ANGLIA RUSKIN UNIVERSITY

FACULTY OF SCIENCE AND ENGINEERING

SCHOOL OF PSYCHOLOGY AND SPORT SCIENCE

GENOTYPES AND PHENOTYPES: IMPLICATIONS OF EXERCISE ON THE INTER-INDIVIDUAL DIFFERENCES IN BIOLOGICAL RESPONSES

DOCTOR OF PHILOSOPHY

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ABSTRACT

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GENOTYPES AND PHENOTYPES: IMPLICATIONS OF EXERCISE ON THE INTER-INDIVIDUAL DIFFERENCES IN BIOLOGICAL RESPONSES

BY HENRY CHUNG

The increase in inactivity and sedentary behaviours has been linked to an increase in people becoming overweight and obese, which leads to serious complications, such as type 2 diabetes, stroke, heart disease, and cancers. Exercise training has been proven to improve the health-related components of fitness, for example endurance, strength, and power and helps tackle these health risks. However, a large proportion of people do not engage in exercise, with a lack of understanding on how to implement exercise efficiently to maximise people's improvements in these components of health-related fitness. Research evidence has shown that exercise genetics play a large role in how people adapt and respond to specific types of exercise training differently. Yet, it is unclear which specific genes are of interest and if this applies to the untrained population, as most research is in elite and well-trained athletes. The aims of this thesis were to first examine the literature-based evidence on the components of health-related fitness responses to different exercise training programmes and the time-courses of these. Secondly, to assemble a list of commonly reported candidate genes and assess the association of these genes to the components of fitness, which has not been done previously. Correlation coefficient showed that training load was significantly associated with the improvements in cardiorespiratory fitness, muscular strength, and anaerobic peak power (R^2 = 0.86, 0.50, 0.90, respectively) across 18 studies. Additionally, there were still large inter-individual differences in the improvements of these three phenotypes, even with matched training load and volume. The second review found that certain exercise genes explained up to 72% of this variability. Following these two reviews, training load, habits, and volume were collected via questionnaires in 661 participants from the UK population and compared with the results from the literature review. The findings were then applied in a group of previously untrained participants during a field-based training study. These participants were then genotyped to identify if there were real-world application with exercise training and genetic information to improve health and fitness phenotypes. The results uncovered that training programmes are complex, due to a mixture of training modes, changes in the programme, and progression. Nevertheless, results found that training in endurance improved participants $\dot{V}O_{2max}$ significantly, yet there were still large differences between participants improvements. Eta-squared (η^2) found that a large proportion of this was explained by allele-specific genotypes (53.5%), establishing the association between genotypes and the improvements in cardiorespiratory fitness.

Key words: Exercise training, $\dot{V}O_{2max}$, Genotypes, Phenotype.

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Declaration

I, Henry Chung, herby declare that the presented work within this thesis is original and completed by me. This thesis has not previously been published or submitted elsewhere in agreement and accordance to the ARU Research Degree Regulations. All literature and online sources by other authors have been cited within and given due acknowledgement, listed in the reference section. This work is non-profit research. This work has been supported and supervised by Anglia Ruskin University Faculty of Science and Engineering (FSE) and the Vice Chancellor (VC) Scholarship. All data is available upon request at the Cambridge Centre for Sport & Exercise Sciences, Anglia Ruskin University, UK.

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List of abbreviations:

Abbreviation	Full phrase
Δ:	Delta
1RM:	One Repetition Maximum
ACSM:	American College of Sport Medicine
a-vO_{2dif}:	Arterio-Venous Oxygen Difference
BLa:	Blood Lactate
BMI:	Body Mass Index
CI:	Confidence Interval
CSA:	Cross Sectional Area
CV:	Coefficient of Variation
EMG:	Electromyography
ES:	Effect Size
GPAQ:	Global Physical Activity Questionnaire
GWAS:	Genome-Wide Association Study
HR:	Heart Rate
IKD	Isokinetic dynamometer
LoA:	Limits of Agreement
M:	Mean
NICE:	National Institute for Health and Care Excellence
NIRS:	Near Infrared Spectroscopy
NHS:	National Health Service
PB:	Personal Best
PHEIC:	Public Health Emergency of International Concern
POMS:	Profile of Mood States
PPO:	Peak Power Output
Q:	Cardiac Output
RER:	Respiratory Exchange Ratio
RPE:	Rating of Perceived Exertion
SD:	Standard deviation
SE:	Standard Error
sRPE:	Session Rating of Perceived Exertion
sTL	Session Training Load
SMD:	Standardised means difference
SNP:	Single Nucleotide Polymorphism
SV:	Stroke Volume
TL:	Training Load
tTL:	Total Training Load
WHO:	World Health Organisation
wTL:	Weekly Training Load

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1. INTRODUCTION

Exercise is a key mediator for health, fitness, and well-being, with a significant amount of evidence demonstrating amelioration of cardiovascular-diseases, psychological, metabolic, and neurological disorders, plus many other physiological benefits (American College of Sports Medicine (ACSM), 2017; Blair, 2015; Lofrano-Prado et al., 2012; McGuigan et al., 2009). There is, however, considerable debate within the research literature in implementing exercise effectively and strategically, as an intervention to maximise these benefits (Blair, 2001; Bouchard 2012). In this connection, the National Health Service (NHS) published findings on untrained, overweight, and obese patients in the UK (Figure 1). 39% of patients reported using some form of weight management aid, whereas only 29% reported engaging in some form of exercise (NHS, 2018). These less active groups are a concern, due to higher risks associated with poor fitness and health-related complications, with this being an increasingly large issue across the world (Chen et al., 2016).

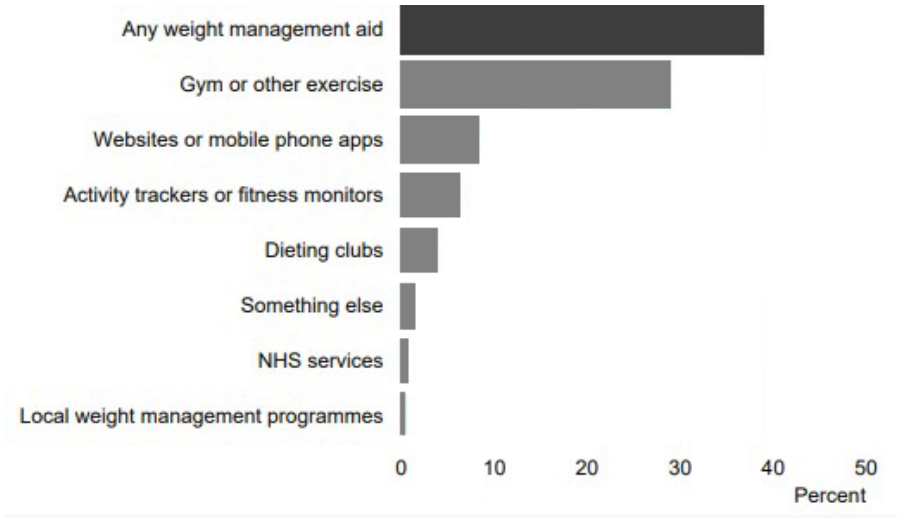


Figure 1. NHS statistics in adult obesity and weight management. Of the overall 39% of patients using weight management aid in dark grey, 74% reported gym or other exercise, equivalent to the total 29%. 50% of people who reported that they were trying to lose weight were currently not using any weight management aids. 11% did not report any desire to lose weight (NHS, 2018 statistics pp 21).

Decreases in physical activity and exercise, and their relationship with increases in overweight and obesity have been a matter of concern for a wide range of public bodies and organisations. The UK Government, NHS, and Public Health England published statistics that found ~65% of adults in the UK were classed as being overweight or obese, with poor physical fitness and lacking regular exercise (NHS, 2018; the National Institute for Health and Care Excellence

(NICE), 2014a). These classifications are defined by a body mass index (BMI) of 25 - 29.9 and ≥ 30 $kg{\cdot}m^2$, respectively (NICE, 2014a). Not only are there serious short-term implications such as, breathlessness, fatigue, and tiredness when performing everyday tasks, there are also serious long-term implications such as, type 2 diabetes, high blood pressure, asthma, and cancers. Additional stress is placed on the NHS and other sectors in the UK to cater to these groups. It is estimated that the NHS spend ~£6.1 billion per-year directly on overweight and obese cases with this estimated to rise to £9.7 billion by 2050, with the total cost to society reaching £49.9 billion per-year (Gov.uk, 2017). In addition, this puts high levels of stress on public sectors and treatments. In 2018 the UK was in the top 10 highest countries for obesity rates in the world (NHS, 2018) with research from NICE estimating these medical costs are 30% greater than those of normal healthy-weight individuals (BMI 18.5 – 24.9 $kg{\cdot}m^2$) (NICE, 2014a). It is estimated that preventing a 1% increase in obesity rates in the UK can save the NHS and local authorities, approximately £97 million per-year (NICE, 2014b; NHS, 2018).

The NHS has stated ~50% of overweight patients do not implement any weight management aid(s), although the majority state that they, "*wanted to lose weight*". Erikssen et al., (1998) and Hautala et al., (2006) showed that even small improvements in health-related components of fitness, have a large impact on the improvement of overall health, everyday mobility and well-bring. In this connection, the ACSM listed the trainable health-related fitness components:

- Aerobic cardiovascular / cardiorespiratory fitness, defined as the capability of an individual to use oxidative pathways and enhance the ability to perform sustained exercise (Astorino and Schubert, 2014; Raghuveer et al., 2020).
- Maximal muscular strength refers to the highest force that can be performed during one maximum voluntary contraction (Hautala et al., 2006; Ratamess, 2011).
- Anaerobic power is the ability of the neuromuscular system to produce the greatest possible action in a given time period (Cometti et al., 2001).

These are essential in developing and accessing physical performance, wellbeing, health, mobility, and fitness (ACSM, 2017; Ratamess, 2011; Sarzynski, Ghosh and Bouchard, 2017; Shamim et al., 2018). Participating in regular exercise seems to be a solution to the management of weight, fitness, health, and well-being, research findings are in agreement that a wide range of factors must also be considered, such as, recovery, training intensities, frequencies, duration, training status, adherence, enjoyment, diet etc., as there exists a number of complexities in exercise training prescriptions and adaptation (Del Coso, et al., 2018; Holden et al., 2014; Laursen, Blanchard and Jenkins, 2002; Peterson, Rhea and Alvar, 2005; Yvert et al., 2016).

Exercise training studies demonstrating highly standardised protocols, even when accounting for these “factors” in participants with similar training status, still find that the results differ significantly with inter-individual variance in the adaptation to training between participants (Hautala et al., 2006; Sarzynski, Ghosh and Bouchard, 2017; Schutte et al., 2016). The research literature highlights that exercise genetics may have a crucial role, due to influences on energy-pathways, metabolism, muscle composition, tissue and cell growth, hormonal, and enzyme interactions (de Vlaming et al., 2017; Keiller and Gordon, 2019; Landen et al., 2019; Spurway and Wackerhage, 2006; Vancini et al., 2014; Zambon et al., 2003). Indeed, evidence suggests that up-to 80% of the variability in the adaptation to training is dependent on the genotype (Bouchard, 2012; Hautala et al., 2006; Huygens et al., 2004; Klissouras, 1971; Komi et al., 1977; Spurway and Wackerhage, 2006). In agreement, studies have shown numerous genes and alleles associated with exercise and athletic performance in trained individuals (Bouchard, 2012; Cieszczyk et al., 2016; Vancini et al., 2014; Zambon et al., 2003). Many of these genes, such as the well documents ACE gene (angiotensin-converting enzyme) have subsequently been found to be linked with the health-related components of fitness, in elite and athletic performance. However, there is less supporting evidence for the untrained and less active populations that are more susceptible to becoming overweight and developing poor health and fitness outcomes (Ma et al., 2013; Sarzynski, Ghosh and Bouchard, 2017; Spurway and Wackerhage, 2006; Noakes, 2000). These concepts could explain why there are degrees of variability regarding adaptation to training, when exposed to generic exercise training (Astorino and Schubert, 2014; Daly et al., 2002; Herring, Sailors and Bray, 2014). The current international guidelines recommend a weekly physical activity structure that consists of 150 minutes of moderate, or 75 minutes of vigorous aerobic exercise, or a combination of both, including strength activities two days per-week (ASCM 2017; NHS 2018; WHO GPAQ, 2002). If an individual’s genetics do play a role in the adaptations to training, these findings may suggest that the current promotion of generic-exercise recommendations are of a questionable value (Carpinelli, Otto and Winett, 2004; Jungblut, 2009; Kraemer, Ratamess and French, 2002; Peterson, Rhea and Alvar, 2005).

1.2. SUMMARY

1. Research evidence indicates that exercise is beneficial to improve health, fitness, and wellbeing, especially if it targets one of the three components of health-related fitness.

2. Minor improvements and adaptations in any of the health-related components of fitness are advantageous in inactive and untrained people, to improving health and overall fitness, especially in those that are classed as vulnerable and susceptible to becoming overweight and obese.

3. Exercise training interventions vary significantly and there is no justification as to how to strategically implement these.

4. Exercise genetics may play an important role in how much individuals adapt and respond to a particular exercise training intervention.

5. Exercise genetics may explain a large proportion of the inter-individual differences between participants even in highly standardised protocols.

6. Increased physical activity and weight management helps NHS and local authorities battle obesity and the wider implications on the public sectors.

CHAPTER 2: LITERATURE REVIEW

A narrative literature review was conducted and aimed to address and expand on the concepts within chapter 1. The main aims were to address the exercise training responses, adaptations, and considerations when creating an intervention. Additionally, consideration is given to how genetics may influence exercise and trainability, where trainability is referred to as an ability and also limit to increases in health-related components of fitness (Bacon et al., 2013 and Bouchard et al., 2010).

2.1. METHODS

For the collection of research literature three separate database platforms were used related to the research area, PubMed (MEDLINE), SportDiscus (EBSCO) and Web of Science (Clarivate Analytics). These databases were selected because PubMed is one of the two biggest commercial, bibliographic databases. It covers scholarly literature from almost any discipline, with approximately 100 million items and 1.4 billion references across multidisciplinary areas. Web of Science is the number one resource for literature in medicine and biological sciences, with more than 30 million papers, which would be advantageous in searches for physiology and genetic research. SportDiscus is specific to this research area of interest and was used for more specific searches. Multiple databases were used to overlap searches to provide extensive and comprehensive searches, additionally to compensate for any missing literature (Needlemen, 2002).

The initial key search terms were "cardiovascular fitness" OR “cardiorespiratory fitness” OR "muscular strength" OR "anaerobic power" as these were highlighted as the key components of fitness (ACSM, 2017; Ratamess, 2011). The second level of the terms searched followed with “training intervention” OR “training program*” implementing ‘AND’ function was also used. The third level of the search consisted of ‘OR’ gene OR genetic OR genotype. This was to pool additional studies linking genes and the components of fitness, rather than restrict the search by combining all areas. The initial search was conducted in May 2020 (3,715 results) and was updated in September 2020 (4,261 results) resulting in a total of 54 relevant studies included in this literature review (Figure 2). Any studies that did not related to the topics listed, those that were not in full-text English, and studies that did not include human participants were excluded.

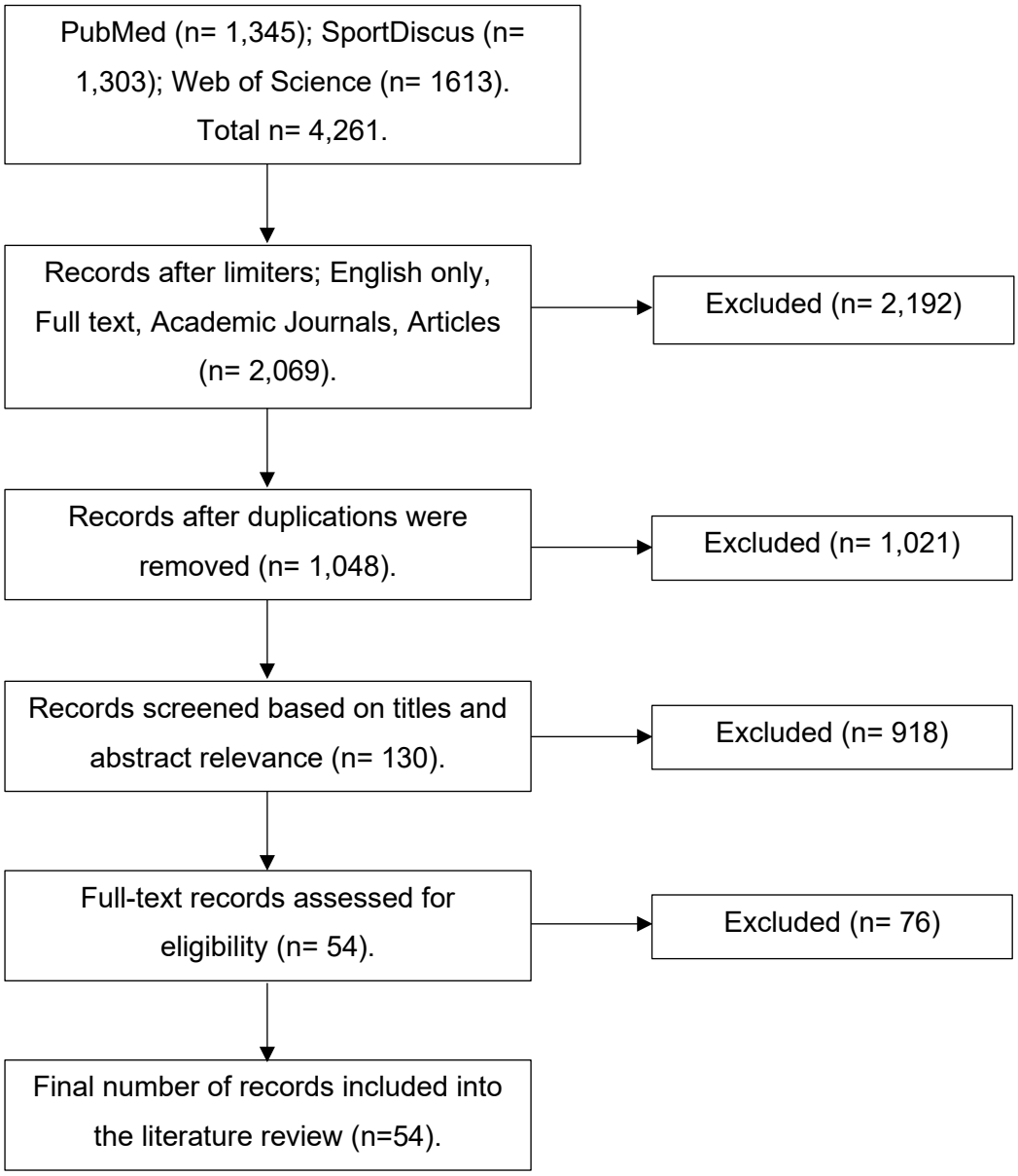


Figure 2. Flow diagram of the component of fitness and gene literature. The inclusion and exclusion of research literature in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Studies were collected from three different databases.

2.2. REVIEW OF LITERATURE

2.2.1. Training theory & Intervention considerations

There are multiple considerations when implementing a training intervention to improve a component of health-related fitness. Additionally, many different tests and measurements can be implemented to examine the training effects. These components of fitness are listed in chapter 1, however other components exist, such as flexibility, agility, balance, co-ordination. Table 1 indicates commonly reported study characteristics that may need to be considered when training, including but not limited to: training status, training intensity, duration of exercise, frequency of sessions, and the intervention time-course. These relate to training theory and are variables that contribute to training adaptations. The purpose of training is for a planned, structured, and purposeful outcome that leads to specific health gains or adaptations. Therefore, being one of the single most important interventions for an improvement in health, fitness, and wellbeing (Herring, Sailors and Bray, 2014). Furthermore, regular training enhances physical performance and education, aside personal development (Farrance, Tsofliou and Clark, 2016; Holden et al., 2014). Reflecting on adaptations to exercise, the general adaptation syndrome (GAS) states that when a stressor, such as exercise is added to a routine the body goes through a series of short and long-term responses to accommodate for that stress (Buckner et al., 2017). Repeated exposure to these stressors (training) eventually leads to a tolerance and adaptation for that stressor. This is also why training progression is needed.

