to note any significant changes in pre- to post-intervention, there was not a standardised dietary protocol prior to blood analysis which may have accounted for some of the changes in individual blood profiles.

One of the main overarching limitations to this thesis is based on the concept of 'training responsiveness'. It has been shown previously and data from this thesis suggest that training responsiveness should not be based on a single factor and is more of a multifaceted phenomenon and may be due to a variety of factors (i.e. exercise intensity prescription, lifestyle behaviours, dietary intake, psychosocial influence, etc.). However, within this thesis, I separated cardiometabolic risk factors and CRF to quantify training responsiveness within each of these categories. While this is a limitation, this methodology also helps to guide future research and provide an understanding of how changes in method of exercise intensity prescription has an impact on both cardiometabolic and cardiorespiratory factors.

8.3 Future Research Directions

Due to the findings and the overall limitations of this thesis as a whole, there are numerous considerations for future research. First, an understanding of differences in pre- to post-intervention changes in the TE and MetS z-score is needed. When using only the baseline TE to quantify VO_2max training responsiveness and the baseline MetS z-score for MetS severity, there is an underlying assumption that post-intervention values are indeed the same. However, to my knowledge, this has not been shown in previous research.

With the notion of exercise being personalised medicine and the main theme of this PhD emphasising the use of an individualised method of exercise intensity prescription, future

research should explore the use of an individualised TE to establish training responsiveness. If training variability is analysed on an individual level, the TE that dictates responsiveness should also be individualised. Future research should focus on differences between group-established TE and individually-establish TE, and how it relates to training responsiveness. Indeed, it may be that participants categorised as a training non-responder have a lower individual threshold (i.e. transitional point from non-responder to responder) for meaningful changes compared to the threshold established as a group and, therefore, could be responsive based on their own individualised TE.

Since training responsiveness is more comprehensive than just based on one factor, future research should explore how to compare all factors at once. For example, developing a process to incorporate all anthropometric, cardiometabolic, and cardiorespiratory measurements to assess training responsiveness at the group and individual level.

Lastly, the research within this thesis was only the third time this specific VT methodology was reported in the literature. Therefore, there is an overall lack in understanding as to how both thresholds (i.e. VT1 and VT2) are changed following a standardised or individualised methodology of exercise intensity prescription. There should also be an emphasis on determining the best exercise progression for the VT method. The research for this thesis and those previously reported utilise a larger target HR zones (target zone between 10 to 15 bpm) and it is not well understood if a smaller and more precise target HR zone for intensity could be used to further the VO_2max training responsiveness.

8.4 Conclusion

This thesis details the importance of individualising method of exercise intensity prescription with the use of the first and second VTs as anchors for HR intensity in comparison to standardised methods using HRR. In summary, it was found that when VT markers were used for method of exercise intensity prescription, there was an optimal increase in the overall training responsiveness with all participants categorised as a 'responder' based on a site- and cohort-specific TE. Furthermore, while the results were not significant, there was a larger increase VO_2max in the individualised group at week 8 of a 12-week intervention in comparison to the standardised group. Similarly, while not statistically significant, there appears to be trends indicating that an individualised approach has a greater impact on reducing MetS severity. Therefore, this body of work

provides strong evidence for the use of an individualised method of exercise intensity prescription in sedentary adults at low-to-moderate risk for CVD.

Through addressing the overreaching research question, '**Does an individualised exercise intensity prescription elicit a greater training responsiveness when compared to a standardised approach?**' this thesis contributes new knowledge related to exercise physiology, exercise prescription, and the area of individual variability following steady-state aerobic exercise training. The wider implications of this research may help to improve the overall effectiveness of exercise interventions within community-based exercise programs for adults at low-to-moderate risk for CVD. The principles and concepts addressed in this thesis should be considered when developing exercise programs or designing experimental studies to enhance the overall training responsiveness and effectiveness of steady-state aerobic exercise.

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8.5 Appendix A: AUTEC approval for the incidence of training responsiveness study

AUTEC Secretariat

Auckland University of Technology
D-88, WU406 Level 4 WU Building City Campus
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

1 August 2016

Nigel Harris
Faculty of Health and Environmental Sciences

Dear Nigel

Re Ethics Application: **16/264 The incidence of training responsiveness (responders and non-responders) to cardiorespiratory fitness and cardiometabolic measures after individualised and standardised exercise prescription.**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 1 August 2019.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 1 August 2019;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 1 August 2019 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Ryan Weatherwax, rweatherwax@western.edu

8.6 Appendix B: Western State Ethics approval for the incidence of training responsiveness study

From: Lance Dalleck
Sent: Tuesday, July 5, 2016 6:18 AM
To: Ryan Weatherwax
Cc: Institutional Review Committee; Lance Dalleck
Subject: Re: Decision on application HRC2016-01-90R6

Dear Mr. Ryan Weatherwax-

Your application has been reviewed and approved by the Human Research Committee:

Please remember to submit the documents to close the study once it is completed per the instructions on the Human Research Committee website (http://www.western.edu/academics/academic-affairs/institutional-research/human-research-committee).

Please cite your internal tracking number (HRC2016-01-90R6) in all future correspondences.

Regards,
Lance Dalleck

Lance Dalleck, PhD
Associate Professor of Exercise and Sport Science
Coordinator, Celebration of Scholarship
Chair, Human Research Committee
Director, Center for Wellness and Human Performance
Western State Colorado University

970.943.7132
ldalleck@western.edu

8.7 Appendix C: Participant Information Sheet (Experimental Group)

Participant Information Sheet

Date Information Sheet Produced:

07 July 2016

Project Title

The incidence of training responsiveness (responders and non-responders) to cardiorespiratory fitness and cardiometabolic measures after individualized and standardized exercise prescription

An Invitation

My name is Ryan Weatherwax and currently a lecturer of Exercise and Sport Science at Western State Colorado University. Currently, I am working toward a Doctor of Philosophy (PhD) through Auckland University of Technology (AUT) in New Zealand. I am doing a research project that investigates the incidence of response (responders and non-responders) to cardiorespiratory fitness training – more explained later in this letter. Your participation in the research is entirely voluntary and you may withdraw at any time, even before all the data has been collected. If you withdraw, or choose not to participate, your referral, interest, or eligibility into the Wellness Elevated program will not be affected in any way.

This research will need men and women ages of 30 to 75, considered low-to-moderate risk for cardiovascular disease, currently sedentary (participating in less than 30 min of moderate intensity physical activity on at least three days a week), have been living at an altitude near 2350 m (about 7700 ft) for at least 6 months, and interested in participating in the Wellness Elevated community-based exercise program.

What is the purpose of this research?

Some people seem to respond well to fitness training, others not. We seek to provide some clarity on why. Traditionally, a standardized approach to exercise prescription (determining the quantity, volume, and frequency – similar to the procedures of determining a drug prescription) has utilized percentages of maximal heart rate or maximal aerobic ability, to some extent, to quantify exercise intensity. This approach fails to consideration individual metabolic responses to exercise. Therefore, we will be investigating a more individualized approach compared to the commonly used methods to determine if individualizing the exercise prescription increases the training response rate.

The overall purpose of this research is to identify if an individualized approach to exercise prescription is superior to the standardized approach (used commonly in research and everyday use) in decreasing the non-response rate to exercise-based criteria (maximal aerobic capability and cardiometabolic factors). If exercise is prescribed (similar to a medication) individually, we believe the response rate to the exercise intervention will be greatly improved.

One secondary purpose of this research is to investigate the changes that occur every 4th week to maximal aerobic capability and cardiometabolic factors. By understanding the differences, if they exist, between these two exercise interventions during a 12-week period, it will allow exercise physiologists more knowledge in how individuals adapt to exercise.

The last secondary purpose of this research is to investigate participants classified as a ‘non-responder’ to 12 weeks of structured exercise and see if they become a ‘responder’ after a second 12-week intervention with a different intensity prescription.

Data obtained from the study will be used to write my PhD thesis document, to write academic papers, and give verbal professional presentations. Your name or identifying information will not be used in any of these documents.

How was I identified and why am I being invited to participate in this research?

You were identified for this research project by one of two methods: 1) You have been referred or referred yourself to the Wellness Elevated program or 2) You have responded to the advertisements for the research study posted online and throughout the Gunnison Valley.

What will happen in this research?

In order to be accepted into this study, you must first have a medical history and general questionnaire document completed or medical history file submitted from your general physician. Viewing these documents will help to determine whether you meet the inclusion criteria listed above.