Training programmes are planned and therefore, should have short, medium, and long-term strategies which justifies their application. In a recent study by Gaitán et al., (2019) they acknowledge that within training studies, there is a wide range of interventions and modalities, but also the time-courses implemented have little justification. In their study after a 2-week intervention in 22 clinically obese males and females, they observed a significant increase in cardiorespiratory fitness ($\dot{V}O_{2max}$, p =.04) and found this correlated with increased fat oxidation rates during endurance-based exercise. This makes sense, as endurance exercise increases aerobic oxidative pathways and enhances capabilities of the respiratory system to perform sustained exercise for longer periods, ultimately increasing cardiorespiratory health. Interestingly, Hautala et al., (2006) despite a similar 2-weeks intervention, reported large heterogeneity in the increase in $\dot{V}O_{2max}$ between participants and the results were not the same (Table 1). Further, the HERITAGE family study (Health, Risk factors, exercise Training And Genetics) was designed to track and monitor cardiorespiratory responses to aerobic exercise training in families, including 720 healthy individuals over a 20-week period (Bouchard et al., 1999). However, when this was compared to the study of Astorino and Schubert, (2014) that

adopted a 12-week intervention, there were large difference in the improvement of $\dot{V}O_{2max}$. In this example, the large differences in time-course (an additional 8-weeks) were not advantageous in improving $\dot{V}O_{2max}$ (18.3% vs 25.1%, respectively), and this questions if the time-course is an important consideration. A likely explanation for this may be the training intensities, durations, and frequencies applied over the time-course.

In terms of strength, Häkkinen, Alen and Komi, (1985) implemented a 24-week high-load strength intervention in 11 males, aged 20-32 years old. They found that increases in strength measured by one repetition maximum (1RM) were due to motor unit recruitment associated with familiar exercises and enlargement of muscle-fibre cross sectional area (CSA), within the first 12-weeks of training. However, the results found no further hypertrophic responses during the following 12-weeks of the study, irrespective of progressive overload, yet 1RM still increased. Indeed, the authors found in the 2nd 12-week block, a further 26.8% increase in isometric strength was significantly correlated ($p < .001$) with the neural activation assessed via electromyography (EMG) in the leg extensor muscles. Whilst these findings agree with previous studies (Radaelli et al., 2015) that found hypertrophic gains in the first 11 weeks, it has been noted by Schoenfeld, (2020) and Seynnes, de Boer and Narici, (2007) that neuromuscular adaptation occurs before hypertrophic gains. Moreover, studies such as, Jones, Rutherford and Parker, (1989), Shaw, Shaw and Brown, (2009) and Vingren et al., (2010), support that a combination of neuromuscular and hypertrophic hormonal elevations occur from the onset of training, suggesting that the adaptations observed, depend on a balance between, intensity, duration, frequency, and volume of the training.

In the study by Laursen, Blanchard and Jenkins, (2002) peak power output (PPO) increased by 4.3%, in as little as four sessions. This was over 2-weeks in 14 highly trained cyclists. They state that this could be due to working at high intensities with short rest periods, therefore requiring a greater high-energy phosphate contribution and improvements in aerobic efficiency and ability to recover. Conversely, Lindsay et al., (1996) found no significant changes in PPO, in the first 2 of a 4-week intervention using a similar training approach with eight highly competitive cyclists. Accordingly, it appears that the training time-course alone, even when highly standardised elicits conflicting outcomes.

There are many other modalities and strategies of training. A method that is growing increasingly popular is the idea of concurrent training, which is a mixture of endurance and strength. The idea behind this type of training is that it targets multiple components of fitness and improves endurance, strength, and power (Chapman et al., 2021). Although it is a commonly used strategy reflecting a real-world training week with positive effects, particularly in untrained healthy people (Shaw, Shaw and Brown, 2009). Evidence also finds that training

in both endurance and strength causes reductions in strength and power when compared to training for strength alone (Chtara et al., 2008), especially when preformed closely together or in the same session (Shamim et al., 2018). Nevertheless, concurrent training will not be explored within this thesis. The objective is to identify the differences between the components of fitness, the genetic influence on specific pathways and the inter-individual difference in phenotypes. Therefore, concurrent training would not be appropriate in terms of identifying specific adaptations and responses as it primarily aims to cause multiple phenotype changes.

A brief overview of the studies in table 1 shows sedentary and untrained participants, for the majority, exhibit larger increases in the components of fitness compared to physically active and highly trained participants. Upon further inspection, the time-course of training does have a role but may not be as important as the intensities, durations, and frequencies of the training itself, in agreement with Gaitán et al., (2019) and Hautala et al., (2006). Conversely, Bouchard et al., (1999) shows differences in the change of $\dot{V}O_{2max}$ despite having all participants perform a highly standardised protocol with a similar intensity, duration, frequency, volume, and time-course. They allude that these inter-individual differences may be due in part to some genetic intrinsic factors. It is apparent, that multiple factors such as, training time-course, intensity, duration, frequency, rest, overload/progression, the pre-training status of the individuals, and the component of fitness variables measured need to be considered when comparing studies. Accordingly, the results gathered in this review, particularly question the application of the training interventions, as observations do not show consistent trends in the physiological outcomes. Furthermore, the literature suggests that training loads (TL) governed by intensity, duration, and frequency (Foster et al., 1996) may explain in-part the inconsistencies of the training adaptations, agreeing with previous statements from Buckner et al., (2017) and Nummela et al., (2016). Therefore, training load will become a focal point moving forwards and the impact it has on the physiological adaptions required to then be applied within a training study.

Table 1. Study information from the initial literature. This table shows studies using different and similar training time-courses, resulting in different outcomes of the components of fitness, where cardiovascular fitness is $\dot{V}O_{2max}$, muscle strength is one-repetition maximum (1RM) and anaerobic power is represented by peak power output (PPO).

Study	Training status	Sample size	Intensity	Duration	Frequency	Intervention time-course	Results
Astorino and Schubert, 2014	Physically active	20	200-300% Wmax	30 seconds all-out SIT	4-6 per-day	2 weeks	$\dot{V}O_{2max}$ ↑ 6.3 ± 5.4% (p = .03)
Astorino and Schubert, 2014	Sedentary	20	80-90% Wmax	10 x 1-minute bouts	3 days per-week	12 weeks	$\dot{V}O_{2max}$ ↑ 25.1 ± 9.5% (p = .002)
Bouchard et al., 1999	Sedentary	95	55% - 75% HRmax	30 – 50 minutes	3 days per-week	20 weeks	$\dot{V}O_{2max}$ ↑ 14.3 ± 5.7%
Bouchard et al., 1999	Sedentary	86	55% - 75% HRmax	30 – 50 minutes	3 days per-week	20 weeks	$\dot{V}O_{2max}$ ↑ 18.3 ± 7.2%
Bouchard et al., 1999	Sedentary	141	55% - 75% HRmax	30 – 50 minutes	3 days per-week	20 weeks	$\dot{V}O_{2max}$ ↑ 14.8 ± 6.3%
Bouchard et al., 1999	Sedentary	159	55% - 75% HRmax	30 – 50 minutes	3 days per-week	20 weeks	$\dot{V}O_{2max}$ ↑ 18 ± 7.3%
Gaitán et al., 2019	Obese	22	90% HRmax 50% HRmax	3 minutes of both for 60 minutes interchangeable	6 days per-week	2 weeks	$\dot{V}O_{2max}$ ↑ 2 ± 0.1 $ml \cdot kg^{1} \cdot min^{-1}$ (p = .04)
Gaitán et al., 2019	Obese	22	70% HRmax	60 minutes continuous	6 days per-week	2 weeks	$\dot{V}O_{2max}$ ↑ 0.1 ± 0.2 $ml \cdot kg^{1} \cdot min^{-1}$ (p > .05)
Hautala et al., 2006	Sedentary	73	70-80% HRmax	30 minutes	5 days per-week	2 weeks	$\dot{V}O_{2max}$ ↑ 8 ± 6% (p = .001)
Hautala et al., 2006	Sedentary	73	62% HRmax	8-12 reps (39 minutes)	3 days per-week	2 weeks	1RM ↑ 4 ± 5% (p = .001)
Häkkinen, Alen and Komi, 1985	Physically active	11	70-100% 1RM	18-30 reps per-session with 1-10 reps per-set	3 days per-week	24 weeks	1RM ↑ 26.8% (p < .001)
Laursen, Blanchard and Jenkins, 2002	Highly trained	14	100% $\dot{V}O_{2max}$ wattage	20 x 1-minute bouts with 2 minutes rest between	3 days per-week	2 weeks	PPO ↑ 4.3% (p < .05)
Lindsay et al., 1996	Highly trained	8	80% PPO	6-8 x 5-minute bouts with 1 minute rest at 100 watts	3 sessions	2 weeks	PPO ↑ 1.65% (p = .08)

Lindsay et al., 1996	Highly trained	8	80% PPO	6-8 x 5-minute bouts with 1 minute rest at 100 watts	6 sessions	4 weeks	PPO ↑ 4.15% (p = .01)
Parra et al., 2000	Untrained	10	"All-out" effort at 0.075 kg on flywheel	2 x 30 seconds all out cycles with 12 minutes rest.	7 days per-week	2 weeks	PPO ↑ 3% (p > .05)
Parra et al., 2000	Untrained	10	"All-out" effort at 0.075 kg on flywheel	2 x 30 seconds all out cycles with 12 minutes rest.	14 sessions	6 weeks	PPO ↑ 20% (p < .05)
Prud'homme et al., 1984	Well-trained	20	80% Heart rate reserve	40 minutes	4-5 days per-week	20 weeks	$\dot{V}O_{2max}$ ↑ 12% (p < .01) PPO ↑ 17%
Radaelli et al., 2015	Untrained	13	8-12 rep maximum	3 x 9 exercises, 60 minutes session with 90-120 seconds recovery.	3 days per-week	24 weeks	1RM ↑ 13.57% (p < .01, 1.01 effect size)
Seynnes, de Boer and Narici, 2007	Recreationally active	7	7 rep maximum	7 reps, 4 sets. 2-minute rest periods	3 days per-week	5 weeks	1RM ↑ 38.9 ± 5.7% (p < .001)
Shaw, Shaw and Brown, 2009	Untrained	13	60% 1RM	15 x 8 reps x 3 sets	3 days per-week	16 weeks	1RM ↑ 39.21% (p = .001)
Schmidt, Biwer and Kalscheuer, 2001	Untrained	8	75% Heart rate reserve	30 minutes continuous	3-5 days per-week	12 weeks	$\dot{V}O_{2max}$ ↑ 10.42% (p < .001)
Songsorn et al., 2016	Untrained	30	"All-out" effort at 7.5% body mass	1 x 20 seconds Wingate sprint	3 days per-week	4 weeks	$\dot{V}O_{2max}$ ↑ 3.3% (p > .05) PPO ↑ 5.13% (p = .03)
Thomis et al., 2004	Untrained	55	60-85% 1 rep maximum	1 set x 14 reps, 2 sets x 12 reps, 3 sets x 10 reps and 5 sets to failure.	3 days per-week	10 weeks	1RM ↑ 51.7 ± 20.7% (p < .01)

- $p \leq .05$ = significant; ↑ = increase; rep = repetitions

2.2.2. Exercise Genetics

The ability to adapt to training is multi-factorial, in general, good health, fitness, and performance require the cohesive combination of many intrinsic and extrinsic factors (Buckner et al., 2017; Spurway and Wackerhage, 2006; Vasenina, Kataoka and Buckner, 2020). For example, exposure to the stimulus, environment, nutrition, technical-tactical training, financial aspects, motivation, innate factors etc. Some of these aspects are in-fact trainable and taught and others are beyond the control of athletes, such as genetic factors (Hautala et al., 2006; Vancini et al., 2014). The research literature has shown that an individuals' genotype affects both heritability and variability in exercise related phenotypes such as aerobic, strength, and power capabilities (Bouchard et al., 2012; Heffernan et al., 2015; Maes et al., 1996; Sarzynski, Ghosh and Bouchard, 2017; Thomis et al., 1998).

Deoxyribonucleic acid (DNA) molecule is composed of two chains that coil around each other to form a double helix carrying the genetic instructions used in the growth, development, functioning, and reproduction of human organisms. Humans have approximately 24,000 genes, within these genes the single nucleotide polymorphisms (SNPs) are the most common type of variance found. There are millions of SNPs in a human genome, with the majority being similar between people (Carlson et al., 2003; Sachidanandam et al., 2001; Zhao and Boerwinkle, 2002). While epigenetics and environmental influences such as training, diet and lifestyle choices are important, it is likely that there are also some genetically innate components to athletic performance suggesting that genetic variations do influence exercise performance per se (Scott and Pitsiladis, 2007).

The evidence for a genetic element and relationship to greater physical capability is expanding and many genetic variants that contribute to variations in physical fitness have been discovered (Scott and Pitsiladis, 2007; Spurway and Wackerhage, 2006). Although there is a wide array of genes, common exercise related SNPs define the internal body make-up, how food is metabolised, how efficiently micronutrients are converted, muscle strength and stamina, athletic performance and injury risk (Bouchard et al., 2012; Goldstein and Cavalleri, 2005; Spurway and Wackerhage, 2006). Commercial research-based evidence shows that a subset of 1,000 SNPs specifically affects human fitness characteristics, injury risks, micro and macro nutrient metabolism and more (https://muhdo.com/).

When comparing studies that assess the same phenotype response, it is easy to assume that the variability in training improvements most likely are attributed to the TL, table 1 illustrates that those with greater intensities, durations, and frequencies, mostly display greater improvements. However, this may in fact only be partly true, when examining studies such as

Bouchard et al., (1999) even with a standardised training protocol and time-course, they still found differences and variability between individuals within the same study. This shows that the response to training differs at an individual level not just between studies but within. This justifies the notion that training adaptations are more complex than just ensuring satisfactory protocol design, further questioning generic protocols. Hence an innate genetic component may play an important role when determining exercise interventions to maximise an individual's response in health-related components of fitness.

2.2.3. Baseline phenotype heritability

The role for genetics in determining exercise performance and success is not a new concept, Klissouras, (1971) was one of the first to show that there are strong heritabilities in baseline phenotypes. More than 10 years later Prud'homme et al., (1984) were the first to report evidence of trainability as having a genetic element. Prud'homme et al., (1984) demonstrated a 12% increase in $\dot{V}O_{2max}$ over a 20-week exercise intervention, and the increase was similar between 10 monozygotic twins. The highest gains in $\dot{V}O_{2max}$ were from those that initially started with lower baseline scores, and that these baseline phenotypes are highly heritable. This suggests that the training intervention in combination with the initial training status has an important role in how the phenotype changes. Thomis et al., (1998) further explored this phenomenon, using strength training in 25 monozygotic and 16 dizygotic twins on elbow flexion. They revealed that 1RM showed a significant genetic influence on baseline strength even before any training was implemented. This would suggest that participants require a different training stimulus to promote initial adaptations when compared to those that might not possess such genes. Additionally, this could suggest that strength and $\dot{V}O_{2max}$ show different response patterns. They concluded that 20% of the variation in strength adaptations were explained by genetics, which is lower than the ~50% observed with $\dot{V}O_{2max}$. Interestingly, unlike Prud'homme's group, higher variations were observed in the pre-intervention strength phenotype amongst twins. This finding agrees with the meta-analysis of Zempo et al., (2017), which found significant influences from genetic and environmental factors for strength and power phenotypes, and that the environmental influences increase with age when approaching adulthood. Furthermore, Schutte et al., (2016) reported that, the baseline individual-variation in health and fitness related phenotypes are large even before training. Their meta-analysis found on average, a baseline variance of ~25%. Accordingly, the literature supports that these inter-individual differences are underpinned by innate genetic factors, as confirmed with previous twin and family studies (Bouchard and Rankinen, 2001; Bouchard et al., 1998; Church et al., 2007; Hautala et al., 2006; Maes et al., 1996).

In contrast, Spurway and Wackerhage, 2006, explain that when comparing twin studies, in most but not all cases, numerous simplifying assumptions are made, especially when age is a factor. For example, some studies assume monozygotic twins are treated and exposed to the same conditions and environments, therefore, being treated as a gold standard, when compared to dizygotic twins or siblings. Instead, they could be developed and raised differently in different environments as they progress into adulthood. Environmental factors have been seen to impact baseline exercise phenotypes, by up to ~55% and genetics ~45%, resulting in baseline heritability being diverse between individuals and even twins (Goldstein and Cavalleri, 2005; Spurway and Wackerhage, 2006; Vancini et al., 2014). McGue and Bouchard, (1984) stress the importance adjusting for age-sex using normative data or a computed twin-based approach corrected through specification of the degrees of freedom for the between-pairs mean square. Either the data is reported in mean and SD for various age-sex categories or in a polynomial function, where a variety of calculations are used (McGue and Bouchard, 1984). In the absence of norm data, estimating regression coefficients from individual twin scores equal to the estimated coefficients computed by regressing the twin pair means on the age-sex variables should be performed (McGue and Bouchard, 1984). However, Lopez et al., (2017) concluded that age, sex, race, and ethnicity have small effects that are not clinically important when adjusting z score calculations (Lopez et al., 2017). It is therefore important to acknowledge this and the groups that are used in genetic studies.

Table 2. Reported heritability of phenotypes. Where phenotype outcome is affected by a mixture of genotype, sampling, technical and environmental variance (Spurway and Wackerhage, 2006).

Phenotype	Authors	Date	Heritability (up to)
$\dot{V}O_{2max}$	Bouchard	2012	43%
$\dot{V}O_{2max}$	Fagard et al	1991	80%
$\dot{V}O_{2max}$	Heffernan et al	2015	80%
$\dot{V}O_{2max}$	Klissouras	1971	93%
$\dot{V}O_{2max}$	Klissouras	1997	75-87%
$\dot{V}O_{2max}$	Maes et al	1996	87%
$\dot{V}O_{2max}$	Mustelin et al	2011	65%
$\dot{V}O_{2max}$	Schutte et al	2016	72%
$\dot{V}O_{2max}$	Sarzynski, Ghosh and Bouchard	2017	47%
% type 1 fibres	Komi et al	1977	96%
% type 1 fibres	Nimmo et al	1985	75%
PPO	Bouchard and Malina	1983	45-90%
Anaerobic energy	Fagard et al	1991	68-77%
PPO	Klissouras et al	1997	86%
PPO	Komi, Klissouras and Karvinen	1973	99%
PPO	Maes et al	1996	23-33%
PPO	Simoneau et al	1986	44-92%
1RM (Arms)	Huygens et al	2004	90%
1RM (Legs)	Huygens et al	2004	70%
1RM (Trunk)	Huygens et al	2004	77%
1RM (Arms)	Maes et al	1996	70%
1RM (Arms)	Thomis et al	1998	77%
1RM (Handgrip)	Zempo et al	2017	63%

- $\dot{V}O_{2max}$ = Maximal aerobic fitness; PPO = peak power output; 1RM = 1 repetition maximum

The collected study data from table 2 estimate that heritability from parental alleles for baseline $\dot{V}O_{2max}$ are between 47-93%, PPO 23-99%, and 1RM 63-90%. It is important to note that despite a 93% influence in genetic factors, this does not mean that 93% is fully inherited and 7% is only from environmental factors, a common mistake when reporting genetic information (Spurway and Wackerhage, 2006). The individual's genetic makeup does not solely determine the phenotype, but rather, the potential for the expression of that phenotype in response to a particular lifestyle and environment. This is because the genotypes are dependent on both the nature and nurture, in terms of development and maximising potential (Del Coso et al., 2018; Goldstein and Cavalleri, 2005). It has been stated in studies such as Bouchard et al., (1990) that trainability is a heritable role. People with the same, or a very similar genetic makeup, might not represent the general population but only the sample population within that area, as environmental factors affect development. Despite nearly 50 years of research, this field is still relatively new and expanding. Nevertheless, it is clear that there are sufficient indications of a genetic influence on training, health, fitness, and well-being in human species and that further exploration is required.

2.2.4. Phenotype variability

In the study by Vancini et al., (2014) they acknowledged that African runners appear to dominate in long-distance events and that this intriguing phenomenon may be attributed to the interaction between genotype and phenotype. They assessed the genetic roles of mitochondrial deoxyribonucleic acid, the Y chromosome, angiotensin-converting enzyme (ACE) and alpha-actinin-3 (ACTN3) on elite athletic performance in African runners. They highlight that these results justify the variability and success observed in these runners. Y chromosome and mtDNA established no evidence to support genetic differences between race in athletic performance, which agrees with previous literature (Colaco and Modi, 2018; Taanman, 1999). Rather, the specific genetic polymorphisms that control a trait at a single genetic locus with two alleles, in this case ACE and ACTN3, explained 50-80% of the inter-individual variance in performance phenotypes. This is further supported by a review from Schutte et al., (2016), that found in a meta-analysis, that more than half of the individual variance in $\dot{V}O_{2max}$ was explained by genetic factors in adolescents to early adulthood. Unsurprisingly, the literature supports this link with the interactions between genes and factors that improve phenotypic traits such as, aerobic, and anaerobic performance. These include but are not limited to, increased cardio-respiratory fitness, metabolic efficiency, haemoglobin concentration, enzyme and hormone profile, muscle fibre recruitment and growth (Bray et al. 2009; Keiller and Gordon, 2019; Rankinen et al. 2011; Sarzynski, Ghosh and Bouchard, 2017; Zambon et al., 2003). The issue is that more than 200 identified genetic variants may contribute to physical fitness, making an individual gene's contribution difficult to assess (Vancini et al., 2014; Zambon et al., 2003). Goldstein and Cavalleri, (2005) argue that even when assessing the millions of polymorphisms that influence human diseases, it is not necessary to directly assess all the individual sites and associations:

> ***"****The polymorphisms' interactions in the human genome are regularly dependent on one another. The presence of a specific genetic variant at one site on a chromosome can predict a variant at another site and its affects."*
> (Goldstein and Cavalleri, 2005).

In agreement, Ahmetov et al., (2016) and Williams and Folland (2008) stated that no single independent gene, or polymorphism, has resulted in a dependent change in a phenotype. Hoppeler, (2018) illustrates this with a model of a human transcription network, and how endurance exercise activates signalling, which interlinks with other pathways and processes causing a cascade effect, inducing genetic expression (Figure 3).

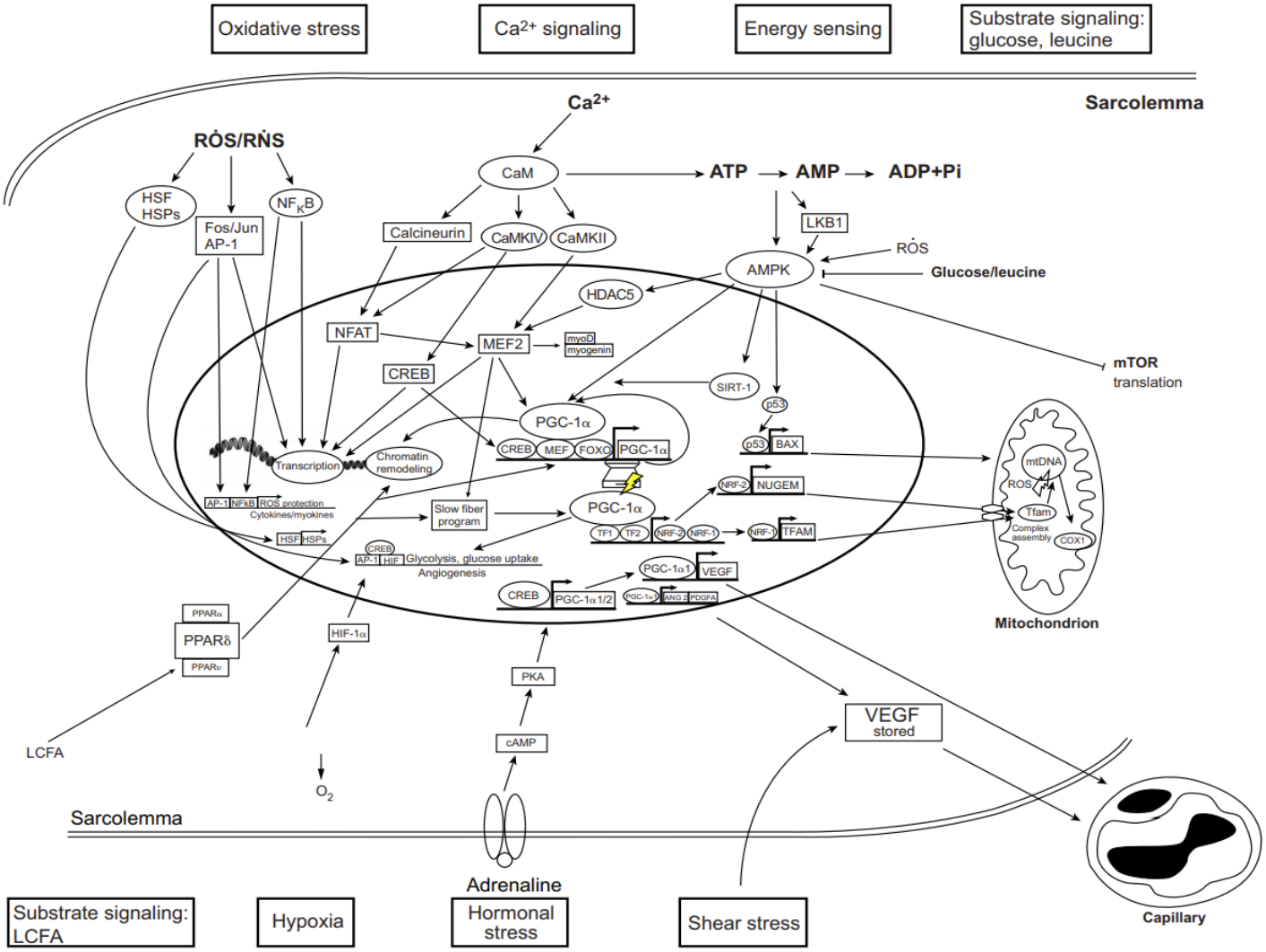


Figure 3. Model of the transcriptomic network during endurance exercise in the skeletal muscle of humans. (Hoppeler, 2018. pp.5).

Figure 3 represents the response of the mitochondria and capillaries to numerous training cues, all of which are affected by epigenomic and epitranscriptomic regulation. This demonstrates the genetic interactions by regulators and changes in other genes for a particular outcome in the phenotype response. For cardiorespiratory fitness, several external stressors, such as oxidative stress, shear stress, hypoxia activate signals, invoke gene expression and ultimately affect mitochondrial biogenesis (Hoppeler, 2018). Thus, no single pathway is responsible for the exercise response in the phenotype and similarly no single gene is responsible for the change in the phenotype as many processes occur simultaneously during exercise.

The gene interactions predictably depend on one another, justifying that it is not necessary to assess every single polymorphism and interaction process that occurs, but rather specific sets of gene interactions that are linked and use similar pathways. Contemporary consensus acknowledges that phenotypes, which are shaped over an individual's development into adulthood by various factors (Epigenetics), have greater influences on successful physiological health outcomes, when compared to the specific genotypes alone (Goldstein and Cavalleri, 2005; Scott and Pitsiladis, 2007; Spurway and Wackerhage, 2006). From a health perspective, studies such as Blair, Cheng and Holder (2001) acknowledge that although genetic contributions to fitness are an important factor, this variance may be less important compared to benefits from the environment and the physical activity participated on a regular basis. They found that increased physical activity is directly associated to an increase in physical fitness and a decrease in coronary heart disease (CHD), stroke, cardiovascular disease (CVD), or cancer. Specifically, a 50% reduction in mortality in both moderately fit men and women and 70% in the high fit groups, when compared with those in the low fitness category. The degree of adaptation, however, is highly variable, regardless of preforming the same exercise programme. These conclusions are supported by Bouchard, (2012) who, in a series of standardised and well-monitored exercise interventions, in groups of sedentary men and women, aged 18–30 years old, found variable training outcomes. In the HERITAGE Family study, it was observed that the genetic variability of the improvement in $\dot{V}O_{2max}$, was equal to 47%, after a 20-week exercise training intervention, when adjusted for age, sex, body mass, and baseline scores. Thus, the heterogeneity observed in the response was not random. Furthermore, in the meta-analysis by Schutte et al., (2016) the overall variance was 55-60% for $\dot{V}O_{2max}$. These training experiments have uncovered a strong genotype-trainability that contributes to the phenotype responses and adaptation.

2.3. CONCLUSION

This literature review, observed that individual variations are primarily an outcome of genetic factors, acted on by environmental influences. Hence phenotype variability might be more important than heritability, as this accounts for environmental changes and other factors during the development of the individual, whereas heritability only estimates how much of the baseline phenotype is genetically associated from parent alleles. Exercise genetics have become increasingly popular, with focus on exploring the roles of specific genes and their alleles, especially in elite and well-trained groups as an attempt for identifying advantageous improvements in performance. Many inferences are made from previous genetic studies, especially twin studies that might not account for phenotype variability but only heritability estimates, as the results from twins are in most cases treated as the “gold-standard”. Finally, less is known in the untrained populations and those in early or late adulthood as the literature is heavily based upon observations in elite and athletic populations, twin, and rat studies.

Exercise interventions and innate genetic factors have important influences on individual adaptations in key health-related components of fitness. This review has identified the common flaws, gaps, and interests within the current literature. Firstly, the large differences in how training programmes are implemented with little justification and how it affects the components of fitness. Secondly, how and what genes effect the variability in the adaptations to training.

2.3.1. Objectives:

1. Conduct a comprehensive systematic literature review with meta-analysis, identifying the different training interventions with untrained individuals and understand how these affect the listed components of health-related fitness.
2. Perform a separate second systematic review with meta-analysis, identifying the genes commonly associated with the improvements in three components of health-related fitness with training.
3. Implement a standardised laboratory-based training study, from on the findings in the first systematic literature review at an attempt to significantly improve phenotype responses in the components of health-related fitness.
4. Identify the variability and inter-individuals’ differences in the phenotype response by genotyping the participants to assess associations in an untrained UK population using the assembled list of candidate genes from the second review.

CHAPTER 3: RESPONSES TO EXERCISE TRAINING PROGRAMMES – A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

3.1. INTRODUCTION

When implementing exercise training, it should be planned, structured, and purposeful. it has been uncovered as one of the single most important interventions for an improvement in health, fitness, and wellbeing (Herring, Sailors and Bray, 2014). A confounding issue with exercise training is that there exist different levels of complexity that are not accounted for such as, training status, type of training, training time-course, amongst others (Farrance, Tsofliou and Clark, 2016; Holden et al., 2014; Jack, McLean, Moffett, and Gardiner, 2010). When constructing an exercise training intervention, it is crucial that multiple variables and factors are considered such as, the individual training status, intervention time-course, type of training, training stimulus, intensity, frequency, duration and rest, exercise goals etc. if the programme is to be beneficial in improving the exercise responses, especially as the training level of the individual increases (Laursen, Blanchard and Jenkins, 2002; Peterson, Rhea and Alvar, 2005).

There is debate within the research literature on how best to implement exercise successfully, and strategically, to maximise its benefits within untrained, inactive, and sedentary individuals. What is important, but often overlooked, is the exercise intervention structure itself and the time-course to train an individual before observing any substantial improvements (Blair, 2001; Bouchard 2012; Smith et al., 2013). The findings from the literature review in chapter 2 demonstrate a broad training time-course of 2-24 weeks. However, other studies have shown to be more than 30 weeks, again with little justification as to why and how this compares to other studies (Daly et al., 2002; Sigal et al., 2014; Herring, Sailors and Bray, 2014). Further, evidence shows that significant aerobic fitness and anaerobic power adaptations can occur in as little as 2-weeks of training, questioning the impact of longer intervention time-courses and if they are advantageous (Astorino and Schubert, 2014; Hautala et al., 2006). This poses a problem when comparing studies and training protocols, especially if the study does not have a matched control group and therefore, open to confounding variables outside of the intervention effects, potentially increasing the bias of a study (Rosenbaum and Rubin, 1985; Williamson, Atkinson and Batterham, 2017) and affecting the statistical analysis of a pre-test–post-test design (Zientek, Nimon and Hammack-Brown, 2016).

As briefly mentioned, within chapter 2, a method used in calculating training loads may be useful in identifying differences in training interventions between studies, as it is a function of

intensity, duration, and frequency that results in an arbitrary (A.U.), but comparable unit (Balsamo et al., 2012; Foster, et al., 1996). This method will help in standardising and quantifying training even if studies use different time-courses, training exercises, and modes.

Initial search results and strategies from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using Scopus, Web of Science, PubMed, SportDiscus, and the Cochrane library database for systematic reviews, in October 2018, found no systematic literature reviews with meta-analyses assessing exercise training intervention time-course on physiological response-rates based on aerobic cardio-respiratory fitness, muscular strength, and anaerobic power in the untrained population, using clear matched control groups as comparators.

Therefore, the aim of this meta-analytical literature review was to compare and highlight the time-course of different training interventions, the response rates linked to these, and how TL may affect the training response phenotypes in an untrained population. This will aid in identifying any possible relationships with the exercise intervention and physiological responses, and how this information can be applied to better understand the structuring of different training interventions.

3.2. METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines of systematic reviews. A detailed search was conducted to encompass the related research literature from four separate databases. The results were then exported and filed within bibliographic management systems (Refworks, ProQuest, USA) for duplication management and study extraction. The remaining papers were then screened for their relevance according to title and abstract. The successfully screened results were then assessed further using a PICOS (Population, Intervention, Comparison, Outcome and Study type/design) strategy and an adapted COSMIN (Consensus-based Standards for the selection of health status Measurement Instruments) checklist, before being included in this review. Complete access to all full text literature articles were achieved due to the support of Anglia Ruskin University's interlibrary loans system and grey literature was also explored.

3.2.1. Literature search

The generation of literature was conducted using a variety of databases (Needleman, 2002). This included Scopus, Web of Science, PubMed and SportDiscus. This was first implemented from December 2018 – January 2019 and updated in November 2019. An initial search was conducted in all the database thesauruses and MeSH terms in an attempt to pool keywords. Alongside this additional search techniques were implemented such as Boolean operators/logic 'AND' and 'OR', 'Phrase searching', truncation, wildcard asterisk and Field codes (Table 3). The searching strategy was repeated (Figure 4), three pearl papers were found in both rounds of the search to show the consistency and repeatability of the search (Needleman, 2002).

Table 3. Training intervention search terms. Search terms used for the generation of literature in all the databases and the number of results. This was initially 14,486 and increased to 14,684.

Database	Hits	Search Terms
Scopus	9234	TITLE-ABS (*"Exercise program*"* OR *"Training program*"* OR *"Sport* program*"* OR *"Workout program*"* OR *"Exercise training"* OR *"Sport training"* OR *"Workout training"* OR *"Exercise class*"* OR *"Training class*"* OR *"Workout class*"* OR *"Exercise intervention"* OR *"Training intervention"* OR *"Sport intervention"* OR *"Physical activity intervention"* OR *"Fitness intervention"* OR *"Exercise regime"* OR *"Training regime"* OR *"Sport* regime"* OR *"Physical activity regime"* OR *"Fitness regime"* OR *"Exercise session"* OR *"Training session"* OR *"Sport* session"* OR *"Physical activity session"* OR *"Fitness session"* OR *"Exercise conditioning"* OR *"Training conditioning"* OR *"Fitness conditioning"*) AND *physiological* AND *adaptation*
Web of Science	802	(TS=("Exercise program*") OR TS=("Training program*") OR TS=("Sport* program*") OR TS=("Physical activity program*") OR TS=("Fitness program*") OR TS=("Workout program*") OR TS=("Exercise training") OR TS=("Sport* training") OR TS=("Physical activity training") OR TS=("Fitness training") OR TS=("Exercise class*") OR TS=("Training class*") OR TS=("Sport* class*") OR TS=("Physical activity class*") OR TS=("Fitness class*") OR TS=("Exercise intervention") OR TS=("Training intervention") OR TS=("Sport* intervention") OR TS=("Physical activity intervention") OR TS=("Fitness intervention") OR TS=("Exercise regime*") OR TS=("Training regime*") OR TS=("Physical activity regime*") OR TS=("Fitness regime*") OR TS=("Exercise session") OR TS=("Training session") OR TS=("Physical activity session") OR TS=("workout session") OR TS=("Exercise conditioning") OR TS=("Training conditioning") OR TS=("Sport* conditioning") OR TS=("Fitness conditioning")) AND TS=(Physiolog*) AND TS=(Adaptation)
PubMed	2100	(("Exercise program*"[Title/Abstract] OR "Training program*"[Title/Abstract] OR "Sport* program*"[Title/Abstract] OR "Physical activity program*"[Title/Abstract] OR "Fitness program*"[Title/Abstract] OR "Workout program*"[Title/Abstract] OR "Exercise training"[Title/Abstract] OR "Sport* training"[Title/Abstract] OR "Physical activity training"[Title/Abstract] OR "Fitness training"[Title/Abstract] OR "Exercise class*"[Title/Abstract] OR "Training class*"[Title/Abstract] OR "Physical activity class*"[Title/Abstract] OR "Fitness class*"[Title/Abstract] OR "Exercise intervention"[Title/Abstract] OR "Training intervention"[Title/Abstract] OR "Sport* intervention"[Title/Abstract] OR "Physical activity

		intervention”[Title/Abstract] OR “Fitness intervention”[Title/Abstract] OR “Exercise regime*”[Title/Abstract] OR “Training regime*”[Title/Abstract] OR “Physical activity regime*”[Title/Abstract] OR “Fitness regime*”[Title/Abstract] OR “Exercise session”[Title/Abstract] OR “Training session”[Title/Abstract] OR “Physical activity session”[Title/Abstract] OR “workout session”[Title/Abstract] OR “Exercise conditioning”[Title/Abstract])) AND Physiolog* AND Adaptation
SPORTDiscus	2548	(“Exercise program*” OR “Training program*” OR “Sport* program*” OR “Physical activity program*” OR “Fitness program*” OR “Workout program*” OR “Exercise training” OR “Sport* training” OR “Physical activity training” OR “Fitness training” OR “Workout training” OR “Exercise class*” OR “Training class*” OR “Sport* class*” OR “Physical activity class*” OR “Fitness class*” OR “Workout class*” OR “Exercise intervention” OR “Training intervention” OR “Sport* intervention” OR “Physical activity intervention” OR “Fitness intervention” OR “Exercise regime*” OR “Training regime*” OR “Sport* regime*” OR “Physical activity regime*” OR “Fitness regime*” OR “Workout regime*” OR “Exercise session” OR “Training session” OR “Sport* session” OR “Physical activity session” OR “Fitness session” OR “workout session” OR “Exercise conditioning” OR “Training conditioning” OR “Sport* conditioning” OR “Fitness conditioning”) AND Physiolog* AND Adaptation

- TITLE-ABS = title and abstract; TS = Topic; * = truncation; “ “ = phrase or joint word; ‘OR’ and ‘AND’ = Boolean operators/logic; HITS = number of results.

3.2.2. Inclusion criteria

The literature collected was restricted to publications that were only available in English and the PICOS strategy further refined the results (Methley et al., 2014). Participants were classed as untrained if they performed lower than the ACSM norm values for the three components of fitness pre-training (Table 4) or has not reported any previous training (Ratamess, 2011). The age range was based on the NHS physical activity results, which had the largest reported cases of susceptibility to becoming inactive (NHS Digital, 2018). Another key aspect was the inclusion of a control group, which has been absent in several training studies across the literature, questioning the bias of the study and the measure comparisons of the constructs. Any studies that did not meet the PICOS criteria were excluded.

Table 4. PICOS strategy. This adapted method combines the normal PICO and the SPIDER methods. After assessing all three methods PICOS was deemed to be the most efficient and compatible when conducting this systematic literature review (Methley et al., 2014).

PICOS	Inclusion assessment
Population or Problem	Human males and females aged 18-55 years old. Untrained (preform less than the recommended ACSM, NHS and WHO physical activity guidelines): $\dot{V}O_{2max}$ = ≤ 45 ml·kg^{-1}·min^{-1} Males, ≤ 40 Females. 1RM = ≤ 1.06 x BW Males, ≤ 0.4 x BW Females (bench press). ≤ 1.91 x BW males, ≤ 1.32 x BW Females (leg press). PPO = ≤ 9.22 W·kg^{-1} Males, ≤ 7.65 W·kg^{-1} Females.
Intervention or Exposure	Duration: ≥ 2 weeks (minimum of 6 sessions, 3 per week). Intervention (must meet one of the components of fitness): Continuous Endurance/Aerobic Interval training. Resistance training/weight training. Anaerobic interval/sprint/ anaerobic training.
Comparison	A control group (not exposed to the intervention condition) to compare against group(s) that are exposed.
Outcome	Studies must include one of the primary variables of interest: $\dot{V}O_{2max}$/ $\dot{V}O_{2peak}$/ Maximal Aerobic power/ fitness. One repetition maximum/ maximal strength. Peak power output.
Study type or design	Quantitative, repeated measures training study with clear pre and post data collection.

- $\dot{V}O_{2max}$ = maximal aerobic fitness; 1RM = one repartition maximum; PPO = peak power output; BW = body weight; W·kg^{-1} = watts per kilogram.

3.2.3. Study retrieval process and quality assessment:

The application of the flow diagram (Moher et al., 2009) illustrates the retrieval process of this review. The updated COSMIN 2018 checklist was implemented to assess the transparency and risk of bias of the 29 collected studies, by assessing the methodological quality (Mokkink et al., 2010). As suggested by Terwee et al., (2012) the 'worst score' approach was set for all items at ≥ 3 threshold score, to meet the satisfactory requirement of study quality. To ensure the consistency and reliability of the quality assessment tool, two reviewers independently assessed the studies using the COSMIN checklist.