Once you have been referred or show interest in participating in the study, you will be contacted by phone to set up an initial consultation to go over details related to the study and provided an informed consent document to complete. After answering any questions you may have and completion of the informed consent document, if you are eligible to participate in the study a time for a baseline assessment will be scheduled.

Baseline Assessment

Conducted in the High Altitude Performance Lab at Western State Colorado University and should take no more than 1.5 hours to complete.

You will be instructed to maintain your normal nutritional habits throughout the study, but will need to refrain from all food and drinks, other than water, and strenuous exertion for 12 hours prior to testing time. Upon arrival to the lab, your height, weight, and waits circumference will be measured. You will then have resting heart rate and blood pressure taken after 5 minutes of seated rest. After completion of these assessments, a small needle will be used to poke the tip of finger and obtain a small blood sample to analyse your blood glucose, total cholesterol, HDL, and LDL measurements. After completion of these tests, you will be able to eat a small snack prior to the exercise testing.

In order to determine your fitness level and gather data to prescribe the exercise intensity, you will complete a maximal exercise test on a treadmill. You will walk or jog at a self-selected pace for the duration of the test. After each minute, the incline of the treadmill will be increased by 1%. You will be encourage to walk or jog for as long as you can and, ideally, until fatigue. In order to gather data on the test, you will be required to wear a mouth piece and nose clip to ensure all exhaled air is captured. There will be a blood pressure cuff attached to your left arm and periodically throughout the test, your blood pressure will be measured. When the test is completed (you stop the test when you can no longer go further or want to end the test), there will be 20 minutes of recovery in which you will be able to walk, lightly cycle, or sit. After the 20 minute rest, you will complete a 2-3 minute test that will be similar to the end of the completed test. During this portion of the test, you will be asked to do the same as before – go as long as you possibly, but the test is ended when you indicate you are done. The exercise test may cause light headedness, shortness of breath and/or muscular fatigue.

Experiment Protocol

You will then be randomized to one of two exercise training groups:

- Group one: Traditional exercise prescription
    - 3 days a week of aerobic exercise in the Wellness Elevated program on the treadmill, cycle, elliptical, or rower
    - Exercise intensity will be determined using your heart rate (pulse)
    - Exercise will progressively become more challenging as your body adapts to the intervention during the subsequent weeks
- Group two: Individualized exercise prescription
    - 3 days a week of aerobic exercise in the Wellness Elevated program on the treadmill, cycle, elliptical, or rower
    - Exercise intensity will be determined by calculated utilizing more detailed information we get from the fitness testing process
    - Exercise will progressively become more challenging as your body adapts to the intervention during the subsequent weeks

The duration of the study is 12 weeks. During the study, you will complete the testing done during 'baseline assessment' protocol (outlined above) every 4th week. These testing sessions will count toward one of your exercise days and your weekly expenditure goals. All testing and exercise sessions will occur in the High Altitude Performance Lab and the Fitness Center at Western State Colorado University. The program will involve the above mentioned information and flexibility and strength training that occur during the Wellness Elevated program. Exercise sessions will be monitored by an exercise physiologist, student of the Exercise and Sport Science program, graduate student in the High Altitude Exercise Physiology program, or a combination of these.

At the completion of the 12-week intervention, will be categorized as a responder or non-responder as it relates to maximum aerobic capability. If you are considered a responder, you will have completed the study and will have the option to continue participating in Wellness Elevated. If you are considered a non-responder, you will be asked to complete a second 12-week intervention in which the exercise intensity will change to the other experimental group. This will help us understand whether a 'non-responder' can become a 'responder' with a different intensity protocol.

What are the discomforts and risks?

The face-to-face meetings and assessment sessions take place in a semi-private consultation room and laboratory, but I may have a student with me to help with the note-taking. All information is treated as confidential and information is recorded on documentation that will NOT have your name on it (just a research code). I will be asking you questions related to your medical conditions (reading from your medical records or information from the medical history document), medications and activity levels - so that I get a better understanding of your lifestyle and medical history.

Exercise and exercise testing can be dangerous. However, every measure is taken to minimize the risk of injury during the exercise tests and exercise training. There is a 1 in 10,000 risk of death during a graded exercise test. Staff are trained in first aid, a defibrillator and direct phone line is in the room in the case of an emergency. During the blood sample and testing you may experience some discomfort with a slight poking feeling just prior to a sample taken and there may be a small amount of bruising on the finger.