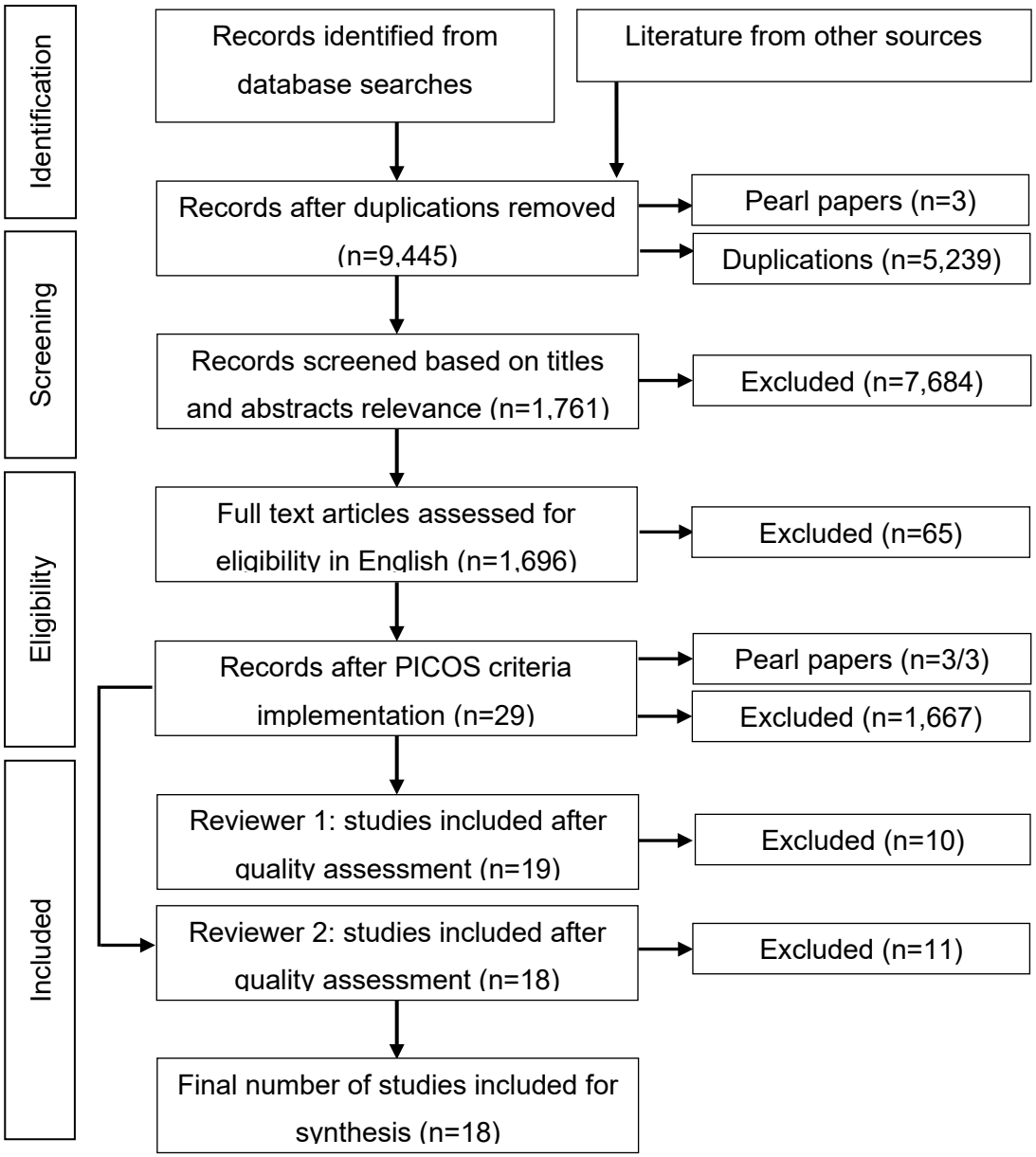


Figure 4. Flow diagram of training studies. Illustrating the method of collecting studies and exclusion at each stage to get the final studies for this review. Where other sources were from unpublished sources and grey literature. This entire process was repeated twice. Three pearl papers were used as a control method.

3.2.4. Data extraction and analysis:

Mean (M) and standard deviations (SD) were manually extracted from the studies into an Excel spreadsheet (Microsoft Excel, Microsoft Corp, Washington, USA). For synthesis of the meta-analysis, a minimum of two studies were required to have reported the same variable to draw a conclusive outcome measurement, otherwise the variable could not be assessed (Brown, Upchurch and Acton, 2003; Valentine, Pigott and Rothstein, 2010). Meta-Essentials 2018 spreadsheet 1.4 (Microsoft Excel 2016, Washington, USA) was used to run the meta-analysis (Suurmond, van Rhee and Hak, 2017; van Rhee, Suurmond and Hak, 2015).

Table 5. Extracted variables from study results. List of physiological and metabolic variables that were measured in all the studies that are of interest to the systematic literature review. This also shows the variables abbreviations and the common units of measurement.

Variable	Abbreviation	Unit of measurement
Maximal aerobic fitness	$\dot{V}O_{2max}$	$ml \cdot kg^{-1} \cdot min^{-1}$ OR $l \cdot min^{-1}$
Maximal heart rate	HR_{max}	$b \cdot min^{-1}$ (bpm)
Body Mass index	BMI	$kg \cdot m^2$
Percentage body fat	BF%	%
1 repetition maximum	1RM	kg OR lb
Peak power output	PPO	W OR $W \cdot kg^{-1}$

- $ml \cdot kg^{-1} \cdot min^{-1}$ = millilitres per kilogram per minute; $l \cdot min^{-1}$ = litre per minute; $b \cdot min^{-1}$ and bpm = beat per minute; $kg \cdot m^2$= kilogram divided meter squared; kg = kilogram; lb = pounds; W= watts: $W \cdot kg^{-1}$ = watts per kilogram.

The M and delta (Δ) M of both exercise and control groups, SD, pooled SD, Standard error (SE), variance (s^1), inverse-variance, Cohens *d* effect size (ES), standardised means difference, (SMD), upper and lower 95% confidence intervals (CI) and the weighted Mean Cohen's *d* (Harrison, 2011), were calculated using the Excel package. Each study was weighted (%) based on its inverse study variance using Meta-Essentials 1.4 and shown in the forest plots (Chapman et al., 2021). Cohen, (1988) determined *d* effect size as 0.2 - 0.49 small, 0.5 – 0.79 medium, and ≥ 0.8 large effect. Statistical power was calculated using ClinCalc LLC (2018). Pre-determination of study sample size for type I and II error was set at 80% (0.8) and alpha at 0.05 as standard. Calculations from estimated known population from chapter 2 found a minimum of nine participants for adequate statistical power in endurance groups, six for resistance and seven participants for PPO. Post-hoc power was then calculated with inputs of endpoint mean, SD and sample size for both exercise and control groups (Cohen, 1988; Suresh, 2012).

3.2.5. Equations List

Eq 1.

$$Cohen's\ d = \frac{(M_2 - M_1)}{SD_{pooled}}$$

Eq 2.

$$SD_{pooled} = \sqrt{\frac{({SD_2}^2 + {SD_1}^2)}{2}}$$

Eq 3.

$$Confidence\ interval = Cohen's\ d \pm 1.96\ \frac{SD_{pooled}}{\sqrt{Number\ of\ participants}}$$

Eq4.

$$Variance = \frac{(M - Average\ M)^2}{No. Participants - 1}$$

Eq 5.

$$Inverse\ variance = \frac{1}{Variance}$$

Eq 6.

$$Mean\ Cohen's\ d = \frac{\sum(d\ of\ each\ study\ x\ Inverse\ variance\ of\ each\ study)}{\sum Inverse\ variance}$$

3.3. RESULTS

The quality assessment of the COSMIN established 18 out of the 29 studies being eligible for this review and meta-analysis (Table 6). Two separate reviewers scored the studies independently (Mokkink et al., 2010).

Table 6. The COSMIN quality control assessment tool. The results of the tool. The 'worst score' approach was used for all items with the overall threshold score of ≥ 3. The average score between reviewers was taken for the final inclusion (Mokkink et al., 2010; Terwee et al., 2012).

Study	Reviewer 1 COSMIN score	Reviewer 2 COSMIN score	Mean scores of reviewers	Included in review (Yes/No)
Chtara et al., 2008	3.00	3.00	3.00	Yes
Collins and Snow, 1993	3.13	3.00	3.07	Yes
Da Silva et al., 2018	2.38	2.38	2.38	No
De Sousa et al., 2018	3.38	3.25	3.32	Yes
Dias et al., 2010	3.13	3.00	3.07	Yes
Donges and Duffield, 2012	2.63	2.50	2.57	No
Greenlee et al., 2017	3.63	3.63	3.63	Yes
Humburg et al., 2007	3.00	3.00	3.00	Yes
Hurley et al., 1984	2.50	2.50	2.50	No
Jordan et al., 2018	2.38	2.38	2.38	No
Kak et al., 2013	2.50	2.38	2.44	No
Kell, 2011	3.38	3.25	3.32	Yes
Khammassi et al., 2018	3.38	3.38	3.38	Yes
Kraemer et al., 2004	2.88	2.88	2.88	No
Levesque et al., 1997	3.00	3.00	3.00	Yes
Lunt et al., 2014	3.25	3.25	3.25	Yes
McBride et al., 2002	2.50	2.50	2.50	No
Moreira et al., 2008	1.75	1.75	1.75	No
Nummela et al., 2016	3.00	2.88	2.94	No
Ocel et al., 2003	3.13	3.13	3.13	Yes
Pollock et al., 1972	3.13	3.13	3.13	Yes
Radaelli et al., 2015	3.13	3.13	3.13	Yes
Remaud, Cornu and Guével, 2010	2.38	2.38	2.38	No
Schmidt, Biwer and Kalscheuer, 2001	3.13	3.13	3.13	Yes
Sellami et al., 2014	3.13	3.00	3.06	Yes
Shaw, Shaw and Brown, 2009	3.25	3.13	3.19	Yes
Shire et al., 1977	3.25	3.13	3.19	Yes
Songsorn et al., 2016	3.50	3.38	3.44	Yes
Surakka 2005	2.75	2.75	2.75	No

3.3.1. Limits of Agreement (LoA)

Following the quality check of bias outcome measurements, a Bland Altman plot was formulated (Figure 5). The plot expresses that all the differences in scores against the average scores were within the 95% limits of agreement (LoA). There were no identifications of systematic differences, fixed bias, or possible outliers between the two reviewers in scoring these studies using the COSMIN checklist, classing the method with acceptable inter-rater reliability and validity. The disadvantage of using LoA is that it can be unreliable with small study sizes, when comparing methods or assessing repeatability. Therefore, it is suggested to calculate the confidence intervals for the 95% LoA (approximate method), which are represented by error bars (Bland and Altman 2010).

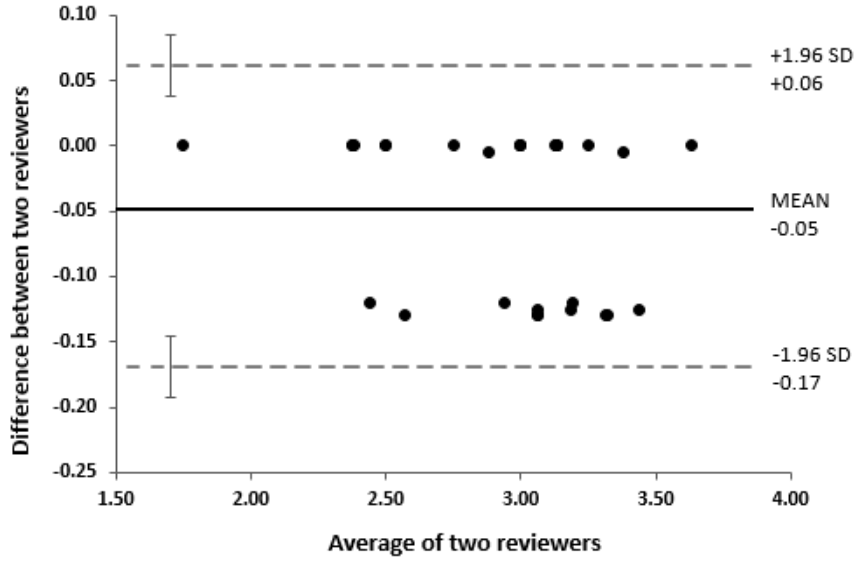


Figure 5. Bland Altman plot of training studies. The plot demonstrations the results of both reviewers using the quality assessment tool, plots are mapped as the difference in scores against the average score (Bias). The 95% LoA are also calculated and represented as the upper +1.96 and lower -1.96 dashed lines, showing the variation limits between the reviewers. The confidence intervals for the 95% LoA were calculated using Bland Altman's approximate method (Bland and Altman 1986-2010).

3.3.2. Overview of studies

Table 7 includes information extracted such as, participant information, training status, age, and group sample size, ranging from 12 – 258, including protocol information such as, intervention time-course that ranges from 2 – 24 weeks. The 18 studies resulted in, 46 groups in total, which comprised of a total of 921 participants.

Table 7. Overview of participants descriptive statistics. Participants Mean ± SD for each study included in this systematic literature review, where training status and age were key inclusion criteria. Table is split based on the three measures for the components of fitness, where the results report the primary variable (VO_{2max}, 1RM/Max strength and PPO). EG = exercise group; CG = Control group; G1 = group 1; G2 = group 2; G3 = group 3.

Study	Sample size (N)	Training Status	Age (years)	Height (cm)	Mass (Kg)
Endurance studies measuring VO_{2max}					
De Sousa et al., 2018 (G1, G2)	91 Participants G1: 26 G2: 46 CG: 19	Untrained, Inactive Males and Females	G1: 23 ± 3.9 G2: 24 ± 5.9 CG: 25 ± 4.7	-	-
Greenlee et al., 2017	258 Participants 132 Males 126 Females	Healthy, Untrained	EG: 24.65 ± 5.55 CG: 24.26 ± 5.59	EG: 173.28 ± 0.88 CG: 173.12 ± 0.83	EG: 74.5 ± 1.47 CG: 73.27 ± 1.58
Khammassi et al., 2018	20 Participants All males	Healthy, Untrained	Study mean 19.4 ± 1.1	-	EG: 91.2 ± 12.1 CG: 89.3 ± 10.5
Levesque et al., 1997	36 Participants 17 Males 19 Females	Healthy, Sedentary	Study mean 24.5 ± 5	-	EG: 61 ± 9 CG: 64.5 ± 7
Lunt et al., 2014	40 Participants 11 Males 29 Females	Inactive, Untrained	EG: 48.2 ± 5.6 CG: 46.3 ± 5.4	-	-
Pollock et al., 1972 (G1, G2)	34 Participants G1: 12 G2: 10 CG: 12	Sedentary, Untrained, All Males	Study mean 30-45 (38.7)	-	G1: 79.4 ± 11 G2: 81.3 ± 11 CG: 82.6 ± 11.3
Schmidt, Biwer and Kalscheuer, 2001	20 Participants EG:12 CG: 8	Inactive, All Females	EG: 20.7 ± 2.5 CG: 20.8 ± 1.6	EG: 161.6 ± 6.9 CG :163.7 ± 4	EG: 81.6 ± 10.8 CG: 83.6 ± 5.8
Shire et al., 1977 (G1, G2)	34 Participants G1: 13 G2: 11 CG: 10	Untrained, All Females	G1: 19.4 ± 1.6 G2: 19.1 ± 1.2 CG: 19.6 ± 1.1	G1: 165.3 ± 5.1 G2: 166 ± 6.7 CG: 166.5 ± 7.1	G1: 61.8 ± 8 G2: 58.7 ± 8.2 CG: 57.4 ± 5.3
Strength studies measuring 1RM					
Chtara et al., 2008	48 Participants All males	Healthy, Untrained,	Study mean 21.4 ± 1.3	Study mean 173.3 ± 0.88	Study mean 72.1 ± 6.3

Collins and Snow, 1993	34 Participants 11 Males 23 Females	Healthy, Untrained	Study mean 26 ± 6.7	Study mean 178.2 ± 5.7	Study mean 66.4 ± 17.5
Dias et al., 2010 (G1, G2)	48 Participants G1: 16 G2: 17 CG 15	Untrained, Navy men	G1: 18.7 ± 1.5 G2: 19.4 ± 1.4 CG: 19 ± 1.6	G1: 167.1 ± 2 G2: 170 ± 4.5 CG: 171.3 ± 3	G1: 68.5 ± 4 G2: 72.7 ± 4.4 CG:73.9 ± 4.4
Humburg et al., 2007 (G1, G2)	51 Participants G1: 22 G2: 22 CG:7	Untrained	G1: 27.1 ± 10 G2: 26 ± 6.7 CG: 23.1 ± 6.6	G1: 176 ± 8 G2: 178 ± 7 CG: 177 ± 8	G1: 74.3 ± 13.7 G2: 76.4 ± 10.7 CG: 71 ± 8.8
Kell, 2011 (G1, G2)	60 Participants G1: 20 G2: 20 CG: 20	Untrained, Males and Females	G1: 22.7 ± 4.1 G2: 22.5 ± 4.6 CG: 23.1 ± 4.8	G1: 178 ± 5 G2: 170 ± 6 CG: 174 ± 5	G1: 78.2±4.1 G2: 59.4± 5 CG: 70.1±4.7
Radaelli et al., 2015 (G1, G2, G3)	48 Participants G1: 12 G2: 13 G3: 13 CG: 10	Inexperienced Resistance Untrained, Navy men	G1: 24.1 ± 0.8 G2: 24.1 ± 1.2 G3: 24.7 ± 1 CG: 24.8 ± 0.6	G1: 177.9 ± 5.2 G2: 174.9 ± 3.4 G3: 172.9 ± 7.3 CG: 173.2 ± 3.4	G1: 79.7 ± 9.4 G2: 76.2 ± 8.1 G3: 82.2 ± 10.7 CG: 79.3 ± 8.2
Shaw, Shaw and Brown, 2009	25 Participants EG: 13 CG: 12	Sedentary, All Males	EG: 25 ± 3.5 CG: 25 ± 2.4	EG:175.5 ± 5.5 CG: 179.3 ± 11.9	EG: 69.1 ± 8.5 CG: 80.3 ± 12.8
Power studies measuring PPO					
Ocel et al., 2003	12 Participants EG: 6 CG: 6	Untrained, All Males	EG: 23.2 ± 2 CG: 23 ± 1	EG: 178 ± 4 CG: 178 ± 4	EG: 91 ± 4 CG: 81 ± 8
Sellami et al., 2014 (G1, G2)	32 Participants G1: 8 CG: 8 G2: 8 CG: 8	Healthy, Sedentary, All Males	G1: 21.4 ± 1.2 CG: 22 ± 1.9 G2: 40.8 ± 2.8 CG: 40.4 ± 2.8	G1:179.6 ± 3.7 CG:179.2 ± 6.5 G2:176.9 ± 5.8 CG:174.3 ± 4.3	G1: 72.8 ± 5.8 CG: 72.2 ± 7.3 G2: 74.8 ± 5.6 CG: 74.6 ± 3.9
Songsorn et al., 2016	30 Participants 10 Males 20 Females	Sedentary	Study mean 24 ± 6	-	EG: 63.6 ± 15.6 CG: 64.4 ± 12.8

3.3.3. $\dot{V}O_{2max}$

Table 8. $\dot{V}O_{2max}$ scores, control vs exercise groups from all studies. Mean ± SD for $\dot{V}O_{2max}$ in $ml \cdot kg^{-1} \cdot min^{-1}$ or $l \cdot min^{-1}$. The difference within group's pre vs post is represented by the delta scores.