The exercise training and exercise test may cause light-headedness, muscular fatigue and/or shortness of breath. By following the exercise recommendations of the researcher and having a thorough warm up and cool down, your risk will be minimized.

What are the benefits?

- The potential benefits to you include:
- improved aerobic and cardiometabolic health
- enhanced understanding of health-related concepts
- 12-week supervised and monitored individualized exercise program
- regular blood pressure and cardiometabolic checks
- regular maximal aerobic capacity testing
- understanding of the effects of exercise on aerobic and cardiometabolic measurements
- knowledge, experience and confidence to continue with independent application of regular exercise training
- The research will benefit me by providing me with:
- understanding of the incidence of response to VO_2max and cardiometabolic factors to the two types of exercise training regimes
- evidence of which of the two training regimes leads to a greater incidence of response
- evidence of whether non-responders to VO_2max can become responders when the exercise intensity prescription is modified for a subsequent 12-week period.
- evidence of the interrelatedness of diabetic markers (glucose control) with diabetic complication variables
- data for a PhD Thesis and academic journal articles
- There is potential for a wider-community understanding to:
- the attenuation of non-responders to cardiorespiratory fitness training
- a reduction in both the future morbidity and mortality rates
- a reduction in the associated health care expenses

What compensation is available for injury?

In the rare event of an injury during testing or while exercising, standard emergency procedures will be followed. The exercise testing facility is located within a few minutes of several agencies providing emergency treatment. If you need emergency care while you are at the research site, it will be provided to you. If you get injured when you are not at the research site, you should call your doctor or call 911 in an emergency. If your injury could be related to the research, tell the doctors or emergency room staff about the research study, the name of the Principal Investigator, and provide a copy of this consent form if possible. Call the principal investigator, Ryan Weatherwax at 970-943-2104, as soon as you can.

There are procedures in place to help attend to your injuries or provide care for you. Costs associated with this care will be billed in the ordinary manner, to you or your insurance company. However, insurance companies, Medicare, and Medicaid may not pay bills that are related to research costs. You should check with your insurance about this and talk to the Principal Investigator if you have concerns.

How will my privacy be protected?

Due to the nature of this study, you may be exercising in an environment with other members from the study. Therefore, we cannot guarantee that your identity will be kept anonymous throughout the study. Please note that no research participant will be able to see or access any personal information. To ensure your safety when exercising, students and faculty members delivering your exercise will be informed of relevant information that may influence how you respond to exercise. Any data collected and displayed in results would be displayed in a way which does not disclose your identity. Each participant will be given an alphabetical and numerical code. The format of the code will be the first initial of the participant's first name and the first 3 letters of their last name, along with a 3-number code. Only the primary researchers will have access to the codes and the identity of the subjects. The sheet with names and code-numbers will be kept in a separate and secure filing cabinet at Western State Colorado University.

What are the costs of participating in this research?

Since this research is involving participants of the Wellness Elevated program, there is a few of $150 (standard enrolment fee per semester for the program). If you decided to opt out of the research project, but still would like to be a participant in Wellness Elevated, there will still be a $150 fee.

What opportunity do I have to consider this invitation?

You will be given a week from our first face-to-face meeting to talk to your family before needing to decide on accepting (or not) the invitation.

How do I agree to participate in this research?

Your participation in this research is voluntary (it is your choice) and whether you choose to participate will neither advantage nor disadvantage you. You are able to withdraw from the study at any time. If you choose to withdraw from the study, then you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used. However, once the findings have been produced, removal of your data may not be possible.

Will I receive feedback on the results of this research?

You will receive written individual feedback for each of the health measures used in the study. On completion of data analysis and dissemination, participants will be given a copy of the research paper with a cover paper highlighting main findings for the lay-public.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Dr. Nigel Harris, at nigel.harris@aut.ac.nz or (09) 921 9999 x 7301. This is an international call, so you must first dial 011 to exit the US numbers, then 64, and finally 1 followed by the above number.

Concerns regarding the conduct of the research should be notified to the Executive Secretary of AUTEC, Kate O'Connor, ethics@aut.ac.nz , (09) 921 9999 ext 6038. This is an international call, so you must first dial 011 to exit the US numbers, then 64, and finally 1 followed by the above number.