Study	Control Group (Pre)	Control group (post)	Exercise group (Pre)	Exercise group (Post)	Delta Δ (Pre-Post)
Collins and Snow, 1993	49 ± 2.2	49.8 ± 4.5	43.8 ± 2.3	46.5 ± 2.1*	CG: 0.8 EG: 2.7
De Sousa et al., 2018 (G1)	37.9 ± 8.9	38.5 ± 9.5	36.9 ± 8.6	41.5 ± 6.4*	CG: 0.6 EG: 4.6
De Sousa et al., 2018 (G2)	37.9 ± 8.9	38.5 ± 9.5	38.7 ± 9.1	43.5 ± 9.7*	CG: 0.6 EG: 4.8
Greenlee et al., 2017	39.86 ± 8.59	39.53 ± 8.3	39.83 ± 9.08	42.55 ± 9.31*	CG: -0.33 EG: 2.72
Khammassi et al., 2018	42.7 ± 5.3	41.6 ± 4.9	41.8 ± 4.7	46.6 ± 5.1*	CG: -1.1 EG: 4.8
Levesque et al., 1997	36.3 ± 3.9	40.6 ± 3	37.6 ± 6.5	45.6 ± 6.0*	CG: 4.3 EG: 8
Lunt et al., 2014	27.1 ± 5.6	25.8 ± 3.7	24.7 ± 6.1	26.5 ± 5.8	CG: -1.3 EG: 1.8
Ocel et al., 2003	3.02 ± 0.7	3.08 ± 0.75	2.85 ± 0.3	3.06 ± 0.7	CG: 0.06 EG: 0.21
Pollock et al., 1972 (G1)	38.5 ± 3.8	42 ± 3.6	36 ± 3	42.8 ± 3.7*	CG: 3.5 EG: 6.8
Pollock et al., 1972 (G2)	38.5 ± 3.8	42 ± 3.6	38.5 ± 3.8	44 ± 3.9*	CG: 3.5 EG: 5.5
Schmidt, Biwer and Kalscheuer, 2001	1.83 ± 0.1	1.84 ± 0.1	1.72 ± 0.04	1.92 ± 0.1*	CG: 0.01 EG: 0.2
Sellami et al., 2014(G1)	43.1 ± 5	43.1 ± 4.2	41.8 ± 6.2	45.6 ± 5.9	CG: 0 EG: 3.8
Sellami et al., 2014(G2)	38.3 ± 3.2	43.1 ± 3.6	37.8 ± 9.8	44.6 ± 11.5	CG: 4.8 EG: 6.8
Shire et al., 1977(G1)	37.6 ± 5.4	38 ± 7.7	34.3 ± 3.8	38.4 ± 4.8*	CG: 0.4 EG: 4.1
Shire et al., 1977(G2)	37.6 ± 5.4	38 ± 7.7	35.2 ± 3.1	39.5 ± 3.6*	CG: 0.4 EG: 4.3
Songsorn et al., 2016	2.07 ± 0.69	2.08 ± 0.68	2.15 ± 0.62	2.22 ± 0.64	CG: 0.01 EG: 0.07

- CG = control group; EG = exercise group; G1 = group 1; G2 = group 2; G3 = group 3 (See table 7); * = significant $p<.05$.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight
De Sousa 2018 (G1)	2	4.60	0.61	0.04	1.18	7.78%
De Sousa 2018 (G2)	2	4.80	0.51	0.09	0.93	8.85%
Songsorn 2016	4	0.07	0.11	-0.64	0.86	6.59%
Ocel 2003	6	0.23	0.65	-0.86	1.71	4.13%
Collins 1993	7	2.70	1.23	0.42	2.04	6.17%
Shire 1977 (G1)	10	4.10	0.95	0.10	1.80	5.96%
Shire 1977 (G2)	10	4.30	1.28	0.31	2.25	5.32%
Khammassi 2018	12	4.80	0.98	-0.01	1.96	5.25%
Lunt 2014	12	1.80	0.30	-0.27	0.87	7.77%
Schmidt 2001	12	0.20	2.63	1.49	3.76	4.45%
Sellami 2001 (G1)	13	3.80	0.63	-0.45	1.73	4.81%
Sellami 2001 (G2)	13	6.80	0.64	-0.46	1.72	4.82%
Levesque 1997	15	8.00	1.28	0.76	1.79	8.16%
Pollock 1972 (G1)	15	6.80	2.02	0.99	3.04	4.98%
Pollock 1972 (G2)	15	5.50	1.43	0.39	2.47	4.97%
Greenlee 2017	16	2.61	0.30	0.05	0.54	9.98%
Mean		3.82	0.97	0.12	1.79	

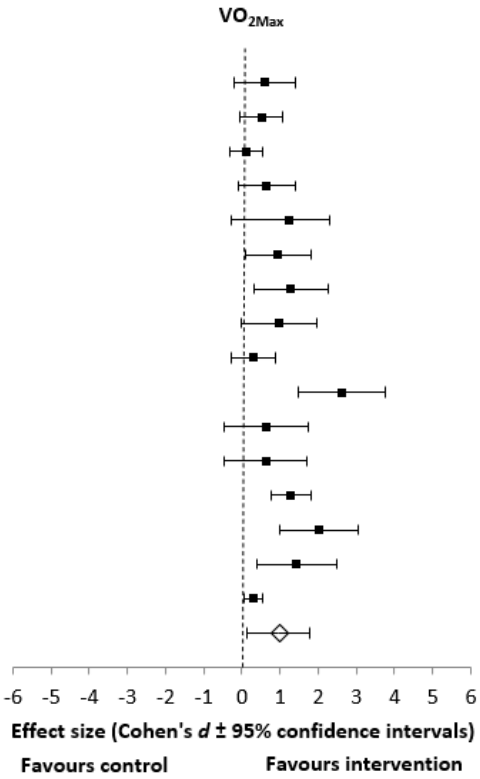


Figure 6. Forest plot of mean change in $\dot{V}O_{2max}$ for 12 studies and subgroups. This plot is sorted by training time-course in weeks. For all plots, the 95% CI were calculated, and the overall mean ES is represented with the diamond. The black squares are the ES of each study. The weight is also automatically calculated based on the ES, variance, sample size and SD.

$\dot{V}O_{2max}$ increased and favoured the exercise intervention groups compared to the control groups in all studies and subgroups. The average change in $\dot{V}O_{2max}$ increased significantly by 10.18 ± 3.9% with intervention compared to the 1.71 ± 4.1% observed in the controls, equal to a large ES of 2.54, which was classed as significant.

3.3.4. Maximum Heart Rate (HR_{max})

Table 9. HR_{max} scores across groups. Mean ± SD of both control and exercise groups, as well as the pre vs post scores. The change in scores are also represented as delta scores.

Study	Control Group (Pre)	Control group (post)	Exercise group (Pre)	Exercise group (Post)	Delta Δ (Pre-Post)
De Sousa et al., 2018 (G1)	139 ± 9.9	134.9 ± 7.9	141.4 ± 12	133 ± 9.4*	CG: -4.1 EG: -8.4
De Sousa et al., 2018 (G2)	139 ± 9.9	134.9 ± 7.9	137.1 ± 11.4	130.3 ± 9.4*	CG: -4.1 EG: -6.8
Khammassi et al., 2018	193.8 ± 9.6	192.4 ± 8.5	191 ± 10.3	190 ± 9.7	CG: -1.4 EG: -1
Lunt et al., 2014	179.0 ± 8.9	176.9 ± 8.7	174 ± 9.9	172.8 ± 10.5	CG: -2.1 EG: -1.2
Ocel et al., 2003	175 ± 4.9	175 ± 9.8	184 ± 6	169 ± 6*	CG: 0 EG: -15
Pollock et al., 1972 (G1)	189 ± 6.2	186 ± 7.6	186.3 ± 9.5	181.5 ± 9.4	CG: -3 EG: -4.8
Pollock et al., 1972 (G2)	189 ± 6.2	186 ± 7.6	189.8 ± 6.2	181.5 ± 6.6*	CG: -3 EG: -8.3
Sellami et al., 2014(G1)	198.1 ± 4.6	200 ± 4.3	200 ± 5.2	198 ± 6.4	CG: 1.9 EG: -2
Sellami et al., 2014(G2)	177.4 ± 5.2	188 ± 5.1	181 ± 5.2	178 ± 3.1	CG: 10.6 EG: -3
Shire et al., 1977(G1)	192.1 ± 9.2	190.6 ± 8.7	194.8 ± 11.1	195.8 ± 11.8	CG: -1.5 EG: 1
Shire et al., 1977(G1)	192.1 ± 9.2	190.6 ± 8.7	190.3 ± 9.7	189.4 ± 11.4	CG: -1.5 EG: -0.9

- CG = control group; EG = exercise group; G1 = group 1; G2 = group 2; G3 = group 3; * = significant $p<.05$.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
De Sousa 2018 (G1)	2	-8.40	-0.78	-1.36	-0.20	13.17%
De Sousa 2018 (G2)	2	-6.80	-0.65	-1.08	-0.23	16.85%
Ocel 2003	6	-15.00	-2.50	-4.35	-0.65	2.93%
Shire 1977 (G1)	10	1.00	0.09	-0.72	0.90	9.25%
Shire 1977 (G2)	10	-0.90	-0.09	-0.97	0.80	8.29%
Khammassi 2018	12	-1.00	-0.10	-1.04	0.84	7.76%
Lunt 2014	12	-1.20	-0.12	-0.69	0.45	13.37%
Sellami 2001 (G2)	13	-3.00	-0.70	-1.79	0.39	6.36%
Sellami 2001 (G1)	13	-2.00	-0.34	-1.42	0.73	6.55%
Pollock 1972 (G1)	15	-4.80	-0.51	-1.37	0.35	8.62%
Pollock 1972 (G2)	15	-8.30	-1.30	-2.32	-0.27	6.84%
Mean		-4.58	-0.64	-1.55	0.28	

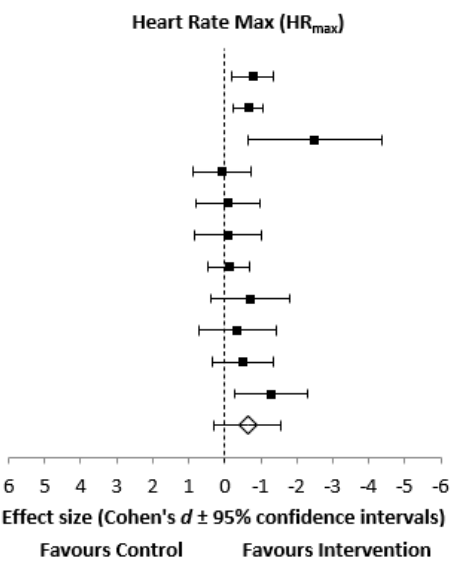


Figure 7. Heart rate max forest plot. For all plots, the 95% CI were calculated, and the overall mean ES (bias) is represented with the diamond/ The black squares represents the ES of each study. This plot was arranged based on training intervention time course in weeks.

Changes in HR_{max} favoured the exercise intervention, when compared to the controls. After exercise training, participants on average decreased their HR_{max} with the exception of group one (G1) in Shire et al., (1977). The forest plot indicates that four studies significantly decreased HR_{max} during a maximal test to exhaustion. The mean ES favoured the intervention with a large effect (0.64). The average decrease in HR for the intervention group was 2.87% compared to the controls of 0.56%, however, the mean error bars overlap 0 making it non-significant.

3.3.5. Body Mass Index (BMI)

Table 10. BMI scores across all groups. Mean ± SD from both control and exercise groups, as well as pre vs post intervention results. The change in scores are also calculated as delta scores.

Study	Control Group (Pre)	Control group (post)	Exercise group (Pre)	Exercise group (Post)	Delta Δ (Pre-Post)
De Sousa et al., 2018 (G1)	23.7 ± 3.9	23.6 ± 3.9	24.5 ± 3.4	24.5 ± 3.4	CG: -0.1 EG: 0
De Sousa et al., 2018 (G2)	23.7 ± 3.9	23.6 ± 3.9	25 ± 4.4	25.1 ± 4.4	CG: -0.1 EG:0.01
Greenlee et al., 2017	24.35 ± 5.34	24.48 ± 5.34	24.76 ± 4.88	24.83 ± 4.66	CG: 0.13 EG: 0.07
Khammassi et al., 2018	29 ± 2.2	29.2 ± 2.2	29.3 ± 2.5	28 ± 1.9	CG: 0.2 EG: -1.3
Levesque et al., 1997	20.5 ± 2.1	20.2 ± 1.4	21.8 ± 2.6	21.6 ± 2	CG: -0.3 EG: -0.2
Lunt et al., 2014	32.7 ± 3.4	32.6 ± 3.4	32.1 ± 3.1	32.1 ± 3.0	CG: -0.1 EG: 0
Schmidt, Biwer and Kalscheuer, 2001	31.4 ± 2.5	32 ± 2.7	31.2 ± 2.8	30.1 ± 3.2	CG: 0.6 EG: -1.1

- CG = control group; EG = exercise group; G1 = group 1; G2 = group 2; G3 = group 3.

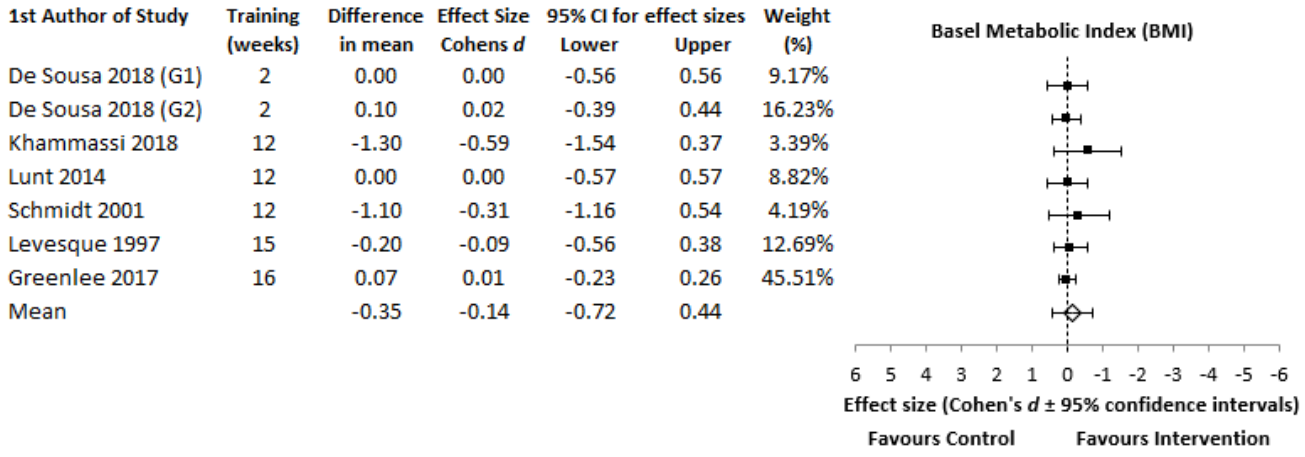


Figure 8. BMI forest plot. Mean ES is represented with the white diamond. Studies are represented by black squares.

The forest plot indicates that BMI was not significantly affected by the exercise intervention. The mean ES of -0.14 shows a small effect towards the intervention in the reduction of BMI. There are also very small differences between control and exercise groups. The control group Δ was 0.05 (0.21%) and the intervention group's average delta was -0.36 (-1.22%). BMI was only recorded in the aerobic exercise studies and no data was present for studies that focused on 1RM or PPO in this respect.

3.3.6. Body fat %

Table 11. Body fat scores across groups. Mean ± SD from both groups, including pre vs post intervention. The change in scores are also calculated for both groups. Measured either by skin fold or by bioelectric impedance.

Study	Control Group (Pre)	Control group (post)	Exercise group (Pre)	Exercise group (Post)	Delta Δ (Pre-Post)
Endurance studies measuring VO_{2max}					
De Sousa et al., 2018 (G1)	22.8 ± 7.5	22.8 ± 7.5	26.5 ± 7.4	26.1 ± 7.4	CG: 0 EG: -2
De Sousa et al., 2018 (G2)	22.8 ± 7.5	22.8 ± 7.5	25.9 ± 11	25.5 ± 11	CG: 0 EG: -2
Khammassi et al., 2018	21.4 ± 1.8	21.6 ± 1.9	22.2 ± 1.6	20.7 ± 1.2*	CG: 0.2 EG: -1.5
Lunt et al., 2014	39.5 ± 5.2	39.0 ± 5.3	39.5 ± 5.4	39.0 ± 5.6	CG: -0.5 EG: -0.5
Pollock et al., 1972 (G1)	23.1 ± 5.4	22.8 ± 5.5	22.9 ± 4	22.1 ± 3.9	CG: -0.3 EG: -0.8
Pollock et al., 1972 (G2)	23.1 ± 5.4	22.8 ± 5.5	23.3 ± 4.4	22.9 ± 4.4	CG: -0.3 EG: -0.4
Shire et al., 1977(G1)	22 ± 5.3	22.4 ± 5.1	26.8 ± 6.7	26.5 ± 5.9	CG: 0.4 EG: -0.3
Shire et al., 1977(G2)	22 ± 5.3	22.4 ± 5.1	25.2 ± 3.7	24.1 ± 4	CG: 0.4 EG: -1.1
Strength studies measuring 1RM					
Chtara et al., 2008	14.6 ± 4	14.6 ± 4.4	14.2 ± 2.2	12.9 ± 2.3	CG: 0 EG: -1.3
Radaelli et al., 2015 (G1)	17.3 ± 2.2	17.3 ± 2.2	16.6 ± 3.1	12.6 ± 3.3*	CG: 0 EG: -4
Radaelli et al., 2015 (G2)	17.3 ± 2.2	17.3 ± 2.2	16.7 ± 3.3	10.7 ± 2.8*	CG: 0 EG: -6
Radaelli et al., 2015 (G3)	17.3 ± 2.2	17.3 ± 2.2	17.1 ± 2.8	11.8 ± 2.6*	CG: 0 EG: -5.3
Power studies measuring PPO					
Sellami et al., 2014(G1)	11.4 ± 1.8	10.7 ± 1.6	11.8 ± 1.6	10 ± 1.1*	CG: -0.7 EG: -1.8
Sellami et al., 2014(G2)	12 ± 2.7	11.4 ± 2.6	12.3 ± 1.1	11.1 ± 1.2*	CG: -0.6 EG: -1.2

- CG = control group; EG = exercise group; G1 = group 1; G2 = group 2; G3 = group 3 (See table 7); * = significant $p<.05$.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
De Sousa 2018 (G1)	2	-2.00	-0.04	-0.60	0.52	9.00%
De Sousa 2018 (G2)	2	-2.00	-0.03	-0.45	0.38	9.90%
Shire 1977 (G1)	10	-0.30	-0.05	-0.86	0.76	7.44%
Shire 1977 (G2)	10	-1.10	-0.29	-1.18	0.61	6.97%
Chtara 2008	12	-1.30	-0.58	-1.59	0.44	6.34%
Khammassi 2018	12	-1.50	-1.06	-2.06	-0.07	6.40%
Lunt 2014	12	-0.50	-0.09	-0.66	0.48	8.92%
Sellami 2001 (G1)	13	-1.80	-1.04	-2.17	0.08	5.80%
Sellami 2001 (G2)	13	-1.20	-1.31	-2.47	-0.15	5.63%
Pollock 1972 (G1)	15	-0.80	-0.20	-1.05	0.64	7.22%
Pollock 1972 (G2)	15	-0.40	-0.09	-1.03	0.85	6.74%
Radaelli 2015 (G1)	24	-4.00	-1.25	-2.17	-0.33	6.78%
Radaelli 2015 (G2)	24	-6.00	-1.96	-2.93	-0.99	6.43%
Radaelli 2015 (G3)	24	-5.30	-1.96	-2.93	-0.99	6.43%
Mean		-2.01	-0.71	-1.58	0.16	

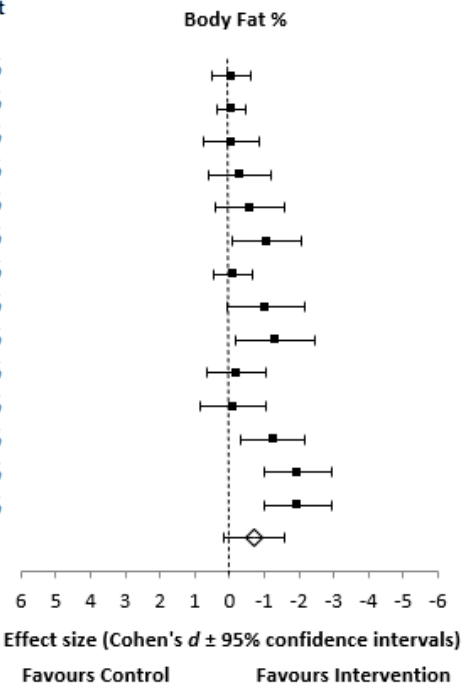


Figure 9A.Body fat forest plot across all studies. The overall mean ES is represented with the white diamond and the black squares represents the ES of each individual study.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
De Sousa 2018 (G1)	2	-2.00	-0.04	-0.59	0.52	17.14%
De Sousa 2018 (G2)	2	-2.00	-0.03	-0.44	0.37	30.33%
Shire 1977 (G1)	10	-0.30	-0.05	-0.86	0.76	8.57%
Shire 1977 (G2)	10	-1.10	-0.29	-1.13	0.55	7.19%
Khammassi 2018	12	-1.50	-1.06	-1.99	-0.13	5.84%
Lunt 2014	12	-0.50	-0.09	-0.65	0.46	16.47%
Pollock 1972 (G1)	15	-0.80	-0.20	-1.00	0.60	7.88%
Pollock 1972 (G2)	15	-0.40	-0.09	-0.97	0.79	6.59%
Mean		-1.08	-0.23	-0.95	0.49	