For local inquires into this study, please contact the following:

Any concerns regarding the nature of this project should be notified in the first instance to the Local Project Supervisor, Dr. Lance Dalleck, at ldalleck@western.edu or (907) 943 7132.

Concerns regarding the local conduct of the research should be notified to the Western State Colorado University Human Research Committee Chair, Lance Dalleck, ldalleck@western.edu, (970) 943 7132.

Whom do I contact for further information about this research?

Please feel welcome to contact me or my project supervisors should you have any questions.

Researcher Contact Details:

Ryan Weatherwax
rweatherwax@western.edu
(970) 943 2104

Project Supervisor Contact Details:

Dr. Nigel Harris
nigel.harris@aut.ac.nz
(09) 921 9999 x 7301

Dr. Lance Dalleck
ldalleck@western.edu
(970) 943 7123

Approved by the Auckland University of Technology Ethics Committee on August 1st, 2016, AUTEC Reference number 16/264.

Approved by the Western State Colorado University Institutional Review Board on July 5th, 2016, HRC Reference number HRC2016-90RS

8.8 Appendix D: Participant Information Sheet (Control Group)

Participant Information Sheet

Date Information Sheet Produced:

07 July 2016

Project Title

The incidence of training responsiveness (responders and non-responders) to cardiorespiratory fitness and cardiometabolic measures after individualized and standardized exercise prescription

An Invitation

My name is Ryan Weatherwax and currently a lecturer of Exercise and Sport Science at Western State Colorado University. Currently, I am working toward a Doctor of Philosophy (PhD) through Auckland University of Technology (AUT) in New Zealand. I am doing a research project that investigates the incidence of response (responders and non-responders) to cardiorespiratory fitness training – more explained later in this letter. Your participation in the research is entirely voluntary and you may withdraw at any time, even before all the data has been collected. If you withdraw, or choose not to participate, your referral, interest, or eligibility into the Wellness Elevated program will not be affected in any way.

This research will need men and women ages of 30 to 75, considered low-to-moderate risk for cardiovascular disease, currently sedentary (participating in less than 30 min of moderate intensity physical activity on at least three days a week), have been living at an altitude near 2350 m (about 7700 ft) for at least 6 months, and interested in participating in the Wellness Elevated community-based exercise program.

What is the purpose of this research?

Some people seem to respond well to fitness training, others not. We seek to provide some clarity on why. The overall purpose of this research is to identify if an individualized approach to exercise prescription is superior to the standardized approach (used commonly in research and everyday use) in decreasing the non-response rate to exercise-based criteria (maximal aerobic capability and cardiometabolic factors). If exercise is prescribed (similar to a medication) individually, we believe the response rate to the exercise intervention will be greatly improved.

Data obtained from the study will be used to write my PhD thesis document, to write academic papers, and give verbal professional presentations. Your name or identifying information will not be used in any of these documents.

How was I identified and why am I being invited to participate in this research?

You were identified for this research project by one of two methods: 1) You have been referred or referred yourself to the Wellness Elevated program or 2) You have responded to the advertisements for the research study posted online and throughout the Gunnison Valley.

What will happen in this research?

In order to be accepted into this study, you must first have a medical history and general questionnaire document completed or medical history file submitted from your general physician. Viewing these documents will help to determine whether you meet the inclusion criteria listed above. You will be contacted by phone to set up an initial consultation to go over details related to the study and provided an informed consent document to complete. After answering any questions you may have and completion of the informed consent document, if you are eligible to participate in the study a time for a baseline assessment will be scheduled.

Baseline Assessment

Conducted in the High Altitude Performance Lab at Western State Colorado University and should take no more than 1.5 hours to complete.

You will be instructed to maintain your normal nutritional habits throughout the study but will need to refrain from all food and drinks, other than water, and strenuous exertion for 12 hours prior to testing time. Upon arrival to the lab, your height, weight, and waits circumference will be measured. You will then have resting heart rate and blood pressure taken after 5 minutes of seated rest. After completion of these assessments, a small needle will be used to poke the tip of finger and obtain a small blood sample to analyse your blood glucose, total cholesterol, HDL, and LDL measurements. After completion of these tests, you will be able to eat a small snack prior to the exercise testing.