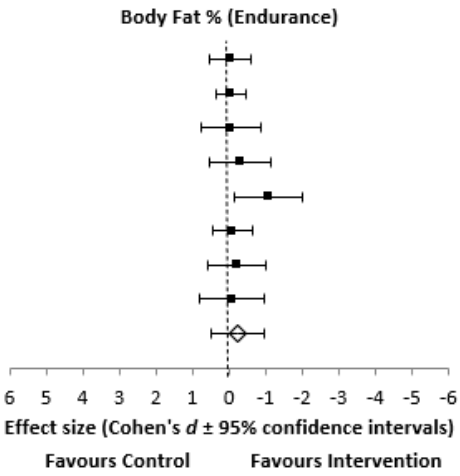


Figure 9B. Body fat forest plot across endurance sub-groups. The overall mean ES is represented with the white diamond and the black squares represents the ES of each study with the CI as error bars.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
Chtara 2008	12	-1.30	-0.58	-1.52	0.36	24.28%
Radaelli 2015 (G1)	24	-4.00	-1.25	-2.12	-0.38	26.31%
Radaelli 2015 (G2)	24	-6.00	-1.96	-2.89	-1.03	24.71%
Radaelli 2015 (G3)	24	-5.30	-1.96	-2.89	-1.04	24.70%
Mean		-4.15	-1.44	-2.35	-0.52	

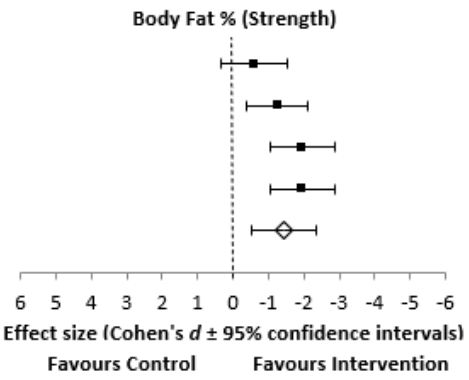


Figure 9C. Body fat forest plot across strength sub-groups. The overall mean ES is represented with the diamond and squares represents the ES of each study.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
Sellami 2001 (G2)	13	-1.20	-1.04	-2.08	-0.01	53.08
Sellami 2001 (G1)	13	-1.80	-1.31	-2.38	-0.24	46.92
Mean		-1.50	-1.18	-2.23	-0.13	

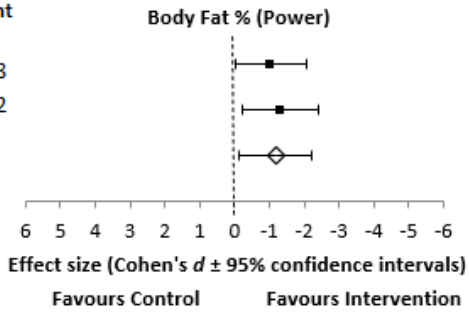


Figure 9D 1. Figure 9D. Body fat forest plot across anaerobic power sub-groups. Mean ES is signified with the diamond and individual ES with squares.

Based on figure 9A body fat scores in all studies and groups, favoured the intervention over the control and BF% decreases in all studies were due to the exercise interventions. Radaelli et al., (2015) exhibited the most meaningful significant change over 24 weeks (-4, -6 and -5.3%; ES (*d*) = -1.25, -1.96 and -1.96).

Further results also show that the mean ES favoured the interventions for all three components of fitness phenotypes. Endurance training ES equal -0.23 and a difference of -1.08% BF% however, was not significant. Strength training results were -1.44 and -4.15%, respectively and was classed as significant according to the plot. Finally, mean power training results were -1.18 and -1.50%, respectively and was also classed as significantly improved.

3.3.7. One Repetition Maximum (1RM)

Table 12. 1RM across studies. The Mean ± SD from both control and exercise groups including pre vs post intervention results. The change in scores are calculated for both groups. 1RM measured by Leg press or squat as this was a consistent measure across studies both testing lower limb strength.

Study	Control Group (Pre)	Control group (post)	Exercise group (Pre)	Exercise group (Post)	Delta Δ (Pre-Post)
Chtara et al., 2008	51.7 ± 7.7	52.7 ± 9.1	51.1 ± 6.9	66.7 ± 8.2*	CG: 1 EG: 15.6
Collins and Snow, 1993	118.8 ± 21.7	113.2 ± 15.5	106.5 ± 8.5	121.4 ± 10*	CG: -5.6 EG: 14.9
Dias et al., 2010 (G1)	56.5 ± 7.5	57.8 ± 7.1	59.7 ± 12.4	83.1 ± 10.9*	CG: -1.3 EG: 23.4
Dias et al., 2010 (G2)	56.5 ± 7.5	57.8 ± 7.1	61.7 ± 9.1	73.2 ± 8.3*	CG: -1.3 EG: 11.5
Humburg et al., 2007 (G1)	156.5 ± 31.5	149.7 ± 33.8	169.5 ± 40.2	183.1 ± 36.1	CG: -6.8 EG: 13.6
Humburg et al., 2007 (G2)	156.5 ± 31.5	149.7 ± 33.8	165.4 ± 38.2	189.91 ± 44.9	CG: -6.8 EG: 24.51
Kell, 2011 (G1)	74.8 ± 12.4	76.6 ± 11.3	92.4 ± 20.6	122.9 ± 19.1*	CG: 1.8 EG: 30.5
Kell, 2011 (G2)	74.8 ± 12.4	76.6 ± 11.3	48.9 ± 9.7	70.3 ± 10*	CG: 1.8 EG: 21.4
Radaelli et al., 2015 (G1)	157.8 ± 21	155 ± 25	170 ± 34.1	196.7 ± 15.5*	CG: -2.8 EG: 26.7
Radaelli et al., 2015 (G2)	157.8 ± 21	155 ± 25	172.5 ± 30.1	199.2 ± 14.4*	CG: -2.8 EG: 26.7
Radaelli et al., 2015 (G3)	157.8 ± 21	155 ± 25	178.5 ± 24.4	201.5 ± 25.4*	CG: -2.8 EG: 23
Shaw, Shaw and Brown, 2009	80.67 ± 16.33	78.75 ± 19.46	85.2 ± 13.94	140.15 ± 20.4*	CG: -1.92 EG: 54.95

- CG = control group; EG = exercise group; G1 = group 1; G2 = group 2; G3 = group 3 (See table 7); * = significant $p<.05$.

1st Author of Study	Training (weeks)	Difference in mean	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
Collins 1993	7	14.90	1.61	0.75	2.46	8.30%
Humburg 2007 (G1)	7	13.60	0.36	-0.26	0.97	9.76%
Humburg 2007 (G2)	7	24.51	0.59	-0.03	1.21	9.71%
Dias 2010 (G1)	8	23.40	2.00	1.13	2.88	8.14%
Dias 2010 (G2)	8	11.50	1.32	0.55	2.09	8.81%
Chtara 2008	12	15.60	2.06	0.85	3.27	6.47%
Kell 2011 (G1)	12	30.50	1.54	0.81	2.26	9.06%
Kell 2011 (G2)	12	21.40	2.17	1.37	2.97	8.57%
Shaw 2009	16	54.95	3.15	1.96	4.33	6.44%
Radaelli 2015 (G1)	24	26.70	1.01	0.11	1.90	8.12%
Radaelli 2015 (G2)	24	26.70	1.13	0.27	2.00	8.26%
Radaelli 2015 (G3)	24	23.00	0.92	0.08	1.77	8.37%
Mean		23.90	1.49	0.63	2.34	

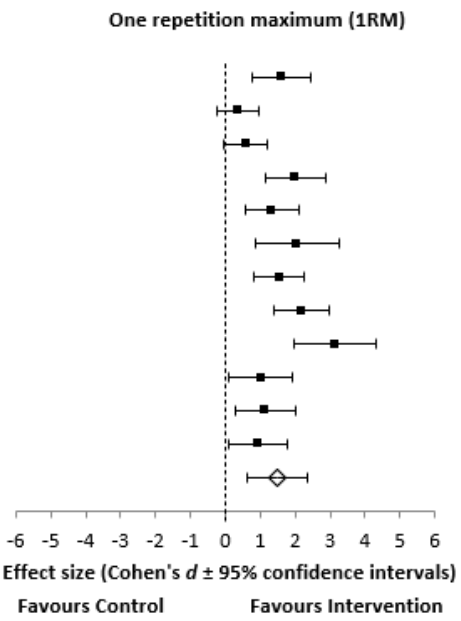


Figure 10. 1RM forest plot across sub-groups. For all data plots the 95% CI were calculated. The mean effect is represented with the diamond and the studies effect with squares.

The scores in all studies were classed as significantly improved after resistance training interventions, except for Humburg et al., (2007). The average increase in strength across all studies was 19.4 ± 4.1%. The control groups all found an average decrease in strength after no training (-1.26 ± 2.8%). The mean ES was significant, favouring the intervention with a large effect of 1.49 and a mean increase in lower body strength of 23.9 ± 11.4kg.

3.3.8. Peak Power Output (PPO)

Table 13. Peak power output scores across studies. Mean ± SD BMI scores from both control and exercise groups, as well as pre vs post intervention results in three studies. The change in scores are calculated as delta scores for both groups. PPO was measured either with W or $W \cdot kg^{-1}$ and on a cycle ergometer.

Study	Control Group (Pre)	Control group (post)	Exercise group (Pre)	Exercise group (Post)	Delta Δ (Pre-Post)
Ocel et al., 2003	248 ± 10	258 ± 25	257 ± 20	298 ± 20*	CG: 10 EG: 41
Sellami et al., 2014(G1)	8.3 ± 1.9	7.9 ± 1.9	7.9 ± 0.9	9 ± 0.8*	CG: 0.2 EG: 1.1
Sellami et al., 2014(G2)	6.9 ± 0.4	7.1 ± 2.4	6.7 ± 1.1	8 ± 0.9*	CG: 1.3 EG: 1.3
Songsorn et al., 2016	180 ± 48	174 ± 43	185 ± 50	195 ± 50	CG: -6 EG: 10

- CG = control group; EG = exercise group; G1 = group 1; G2 = group 2; G3 = group 3 (See table 7); * = significant $p<.05$.

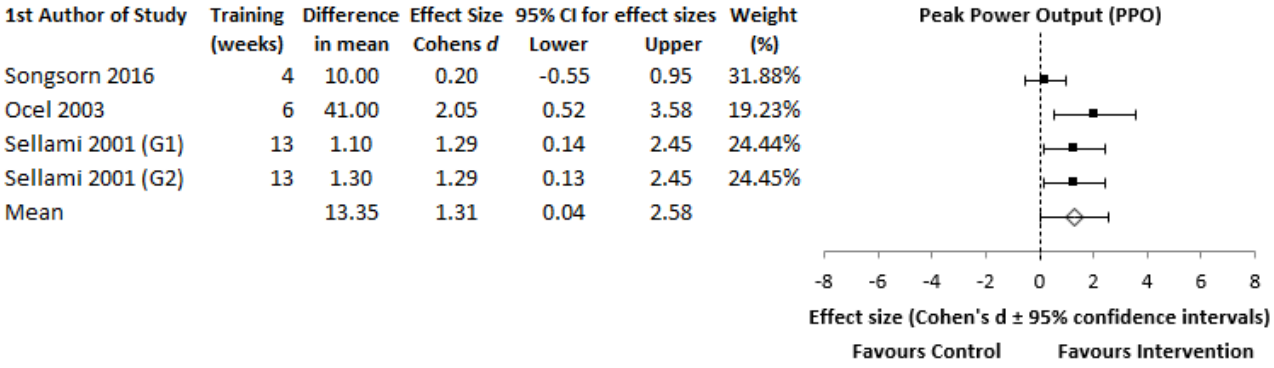


Figure 11. PPO forest plot. This plot was arranged in time-course in weeks. For all plots, the 95% CI's were calculated, and the mean ES is represented with the diamond and the study ES with squares.

PPO in all studies favoured the intervention. The mean change in the intervention groups was 11.8 ± 4.7% and the controls were 1. 4 ± 6.6%. The mean of the studies was significant at 1.29 large ES, favouring intervention over controls.

In summary, the measured variables favour exercise training interventions over the controls, especially in the three components of health-related fitness ($\dot{V}O_{2max}$, 1RM, and PPO), outlined in figure 12. Statistical power is shown in table 14. All study groups achieved the minimum group sample size for all three components of fitness (Cohen, 1988; ClinCalc LLC, 2018; Suresh, 2012). Additionally, 11 of the 18 studies met the ≥0.8 (80%) post-hoc statistical power.

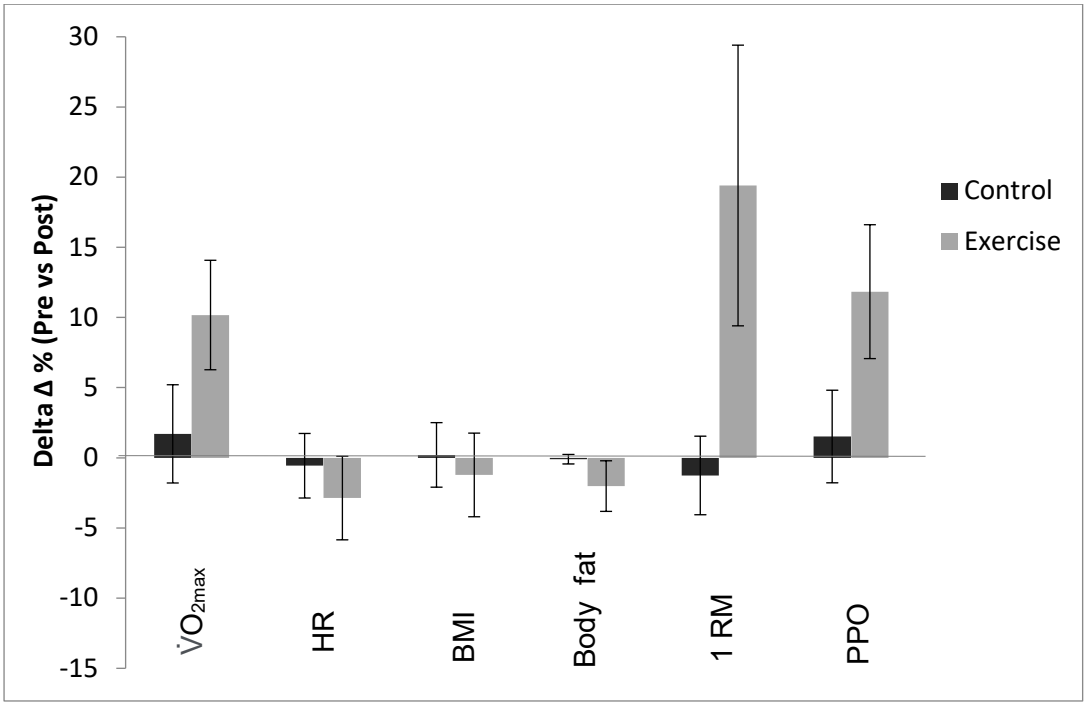


Figure 12. Summary of primary study results. Delta scores pre vs post intervention for both controls and exercise groups. Where $\dot{V}O_{2max,}$ 1RM and PPO increased and HR, BF% and BMI positively decreased with exercise. In control groups only, strength sees negative deterioration without training interventions, whereas all other variables display no or very slight changes but not significant.

A funnel plot was also implemented to assess the publication bias and precision of the studies that were included in this review using the reported outcomes of the study results on the main variables of interest (Figure 13) (Light and Pillemer, 1984; Egger, Smith, Schneider and Minder, 1997). The results of the Egger's test found signs of publication bias in the studies collected, which is not surprising as there were no studies that displayed low ES with high SE ($t = 2.55$, $p = 0.02$).

Table 14. Statistical power (β) and effect size. Power threshold was based at 80% as recommended by Cohen (1988) and Suresh (2012). Post-hoc power analysis was calculated for all studies.

Study	Sample size (N)	Statistical power (%)	Effect size (*d*) EG	Effect size (*d*) CG	Results used
Chtara et al., 2008	9	99.2	2.06	0.12	1RM
Collins and Snow, 1993	15	99.3	1.61	-0.30	1RM
De Sousa et al., 2018	26	59.0	0.61	0.07	$\dot{V}O_{2max}$
Dias et al., 2010	17	97.1	1.32	0.18	1RM
Greenlee et al., 2017	129	66.1	0.30	-0.04	$\dot{V}O_{2max}$
Humburg et al., 2007	10	25.9	0.59	-0.21	1RM
Kell, 2011	20	99.8	1.54	0.15	1RM
Khammassi et al., 2018	10	59.0	0.98	-0.22	$\dot{V}O_{2max}$
Levesque et al., 1997	30	100	1.28	1.21	$\dot{V}O_{2max}$
Lunt et al., 2014	11	10.6	0.30	-0.27	VO_{2max}
Ocel et al., 2003	6	94.4	2.05	0.53	PPO
Pollock et al., 1972	12	89.1	1.43	0.94	$\dot{V}O_{2max}$
Radaelli et al., 2015	13	82.3	1.13	-0.12	1RM
Schmidt, Biwer and Kalscheuer, 2001	12	100	2.63	0.10	$\dot{V}O_{2max}$
Sellami et al., 2014	8	73.5	1.29	-0.20	PPO
Shaw, Shaw and Brown, 2009	13	100	3.15	-0.11	1RM
Shire et al., 1977	11	85.1	1.28	0.06	$\dot{V}O_{2max}$
Songsorn et al., 2016	15	79.0	0.20	-0.13	PPO

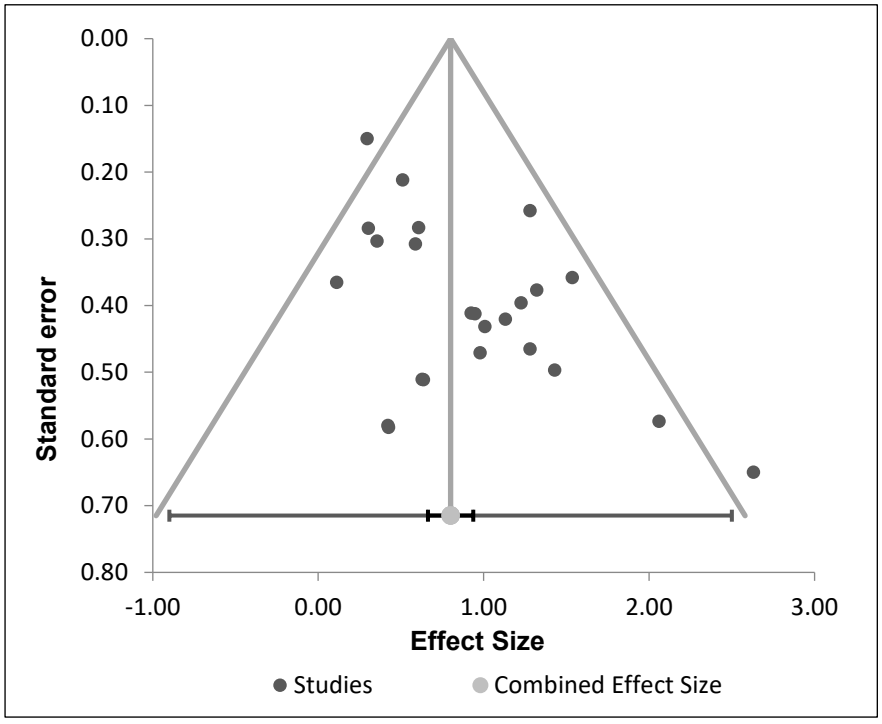


Figure 13. Funnel plot of training studies. Studies SE plotted against the ES of the delta primary variable (Meta-Essentials 2018 spreadsheet 1.4 Microsoft Excel 2016, Washington, USA).

3.3.9. Training load

Training load equals intensity multiplied by duration, multiplied by frequency of sessions, OR intensity, multiplied by total reps per-session, plus any active recovery during rests, multiplied by total sets per-session (Balsamo et al., 2012: Foster et al., 1996). These results are quantified with arbitrary but comparable units across studies.

In the first instance figures' 14A, 15A and 16A indicate no relationship between ES and the total number of weeks in the intervention alone and would appear to be random. R^2 correlation coefficient on the ES and TL was the strongest in TL per-session and per-week (sTL and wTL), when compared to the entire training intervention (tTL) for all three components of health-related fitness (R^2 = 0.86; 0.50; 0.90, respectively), showing a positive correlation between ES and TL for all studies included in this review. Overall, the gradient was the greatest in sTL, followed by wTL and finally tTL, which demonstrates the spread of TL throughout the entire training interventions, which may not be time-dependant.

For cardiorespiratory fitness, Schmidt, Biwer and Kalscheuer, (2001) had the largest ES of 2.63 with five days' worth of training over 12-weeks. For maximal strength, Shaw, Shaw and Brown, (2009) had the largest ES of 3.15 with three days' worth of training for 16-weeks, and for anaerobic peak power, Ocel et al., (2003) had the largest ES of 2.05 with four sessions per-week for 6-weeks.

Training load figures 14, 15, and 16 where the effect size equals ≥0.8 on the y-axis, intercepts reveals the estimated TL to achieve that effect for the component of fitness. This method is known as interpolation, where the estimate is between two known points and if this is outside the data set than extrapolation of the graph is required. Interpolation of sTL in $\dot{V}O_{2max}$ was equal to 1,700 A.U. and estimated to achieve a large ES. This is equivalent to one set of 25-30 minutes continuous endurance exercise, between 65-70% intensity or equivalent and equal to 5,000-6,000 A.U. wTL, corresponding to three sessions per-week in accordance to figure 14. 1RM has more variation as the ES is generally high, resulting in equal 7,000-8,000 sTL, 21,000-24,000 wTL as estimated using figure 15. Finally, PPO was much lower due to interval training lasting less than 1-minute per-interval, sTL equals 267 A.U. equivalent to 920 A.U per-week. Therefore, a combination of these are similar to many recommendations for daily exercise in healthy individuals.

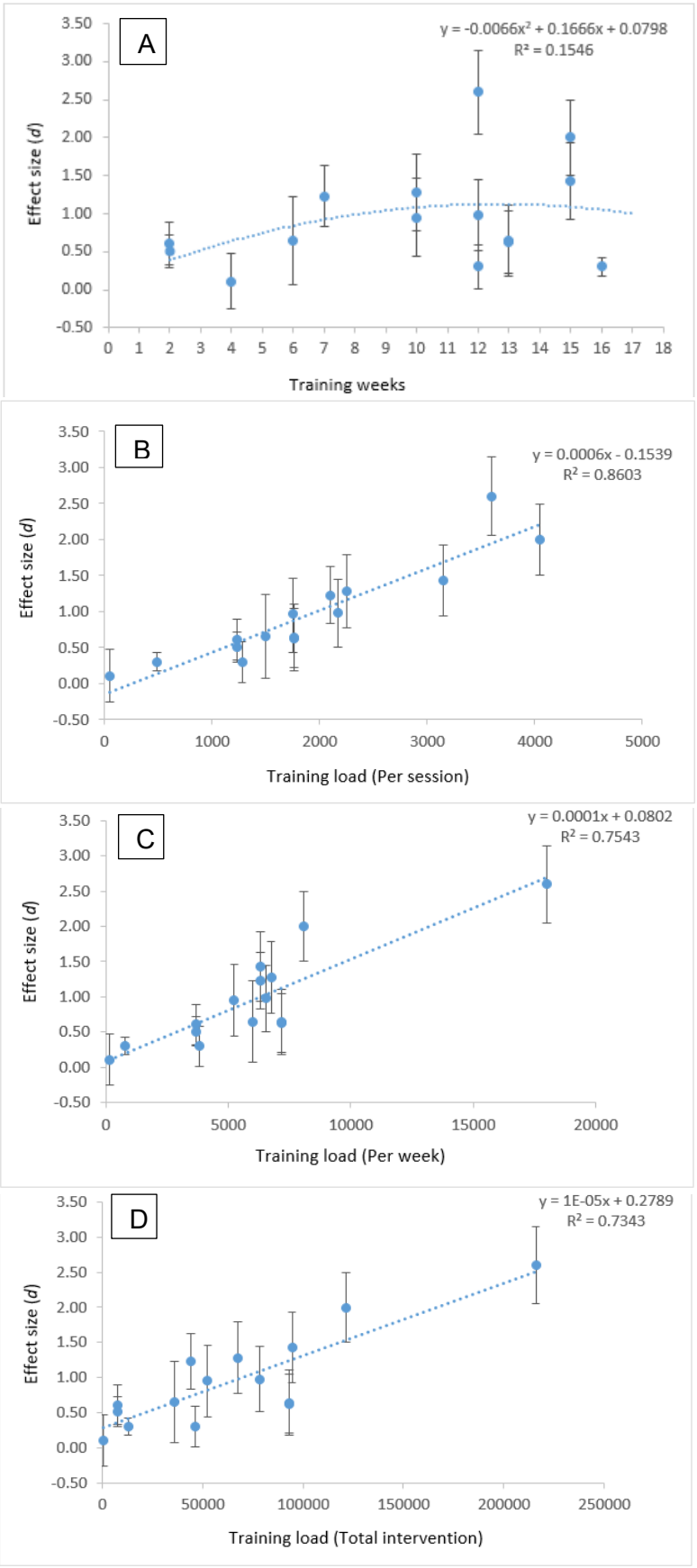


Figure 14. $\dot{V}O_{2max}$ ES and TL. Each study showed that ES and total amount of weeks in graph A had little correlation, graph B, C and D have a positive correlation regression line. 95% CI have also been plotted on all data points via the standard error measurement of the ES.

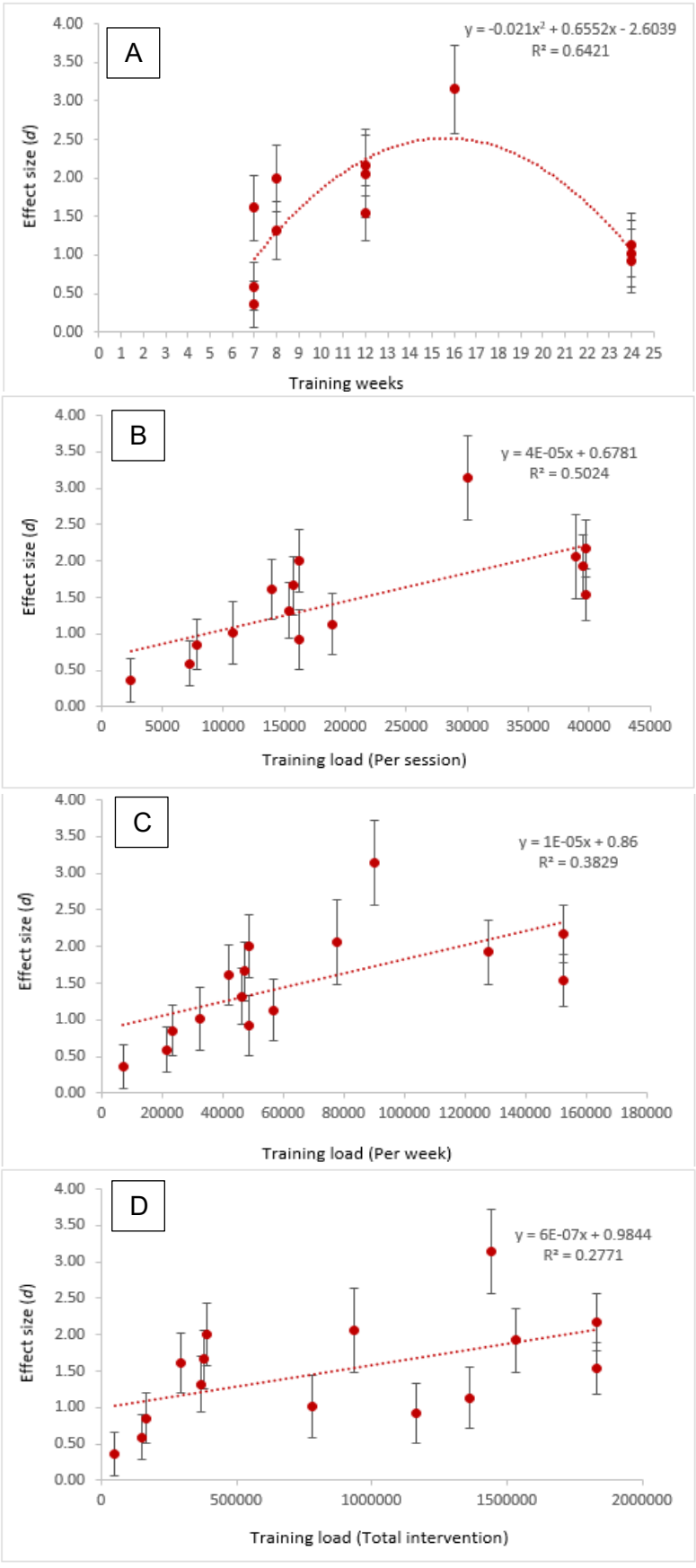


Figure 15. 1RM ES and TL. ES against total amount of weeks (A) and TL (B, C and D). TL was positively correlated to 1RM ES response. 95% CI have also been plotted on all data points via the standard error measurement of the ES.

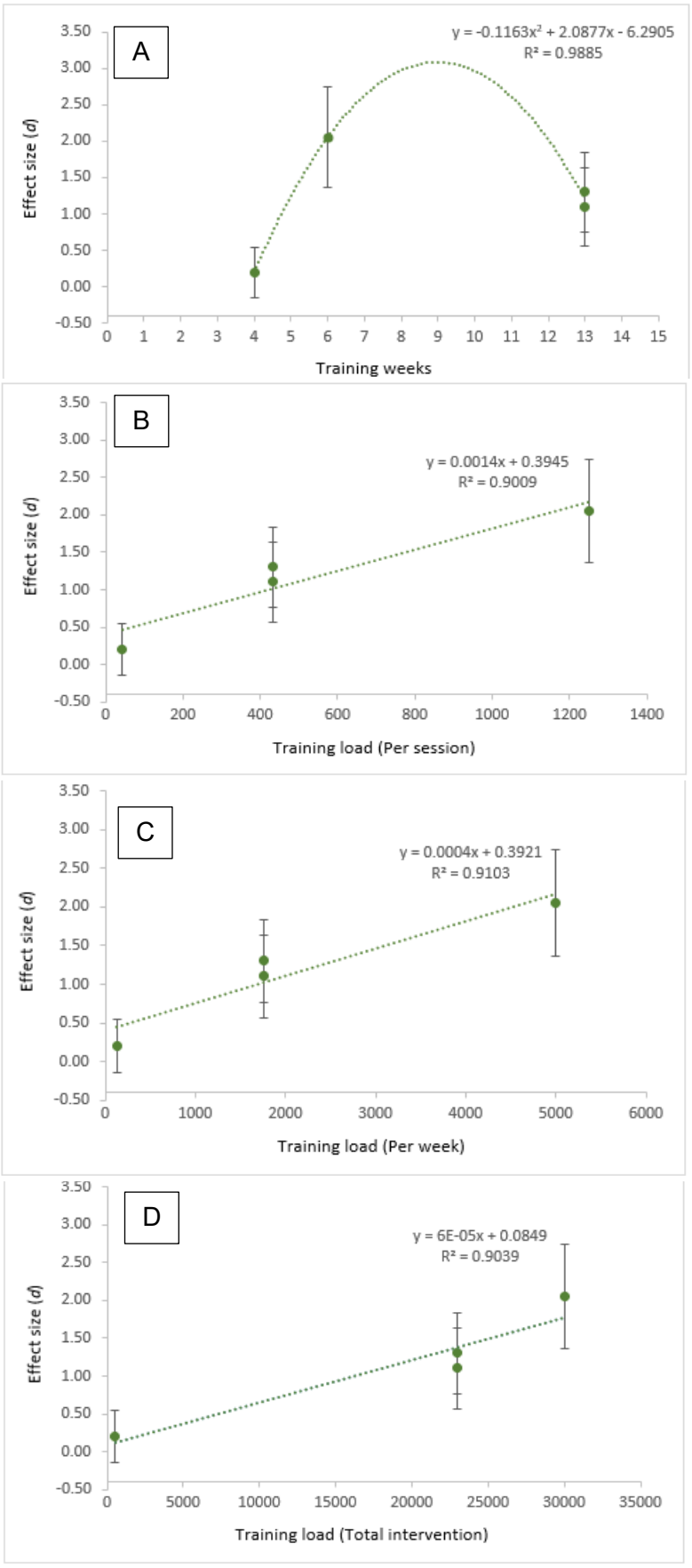


Figure 16. PPO ES and TL. Total amount of weeks in graph A had no correlation, graphs B, C and D ES and TL have a positive correlation represented by the dashed regression lines. 95% CI have also been plotted on all data points.

3.4. DISCUSSION

The aim of this systematic literature review with meta-analysis was to assess the differences in training intervention across studies on the three components of health-related fitness, and how the physiological and metabolic responses are linked to the training variables. The results have demonstrated some key findings.

The funnel plot showed signs of publication bias within the research literature, where important outcomes only seem to be published over non-significant results (Figure 13). However, Egger et al., (1997) stated, that analysis of heterogeneity is dependent on the number of trials comprised in the meta-analysis, which is often low and therefore, asymmetry may arise from chance. Following this, statistical power was calculated (ClinCalc LLC, 2018), resulting in 11 of the 18 studies meeting the post-hoc power threshold, whereas all of them met the pre-power calculations. It was considered to analyse the results with only the 11 powered studies, however the low study number within the meta-analysis, especially when split into the three components of fitness also caused issues with statistical significance testing. As power increases, the probability of type II error decreases, if power is low the probability that falsely accepting an incorrect hypothesis is increased. This could also indicate if a group is truly homogenous due to the wide differences in standard deviations, error, and bias. Caution is needed when conducting an initial power calculation to determine sample size, as studies such as Greenlee et al., (2017) with a sample size of 129 per-group still did not meet the post-hoc power, although having a 10-fold greater initial estimated pre-power and Bayesian approach should be acknowledged. The benefit of calculating both a *priori* and *post-hoc* power, in addition to ES in combination is the ability to inspect the real magnitude of the phenomenon, rather, than solely relying on individual tests alone. This complements statistical hypothesis, error, and bias testing (Peterson, Rhea and Alvar, 2005).

3.4.1. $\dot{V}O_{2max}$ and HR_{max}

All study interventions showed an increase in $\dot{V}O_{2max}$ compared to the control group, regardless of the training protocol. There was a significant mean increase in $\dot{V}O_{2max}$ of 10.18%, which agrees with previous research (Astorino and Schubert, 2014; Hautala et al., 2006; Helgerud et al., 2007; Laursen, Nummela et al., 2016). Interestingly, when assessing figures 14B, C and D, they show a positive correlation between ES and TL. This could explain why studies such as Lunt et al., (2014), Greenlee et al., (2017) and Songsorn et al., (2016) exhibited lower ES, as TL was also low, irrespective of the study's overall intervention time-course. This is reinforced by the fact that De Sousa et al., (2018) found meaningful ES and increases in $\dot{V}O_{2max}$ with only 2-weeks of training, compared to the 12, 16 and 4-weeks,

respectively. In fact, De Sousa's group displayed a greater sTL (Approx. 1,234 A.U.) and wTL (Approx. 3,702 A.U.), regardless of having a lower tTL (Approx. 7,404 A.U.), when compared to Greenlee et al., (2017), (Approx. 409 A.U. per-session, 796 A.U. per-week and 12,740 A.U. total), having a two-fold increase in ES of $\dot{V}O_{2max}$ improvements.

This review agrees with findings from Helgerud et al., (2007), in their study, 40 moderately trained individuals were randomly assigned to one of four aerobic training groups. All groups displayed an increase in $\dot{V}O_{2max}$ across 8-weeks, irrespective of the training protocol. However, the improvements in scores were different between groups and even participants in the same group, this is partly due to the training protocol, more specifically the different training loads and volumes. They stated exercise volume and intensity per-session are more important than the overall number of sessions and noted that higher intensities resulted in greater improvements when compared to lower intensities, even when matched with overall load and volume ($p < 0.01$). This notion is supported by early findings from Pollock (1977), Thomas, Adeniran and Etheridge (1984) and Wenger and Bell (1986), which concluded that training intensity cannot be compensated for by longer durations in the training intervention. However, Laursen, Blanchard and Jenkins (2002) found that if intensities are too high, significant aerobic adaptations may not be observed. This could be in part due to them using highly trained cyclists, as it has been well established that baseline training status affects outcomes of $\dot{V}O_{2max}$ (Hautala et al., 2006). MacDougall et al., (1998) found untrained participants were different in this respect. Implementing interval bouts of 'all-out' intensities significantly improved muscle glycolytic, oxidative enzyme activity and $\dot{V}O_{2max}$ due to peripheral adaptations from both aerobic and anaerobic respiration and replenishment in phosphocreatine stores during the recovery phases of the bouts, agreeing with similar work by Tabata et al., (1996). This review also illustrates that reductions in HR_{max} can occur within as little as 2-weeks of training (De Sousa et al., 2018). $\dot{V}O_{2max}$ is governed by the 'Fick equation':

Maximum Cardiac Output ($\dot{Q}$) x *Maximum arterio-venous oxygen difference (a-vO_{2dif}).*

Therefore, there must be an increase in either a-vO_{2dif}, stroke volume (SV) or both, because of the decrease in HR_{max}. The heart must become more efficient and stronger due to the increase in oxygen demand and delivery (Midgley et al., 2007; Moxnes and Hausken, 2012). In agreement, Wagner (1996) states that, where $\dot{V}O_{2max}$ is limited by oxygen supply, Q is the major factor that regulates oxygen delivery as supply tries to meet the demand. The literature suggests that, in many cases, especially in untrained populations, SV increases with exercise intensity up until ~50% of $\dot{V}O_{2max}$ where upon it plateaus. Evidence shows that this is a trainable response, which is often linked to the increase in $\dot{V}O_{2max}$ (Hautala et al., 2006;

Higginbotham et al., 1986). Yet, none of the 18 studies in this review measured Q, SV or a-vO_{2dif} and therefore, conclusions are speculative in this respect. In addition, other variables could contribute to this change such as, blood and plasma volume, water retention, red blood cell count, peripheral resistance, blood pressure etc. (Convertino, 1991; Hambrecht, 2000; Montero et al., 2019). However, these also were not recorded within the studies in this review.

3.4.2. BMI and Body Fat %

In this review decreases in BMI favoured the exercise group compared to the controls. In terms of body mass, it did not significantly change over the observed studies. However, decreases in BF% favoured the exercise groups. This could be explained by an increase in muscle mass and a decrease in fat mass causing an equilibrium in overall mass, especially in the resistance training studies. This review did demonstrate that, endurance, strength, and power training had small to large effects on BF%, with an average decrease in of 2.01%, classed as a large effect. Khammassi et al., (2018) did find significant decreases in BF% with 12-weeks of interval training three times per-week, Sellami et al., (2014) with sprint interval training over 13-weeks four times per-week, and Radaelli et al., (2015) with resistance training three times per-week over 24-weeks. In the study by Willis et al., (2012), they examined 119 sedentary, overweight, and obese adults in three training modes: aerobic training, resistance training and a mix of both (concurrent), three days per-week for 35-weeks. They found that aerobic training decreased total body mass and fat mass more than the resistance training (p<0.05), but resistance and concurrent training increased lean body mass more than aerobic training (p<0.05). These findings agree with the changes observed in this review, given the length of the intervention time-course. Radaelli et al., (2015) displayed the most significant change over 24-weeks, especially when compared to the shorter interventions.

Although training volume, intensity, and load play a large role in structuring the intervention, weight management and BF% require multiple considerations, such as training time, participant's status, diet (energy intake) and energy expenditure (Blair, 2015). The findings in this review suggest that changes in body mass are dependent on training specificity and overall duration. It was also concluded by Willis et al., (2012), that a combination of endurance and resistance training, could interfere with training adaptations and responses in a specific mode.

3.4.3. 1RM

1RM favours the intervention, regardless of training protocol within the included studies with a mean ES of 1.79. Of all the variables estimated in this review, the increase in 1RM was the

largest at 19.4% in the untrained participants. Interestingly, the results exhibit that 1RM decreases over time when no intervention is used (1.26% in control group). Figure 15A, B, C and D are similar to the findings of the $\dot{V}O_{2max}$ results in this review. This suggests that the magnitude of the effect in 1RM is independent of overall intervention time-course and instead, is strongly dependant of TL per-session and frequency per-week. When comparing results, Dias et al., (2010) found an ES of 2.00. This is equal to a 28.16% increase in 1RM in three days per-week over 8-weeks of training. When compared to Radaelli et al., (2015) whose participants trained for three days per-week but over 24-weeks, finding a lower 1.01 ES (13.57% increase). Because the frequency per-week was equal in terms of training days, the result in this review showed that sTL and therefore, wTL was greater in Dias et al., (2010) compared to Radaelli et al., (2015), sTL = 16,200 A.U. vs 10,800 A.U. and wTL = 48,600 A.U. vs 32,400 A.U. respectively. This shows no advantage of implementing a 24-week programme compared to 8-weeks in terms of ES.