In order to determine your fitness level and gather data to prescribe the exercise intensity, you will complete a maximal exercise test on a treadmill. You will walk or jog at a self-selected pace for the duration of the test. After each minute, the incline of the

treadmill will be increased by 1%. You will be encouraged to walk or jog for as long as you can and, ideally, until fatigue. In order to gather data on the test, you will be required to wear a mouth piece and nose clip to ensure all exhaled air is captured. There will be a blood pressure cuff attached to your left arm and periodically throughout the test, your blood pressure will be measured. When the test is completed (you stop the test when you can no longer go further or want to end the test), there will be 20 minutes of recovery in which you will be able to walk, lightly cycle, or sit. After the 20-minute rest, you will complete a 2-3-minute test that will be similar to the end of the completed test. During this portion of the test, you will be asked to do the same as before – go as long as you possibly, but the test is ended when you indicate you are done. The exercise test may cause light headedness, shortness of breath and/or muscular fatigue.

What are the discomforts and risks?

The face-to-face meetings and assessment sessions take place in a semi-private consultation room and laboratory, but I may have a student with me to help with the note-taking. All information is treated as confidential and information is recorded on documentation that will NOT have your name on it (just a research code). I will be asking you questions related to your medical conditions (reading from your medical records or information from the medical history document), medications and activity levels - so that I get a better understanding of your lifestyle and medical history.

Exercise and exercise testing can be dangerous. However, every measure is taken to minimize the risk of injury during the exercise tests and exercise training. There is a 1 in 10,000 risk of death during a graded exercise test. Staff are trained in first aid, a defibrillator and direct phone line is in the room in the case of an emergency. During the blood sample and testing you may experience some discomfort with a slight poking feeling just prior to a sample taken and there may be a small amount of bruising on the finger.

The exercise training and exercise test may cause light-headedness, muscular fatigue and/or shortness of breath. By following the exercise recommendations of the researcher and having a thorough warm up and cool down, your risk will be minimized.

What are the benefits?

You will get over $250 in health and fitness-based testing for FREE, gain a detailed understanding of your cardiometabolic risk factors, further understand the chances of developing cardiovascular disease in the future, receive an exit interview on how to improve the factors that were tested, and have the chance to win a FREE year or month membership at the Mountaineer Field House!

What compensation is available for injury?

In the rare event of an injury during testing or while exercising, standard emergency procedures will be followed. The exercise testing facility is located within a few minutes of several agencies providing emergency treatment. If you need emergency care while you are at the research site, it will be provided to you. If you get injured when you are not at the research site, you should call your doctor or call 911 in an emergency. If your injury could be related to the research, tell the doctors or emergency room staff about the research study, the name of the Principal Investigator, and provide a copy of this consent form if possible. Call the principal investigator, Ryan Weatherwax at 970-943-2104, as soon as you can.

There are procedures in place to help attend to your injuries or provide care for you. Costs associated with this care will be billed in the ordinary manner, to you or your insurance company. However, insurance companies, Medicare, and Medicaid may not pay bills that are related to research costs. You should check with your insurance about this and talk to the Principal Investigator if you have concerns.

How will my privacy be protected?

Due to the nature of this study, you may be exercising in an environment with other members from the study. Therefore, we cannot guarantee that your identity will be kept anonymous throughout the study. Please note that no research participant will be able to see or access any personal information. To ensure your safety when exercising, students and faculty members delivering your exercise will be informed of relevant information that may influence how you respond to exercise. Any data collected and displayed in results would be displayed in a way which does not disclose your identity. Each participant will be given an alphabetical and numerical code. The format of the code will be the first initial of the participant's first name and the first 3 letters of their last name, along with a 3 number code. Only the primary researchers will have access to the codes and the identity of the subjects. The sheet with names and code-numbers will be kept in a separate and secure filing cabinet at Western State Colorado University.

What are the costs of participating in this research?

None to you except the time to have tests conducted.

What opportunity do I have to consider this invitation?

You will be given a week from our first face-to-face meeting to talk to your family before needing to decide on accepting (or not) the invitation.

How do I agree to participate in this research?

Your participation in this research is voluntary (it is your choice) and whether or not you choose to participate will neither advantage nor disadvantage you. You are able to withdraw from the study at any time. If you choose to withdraw from the study, then you will be offered the choice between having any data that is identifiable as belonging to you removed or allowing it to continue to be used. However, once the findings have been produced, removal of your data may not be possible.

Will I receive feedback on the results of this research?

You will receive written individual feedback for each of the health measures used in the study. On completion of data analysis and dissemination, participants will be given a copy of the research paper with a cover paper highlighting main findings for the lay-public.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Dr. Nigel Harris, at nigel.harris@aut.ac.nz or (09) 921 9999 x 7301. This is an international call, so you must first dial 011 to exit the US numbers, then 64, and finally 1 followed by the above number.

Concerns regarding the conduct of the research should be notified to the Executive Secretary of AUTEC, Kate O'Connor, ethics@aut.ac.nz , (09) 921 9999 ext 6038. This is an international call, so you must first dial 011 to exit the US numbers, then 64, and finally 1 followed by the above number.

For local inquires into this study, please contact the following:

Any concerns regarding the nature of this project should be notified in the first instance to the Local Project Supervisor, Dr. Lance Dalleck, at ldalleck@western.edu or (907) 943 7132.

Concerns regarding the local conduct of the research should be notified to the Western State Colorado University Human Research Committee Chair, Lance Dalleck, ldalleck@western.edu, (970) 943 7132.

Whom do I contact for further information about this research?

Please feel welcome to contact me or my project supervisors should you have any questions.

Researcher Contact Details:

Ryan Weatherwax

rweatherwax@western.edu

(970) 943 2104

Project Supervisor Contact Details:

Dr. Nigel Harris	Dr. Lance Dalleck
nigel.harris@aut.ac.nz	ldalleck@western.edu
(09) 921 9999 x 7301	(970) 943 7123

Approved by the Auckland University of Technology Ethics Committee on August 1st, 2016, AUTEC Reference number 16/264.

Approved by the Western State Colorado University Institutional Review Board on July 5th, 2016, HRC Reference number HRC2016-90RS

8.9 Appendix E: Informed Consent

Consent Form

Project title: ***The incidence of training responsiveness (responders and non-responders) to cardiorespiratory fitness and cardiometabolic measures after individualized and standardized exercise prescription***

Project Supervisor: ***Dr. Lance Dalleck and Dr. Nigel Harris***

Researcher: ***Ryan Weatherwax***

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 07 July 2016.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I fulfil all of the inclusion criteria for the study. If I am not sure, I have asked and had the inclusion criteria further explained to me.
- ○ I agree to provide to undertake all assessments and exercise sessions that are stated in the information sheet that I read and fully understand their purposes.
- ○ I understand that members of the research team will be able to view my medical history documents that are required for me to be a participant in Wellness Elevated.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ I understand that if I withdraw from the study then I will be offered the choice between having any data that is identifiable as belonging to me removed or allowing it to continue to be used. However, once the findings have been produced, removal of my data may not be possible.
- ○ I agree to take part in this research.
- ○ I wish to receive a summary of the research findings (please tick one): Yes○ No○

Participant's signature: ..... Date : .....

Participant's name: .....

Participant's Contact Details (if appropriate):

.....

.....

.....

.....

Approved by the Auckland University of Technology Ethics Committee on August 1st, 2016, AUTEC Reference number 16/264.

Approved by the Western State Colorado University Institutional Review Board on *July 5th, 2016*, HRC Reference number *HRC2016-90RS*.

Note: The Participant should retain a copy of this form

8.10 Appendix F: Medical History and General Questionnaire

Medical History and General Questionnaire

First Name_____ Last Name_____ Date ____/____/____

☐ Male ☐ Female Age_____ Height_____ Weight_____ Date of Birth ____/____/____

Do you have known heart, vascular, lung, liver kidney, metabolic or thyroid disease? ☐ yes ☐ no

If yes, are you currently taking medication for any of the above conditions? ☐ yes ☐ no

Has a first-degree relative had a myocardial infarction, coronary revascularization, or died suddenly at an early age (before 55 if male or 65 if female?) ☐ yes ☐ no

Are you a current or previous smoker? ☐ yes ☐ no

If you were a previous smoker, when did you quit? _____

Do you currently exercise? ☐ yes ☐ no

If yes, how many times a week do you exercise 30 or min a day? _____

Do you currently have high blood pressure? ☐ yes ☐ no

Are you currently taking medication for high blood pressure? ☐ yes ☐ no

Is your blood cholesterol level 200mg/dl or higher? ☐ unsure ☐ yes ☐ no

Is your blood LDL (bad) cholesterol 130mg/dl or higher? ☐ unsure ☐ yes ☐ no

Is your blood HDL (good) cholesterol below 40mg/dl? ☐ unsure ☐ yes ☐ no

Is your blood HDL (good) cholesterol 60mg/dl or higher? ☐ unsure ☐ yes ☐ no

Are you currently taking medication for your cholesterol and/or triglycerides? ☐ yes ☐ no

Is your fasting blood glucose (sugar) 100mg/dl or higher? ☐ unsure ☐ yes ☐ no

Are you currently taking medication for diabetes? ☐ yes ☐ no

What do you consider a good weight for yourself? _____lbs

■ Please list any injuries or limitations that may inhibit you with exercise or physical activity

_____

_____

_____

_____

■ List any medications you are currently taking and the reason for taking them

_____

_____

_____

_____

In the past 12 months

Has your weight fluctuated more than a few pounds?	☐ yes	☐ no
Did you attempt to bring about this weight change through diet or exercise?	☐ yes	☐ no
Have you experienced any faintness, light-headedness, or blackouts?	☐ yes	☐ no
Have you occasionally had trouble sleeping?	☐ yes	☐ no
Have you experienced any blurred vision?	☐ yes	☐ no
Have you had any severe headaches?	☐ yes	☐ no
Have you experienced chronic morning cough?	☐ yes	☐ no
Have you experienced any temporary change in your speech pattern, such as slurring or loss of speech?	☐yes	☐no
Have you felt unusually nervous or anxious for no apparent reason?	☐ yes	☐ no
Have you experienced unusual heartbeats such as skipped beats or palpitations?	☐ yes	☐ no
Do you experience shortness or loss of breath while walking with others your own age?	☐ yes	☐ no
Do you experience sudden tingling, numbness, or loss of feeling in your arms, hands, feet, or face?	☐ yes	☐ no
Do you experience swelling of your feet or ankles?	☐ yes	☐ no
Do you get pains or cramps in your legs?	☐ yes	☐ no
Do you experience any pain or discomfort in your chest?	☐ yes	☐ no

I have read, understood and completed this questionnaire to the best of my ability by answering the questions faithfully. Any questions I had were answered to my satisfaction.

Name_____

Signature_____ Date _____

8.11 Appendix G: International Physical Activity Questionnaire (Short)

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ days per week

   ☐ No vigorous physical activity → skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?

   _____ hours per day

   _____ minutes per day

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis?
   DO NOT include walking.

   _____ days per week

   ☐ No moderate physical activity → skip to question 5

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

   _____ hours per day

   _____ minutes per day

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

   _____ days per week

   ☐ No walking → skip to question 7

6. How much time did you usually spend **walking** on one of those days?

   _____ hours per day

   _____ minutes per day

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

   _____ hours per day

   _____ minutes per day

This is the end of the questionnaire, thank you for participating.

8.12 Appendix H: 3-Day Dietary Intake Form

3-day Diet Analysis Intake Form.
Fill out the following information as accurately as possible. Include one weekend day and 2 other days to provide a record that reflects day-to-day variability in your food consumption. Our analysis will average these 3 days. Incomplete forms **cannot** be analyzed. Use the example given as a guide to develop your detailed food intake record. Use additional pages as necessary.

Name: _____

Day of week and meal eaten	**Food or Beverage** Give a detailed description including type of food, brand name, or restaurant	**Amount Eaten** Give as tsp, tbsp, cups, oz, weight or portion	**How Prepared?** Provide description, product label or recipe if available.	**Where eaten?**	**Added fat, salt or sugar?**
Example: Mon 1/9 breakfast	*Scrambled eggs*	*1 whole large egg*	*Scrambled in 1tsp butter with 1 tbsp 1% milk added*	*In front of TV*	*Dash of salt & pepper*
Mon 1/9 breakfast	*Bread with margarine and jelly*	*1 slice 1tsp of each*	*Toasted*	*Same as above*	*1 tsp marg (butter or marg) + 1 tsp jelly (regular or lite)*
Mon 1/9 breakfast	Orange Juice	16 oz	Jewel-Osco brand	Same as above	100% juice; not sweetened