The findings discussed agree with a previous a meta-analysis from Peterson, Rhea and Alvar (2005), which focused on muscular strength development in a wide range of training groups. They agreed when comparing studies, that training status may affect the results of adaptation and in general untrained groups see larger increases in strength compared to well-trained. Peterson's group found that training response varies at an individual level, greater adaptations are achievable with greater session loads, rather than overall sessions in a training programme, even for untrained and especially for trained groups. They recommend prescribing only two days per-week of training at 80-90% of 1RM for athletic populations, as the session intensity and recovery are most important. Also, the 'Law of diminishing return' needs to be considered, which states:

> *"As quantities of a training input (dose) increases, the resulting rate of output (strength gains) eventually decreases"*
> (Hirschey, 2003).

Neural adaptations from resistance training play a critical role in the development of strength, together with muscle hypertrophy, motor performance, motor unit activation, and local muscular endurance (Kraemer and Ratamess, 2004). Additionally, evidence highlights that resistance training also has small to medium increases on $\dot{V}O_{2max}$ and endurance performance, which could be part due to aerobic respiration and energy replenishment stores via aerobic pathways during the recovery between resistance training sets (Hautala et al., 2006; Kraemer et al., 2002). However, studies in this review did not assess both $\dot{V}O_{2max}$ and 1RM together, making it difficult to agree with these findings in the improvement of both components of health-related fitness. Nevertheless, there is clearly a relationship with the TL and the improvement in 1RM.

3.4.4. PPO

Peak power output increased significantly with a mean ES of 1.29 (11.84%) with training. Ocel et al., (2003) found the largest increase with as little as four days of training over 6-weeks. This agrees with work from Sarabia et al., (2017) and McGuigan et al., (2009) that found a 9.8% increase in PPO. The results highlight that TL in PPO development follows a similar trend to $\dot{V}O_{2max}$ and 1RM, that it is a trainable parameter relying heavily on the intervention training loads. Figures 16B, C, and D show a positive R^2 correlation coefficient with ES. Figure 16A exhibits that there is little relationship with ES and the intervention time-course alone. In agreement, Astorino and Schubert, (2014) found significant improvements in PPO using "all-out" sprint interval training (SIT) for 30 seconds, three times per-week over just 2-weeks of training in 20 active men. Similarly, Laursen, Blanchard and Jenkins (2002) found a 4.3% increase in PPO with as little as four sessions spread over 2-weeks in 14 highly trained cyclists. Conversely, Lindsay et al., (1996) did not find significant changes in PPO after 2-weeks of training. They further implied that PPO could increase with high intensity work bouts and shorter rest intervals, leading to contributions in high-energy phosphate compounds. This could be attributed to either increased splitting rates or greater availability of adenosine triphosphate (ATP), phosphocreatine (PCr) and improvements in skeletal muscle buffering capacity, making the session more demanding, (Komi, Klissouras and Karvinen, 1973; MacDougall et al., 1998; Tabata et al., 1996). Neuromuscular adaptations from resistance training play a critical role in the development of both strength and anaerobic power due to the motor performance, motor unit activation and local muscular endurance to sustain high workloads and wattages at PPO (Hautala et al., 2006; Kraemer et al., 2002).

This review shows that it is possible to use TL as an aid to guide an intervention to meet adequate effect sizes in the three components of health-related fitness. It is possible to use interpolation and extrapolation of figures 14, 15 and 16 to estimate the amount of training load in respect to effect size. Interestingly if a 0.8 effect size is required, using the graphs where the y-axis intercepts the trendline the x-axis should reveal the training load required to meet such effect sizes (x = training load). This systematic literature review and meta-analysis focused on untrained and sedentary individuals, aged between 18-55 years, which the NHS found to have the highest susceptibility rates to becoming inactive, overweight, and obese. It is important to account for training load rather than the time-course of the entire intervention. There is a large amount of evidence that structured exercise programmes can improve health status, weight management and susceptibility of life-threatening conditions, which is applicable for all populations. Based on these findings in this review, training time-course and exercise responses differ because of the applied training intervention methods, intensities,

frequencies, durations, recovery, and component of health-related fitness assessed, irrespective of the overall intervention timeframe implemented.

3.5. LIMITATIONS

The PICOS criteria in this review may have been too specific as there were many levels to accepting studies such as a specific control group, population, outcomes, and the type of study design, leading to a large exclusion rate for studies. This could have also affected the publication bias. A main limitation leading from this was the difficulty to compare variables as well as missing variables from this review such as, stroke volume, cardiac output, and a-vO_{2diff}. However, this provides more evidence of the limited quality of research that exists within this area. Another limitation was that in most cases, these laboratory training studies do not represent real world training programmes, where the training is mixed with additional sessions throughout a week, built of multiple components with different intensities, durations, frequencies, and volumes making it much more difficult to measure. TL only gives a limited perspective to the real training performed and future studies need to be more precise in the exact TL prescribed. In this respect, traditional endurance sessions are the simplest to calculate, as there are normally no rest periods or stoppages, and fluctuations in intensity to account for. However, once training has multiple components, various exercises, duration, frequencies, and volumes it becomes much more difficult to calculate. Alternatively, TRIMP (Training impulse) is another way of calculating training using heart rate data, however, this is also limited in the fact that duration in time (minutes) is needed, and that heart rate needs to be monitored throughout the session.

3.6. CONCLUSION

This review concludes that untrained individuals can significantly improve physiological and metabolic responses with exercise training. Many of the findings in this review agree with the research literature when compared to trained populations or studies that do not have control groups. The higher volumes and intensities of the training per-session has a large role in the physiological and metabolic adaptations compared to the lower intensities per-session, irrespective of adopting more weeks of overall sessions to compensate. Training load also appears to have an important role in determining adequate responses to training, however this may vary depending on the component of health-related fitness. Therefore, when planning a training programme, current baseline training status, along with session and weekly stimulus are fundamental factors to consider for adequate time-course and advantageous response rates.

CHAPTER 4: WHICH GENES BEST DEFINE EXERCISE-ADAPTATIONS AND RESPONSES - A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

4.1. INTRODUCTION

Based on the findings from Chapter 3, exercise-training interventions positively affect the three components of health-related fitness namely, cardiorespiratory fitness, muscular strength, and peak anaerobic power, in an untrained population. There are also associated improvements in other physiological and metabolic responses, following these interventions that can be explained in-part from the calculated training loads. This agrees with previous work, such as Schutte et al., (2016) who demonstrated responsiveness to exercise training varies significantly depending on the precise exercise-stimulus. These findings suggest that the current paradigm of generic-exercise prescriptions discussed from ACSM, NHS and WHO may be of limited value at an individual level. Evidence also shows that a genetic component for responsiveness to exercise training can explain up-to 80% of the variability in aerobic, strength and power adaptations (Bouchard, 2012; Hautala et al., 2006; Huygens et al., 2004; Komi et al., 1977; Schutte et al., 2016; Spurway and Wackerhage, 2006; Zempo et al., 2017). This is due to genetic influences on energy-pathways, metabolism, muscle composition, storage, tissue and cell growth, protein, hormonal, and enzyme interactions etc. (Komi et al., 1977; Vancini et al., 2014; Zambon et al., 2003). Research within elite performance shows certain genetic variants influence specific exercise adaptations and responses (Ahmetov et al., 2016; Prud'Homme and Fontaine, 1984; Spurway and Wackerhage, 2006).

Moreover, further research has identified several well-known genes such as the ACE and ACTN3 gene, to be associated with exercise trainability and successful performance (Cieszczyk et al., 2016; Gentil et al., 2012; McPhee et al., 2011; Sarzynski, Ghosh and Bouchard, 2017). Accordingly, these candidate genes might be a useful indicator in predicting and successful exercise training responses. For example. an improved cardiorespiratory system and higher levels of $\dot{V}O_{2max}$ would enable better oxygen delivery to tissues during exercise, more efficiency for oxygenated blood delivery prolonging the time to exhaustion and increasing the ability to sustain exercise at greater intensities (Midgley et al., 2007). Such an outcome is advantageous in high level athletes but also untrained and inactive populations. These improvements are supported by the observation from training, but also in well documented candidate genes, such as the ACE Insertion (I) genotype, and its association with higher aerobic performance phenotypes (Cam et al., 2007).

However, an increasing concern is the current strategy of identifying and selecting individual candidate genes associated with exercise (Bouchard, 2012; Schutte et al., 2016; Spurway and Wackerhage, 2006). Numerous amounts of the existing research are based upon studies that only investigate relatively few independent genes (Del Coso, et al., 2018; Spurway and Wackerhage, 2006). In these cases, the research has been overly simplified, as factors that contribute to successful improvements in fitness are complex (Del Coso, et al., 2018; Yvert et al., 2016). In agreement, Ahmetov et al., (2016) and Williams and Folland, (2008) reported that, regardless of a high heritability of genotypes associated with exercise responses, no single gene, or its polymorphism, has shown to be a definitive controlling factor of the physiological variables associated with aerobic, strength, and power variables (phenotypes) due to the large number of genetic polymorphisms involved. They also note that the same gene variant can produce different responses, even within the same population.

Accordingly, the aim of this systematic literature review and meta-analysis was to identify which genes and alleles best define exercise adaptation and responses in untrained humans in the presence of exercise training interventions, by assessing the current research literature, utilising studies that identify genotypes associated with exercise training, based on cardiorespiratory fitness, muscular strength, and anaerobic peak power. This will provide a variety of candidate genes for the determination of predictability in associated exercise adaptations and responses. Group and sub-group analysis will be advantageous, rather than individual study comparisons to determine any association with phenotypic variance to exercise training. Critically, searches in Scopus, Web of Science, PubMed, SportDiscus and the Cochrane library database for systematic reviews, found no systematic meta-analytical reviews published up to April 2019 comparing studies that have assessed genes associations with exercise interventions in aerobic, strength, and power variables across the untrained population.

4.2. METHODS

This review was conducted in accordance with the PRISMA and the Cochrane guidelines for systematic reviews (Moher et al., 2009). A comprehensive literature search was conducted to identify relevant research literature from multiple database searches (Table 15). All flagged studies were exported, filed, and managed using bibliographic management software (Refwork, ProQuest, USA). A similar protocol was used from Chapter 3, extracted studies were manually reviewed for relevance according to title and abstracts. Successfully screened studies underwent a PICOS criteria (Methley et al., 2014) and a COSMIN checklist (Mokkink et al., 2010), before being included in this review. Additionally, limited of agreement, statistical power, effect sizes and bias testing was also performed.

4.2.1. Literature search

Relevant literature was generated using four separate database platforms: Scopus (Elsevier), Web of Science (Clarivate Analytics), PubMed (MEDLINE) and SportDiscus (EBSCO). The final search terms were generated over the period April 2019 – May 2019. In total, 3,960 potentially relevant studies were identified. This search strategy was repeated to assess the consistency and repeatability of this search method (Kitchenham et al., 2011).

Table 15. Exercise genetic search results. Search terms that were implemented for the generation of literature in all the databases and the number of results shown by hits. Initial results were 3,901 in April and increased to 3,960 in the space of the collection period ending in May 2019.

Data Base	Hits	Search Terms
Scopus	3,260	TITLE-ABS-KEY ("Gene" OR "Genes" OR genetic* OR geno* OR genotype* OR mutation* OR phenotype* OR dna OR rna OR allele* OR chromosome* OR haplotype* OR haplogroup* OR snp* OR polymorphism* OR heterozygous OR homozygous OR "Deoxyribonucleic acid" OR "Ribonucleic acid" OR nucleotide OR "epigenetics" OR "methylation" OR "demethylation" OR "acetylation" OR "deacetylation") AND ("Exercise intervention" OR "Exercise training" OR "Exercise program*" OR "Exercise session" OR "Exercise regime*" OR "Training program*" OR "Training intervention" OR "Training session" OR "Training regime*" OR "Physical activity program*" OR "Physical activity intervention" OR "Physical activity session" OR "Fitness intervention" OR "Fitness program*" OR "Fitness training" OR "Sport* intervention" OR "Sport* training" OR "Training weeks" OR "Intervention weeks" OR "Exercise weeks") AND ("VO2*" OR "Cardiovascular endurance" OR "Aerobic fitness" OR "Maximal Aerobic Power" OR "Muscle strength" OR "1RM" OR "1 repetition maximum" OR "Anaerobic Power" OR "Peak power output" OR "PPO")
Web of Science	318	((TS=(“Gene”) OR TS=(“Genes”) OR TS=(Genotype*) OR TS=(Geno*) OR TS=(Mutation*) OR TS=(Phenotype*) OR TS=(DNA) OR TS=(RNA) OR TS=(Allele*) OR TS=(Chromosome*) OR TS=(Haplotype*) OR TS=(Haplogroup*) OR TS=(SNP*) OR TS=(Polymorphism*) OR TS=(Heterozygous) OR TS=(Homozygous) OR TS=(Deoxyribonucleic acid) OR TS=(Ribonucleic acid) OR TS=(Nucleotide) OR TS=(Epigenetics) OR TS=(Methylation) OR TS=(Demethylation) OR TS=(Acetylation) OR TS=(Deacetylation)) AND (TS=(“Exercise intervention”) OR TS=(“Exercise training”) OR TS=(“Exercise program*”) OR TS=(“Exercise session”) OR TS=(“Exercise regime*”) OR TS=(“Training program*”) OR TS=(“Training intervention”) OR TS=(“Training session”) OR TS=(“Training regime*”) OR TS=(“Physical activity program*”) OR TS=(“Physical activity intervention”) OR TS=(“Fitness intervention”) OR TS=(“Fitness program*”) OR TS=(“Fitness training”) OR TS=(“Sport* intervention”) OR TS=(“Sport* training”) OR TS=(“Training weeks”) OR TS=(“Intervention weeks”) OR TS=(“Exercise weeks”)) AND (TS=(“VO2*”) OR TS=(“Cardiovascular endurance”) OR TS=(“Aerobic fitness”) OR TS=(“Maximal Aerobic Power”) OR TS=(“Muscle strength”) OR TS=(“1RM”) OR TS=(“1 repartition maximum”) OR TS=(“Anaerobic Power”) OR TS=(“Peak power output”) OR TS=(“PPO”)))
Pubmed	180	((((“Gene”[Title/Abstract] OR “Genes”[Title/Abstract] OR Genetic*[Title/Abstract] OR Geno*[Title/Abstract] OR Genotype*[Title/Abstract] OR Mutation*[Title/Abstract] OR Phenotype*[Title/Abstract] OR DNA[Title/Abstract] OR RNA[Title/Abstract] OR Allele*[Title/Abstract] OR Chromosome*[Title/Abstract] OR Haplotype*[Title/Abstract] OR Haplogroup*[Title/Abstract] OR SNP*[Title/Abstract] OR Polymorphism*[Title/Abstract] OR Heterozygous[Title/Abstract] OR

		Homozygous[Title/Abstract] OR “Deoxyribonucleic acid”[Title/Abstract] OR “Ribonucleic acid” [Title/Abstract] OR Nucleotide[Title/Abstract] OR "Epigenetics"[Title/Abstract] OR "Methylation"[Title/Abstract] OR "Demethylation"[Title/Abstract] OR "Acetylation"[Title/Abstract] OR "Deacetylation"[Title/Abstract])) AND (“Exercise intervention”[Title/Abstract] OR “Exercise training”[Title/Abstract] OR “Exercise program*”[Title/Abstract] OR “Exercise session”[Title/Abstract] OR “Exercise regime*”[Title/Abstract] OR “Training program*”[Title/Abstract] OR “Training intervention”[Title/Abstract] OR “Training session”[Title/Abstract] OR “Training regime*”[Title/Abstract] OR “Physical activity program*”[Title/Abstract] OR “Physical activity intervention”[Title/Abstract] OR “Physical activity session”[Title/Abstract] OR “Fitness intervention”[Title/Abstract] OR “Fitness program*”[Title/Abstract] OR “Fitness training”[Title/Abstract] OR “Sport* intervention”[Title/Abstract] OR “Sport* training”[Title/Abstract] OR “Training weeks”[Title/Abstract] OR “Intervention weeks”[Title/Abstract])) AND ("VO2*"[Title/Abstract] OR “Cardiovascular endurance”[Title/Abstract] OR “Aerobic fitness”[Title/Abstract] OR “Maximal Aerobic Power”[Title/Abstract] OR “Muscle strength”[Title/Abstract] OR “1RM”[Title/Abstract] OR “Anaerobic Power”[Title/Abstract] OR “Peak power output”[Title/Abstract] OR “PPO”))
SPORTDiscus	202	(“Gene” OR “Genes” OR Genetic* OR Geno* OR Genotype* OR Mutation* OR Phenotype* OR DNA OR RNA OR Allele* OR Chromosome* OR Haplotype* OR Haplogroup* OR SNP* OR Polymorphism* OR Heterozygous OR Homozygous OR “Deoxyribonucleic acid” OR “Ribonucleic acid” OR Nucleotide OR "Epigenetics" OR "Methylation" OR "Demethylation" OR "Acetylation" OR "Deacetylation") AND (“Exercise intervention” OR “Exercise training” OR “Exercise program*” OR “Exercise session” OR “Exercise regime*” OR “Training program*” OR “Training intervention” OR “Training session” OR “Training regime*” OR “Physical activity program*” OR “Physical activity intervention” OR “Physical activity session” OR “Fitness intervention” OR “Fitness program*” OR “Fitness training” OR “Sport* intervention” OR “Sport* training” OR “Training weeks” OR “Intervention weeks” OR “Exercise weeks”) AND ("VO2*" OR “Cardiovascular endurance” OR “Aerobic fitness” OR “Maximal Aerobic Power” OR “Muscle strength” OR “1RM” OR “Anaerobic Power” OR “Peak power output” OR “PPO”)

- TITLE-ABS = title and abstract; TS = Topic; * = truncation; “ “ = phrase or joint word; ‘OR’ and ‘AND’ = Boolean operators/logic; HITS = number of results; SNP = single nucleotide polymorphisms.

4.2.2. Inclusion criteria

Literature collected in this review was further restricted to publications that were only available in English and full text articles. The adapted PICOS criteria was constructed to refine the results (Methley et al., 2014). Any studies that did not meet the PICOS were excluded. The population(s) must be classed as untrained and meet the criteria for one of the three components of fitness, similar to Chapter 3 (ACSM, 2017; Angel, 2013; Ratamess, 2011). Finally, the intervention time-course was determined from chapter 3 using studies such as, Astorino and Schubert, (2014) and Hautala et al., (2006) (Table 4).

Table 16. PICOS criteria. The criteria were set based on previous findings from the ACSM, NHS and previous literature. To ensure internal consistency remained the methods were similar in both reviews.

PICOS	Inclusion assessment
Population or Problem	*Adults classed as untrained (must meet one of these):* - $\dot{V}O_{2max}$ = ≤ 45 ml·kg^{-1}·min^{-1} Males, ≤ 40 Females. - 1RM = ≤ 1.06 x BW Males, ≤ 0.4 x BW Females (bench press). ≤ 1.91 x BW males, ≤ 1.32 x BW Females (leg press). - PPO = ≤ 9.22 W·kg^{-1} Males, ≤ 7.65 W·kg^{-1} Females. *Population group:* - Healthy human males and/or females aged 18-55 years old. - Grouped by gene or genotype for comparisons.
Intervention or Exposure	*Duration:* ≥ 2 weeks (minimum of 6 sessions, 3 per-week). *Intervention (must meet one of the components of fitness):* - Continuous Endurance/ Aerobic interval training. - Resistance training/ weight training. - Anaerobic interval/ sprint/ anaerobic training.
Comparison	- Pre vs Post changes in primary variables. - Group comparisons.
Outcome	*Study must include one of the Primary variables of interest:* - $\dot{V}O_{2max}$/ $\dot{V}O_{2peak}$/ Maximal Aerobic power/ fitness. - One repetition maximum/ maximal strength. - Peak power output (PPO). *Study must include:* - Gene association with a primary variable of interest.
Study type or design	Quantitative repeated measures study with clear pre and post data collection.

- $\dot{V}O_{2max}$ = maximal oxygen consumption; 1RM = 1 repartition maximum; PPO = peak power output; BW = body weight; W·kg^{-1} = watts per kilogram.

4.2.3. Study retrieval process and quality assessment

A flow diagram was used to demonstrate the retrieval process of this review (Moher et al., 2009). The updated COSMIN 2018 checklist was applied to assess the transparency and risk of bias of the collected studies by assessing the methodological quality (Mokkink et al., 2010). The 'worst score' approach was set for all items at ≥ 3 threshold score, parallel to Chapter 3. To ensure the consistency and reliability of the quality assessment tool, two independent reviewers evaluated the 43 studies identified.

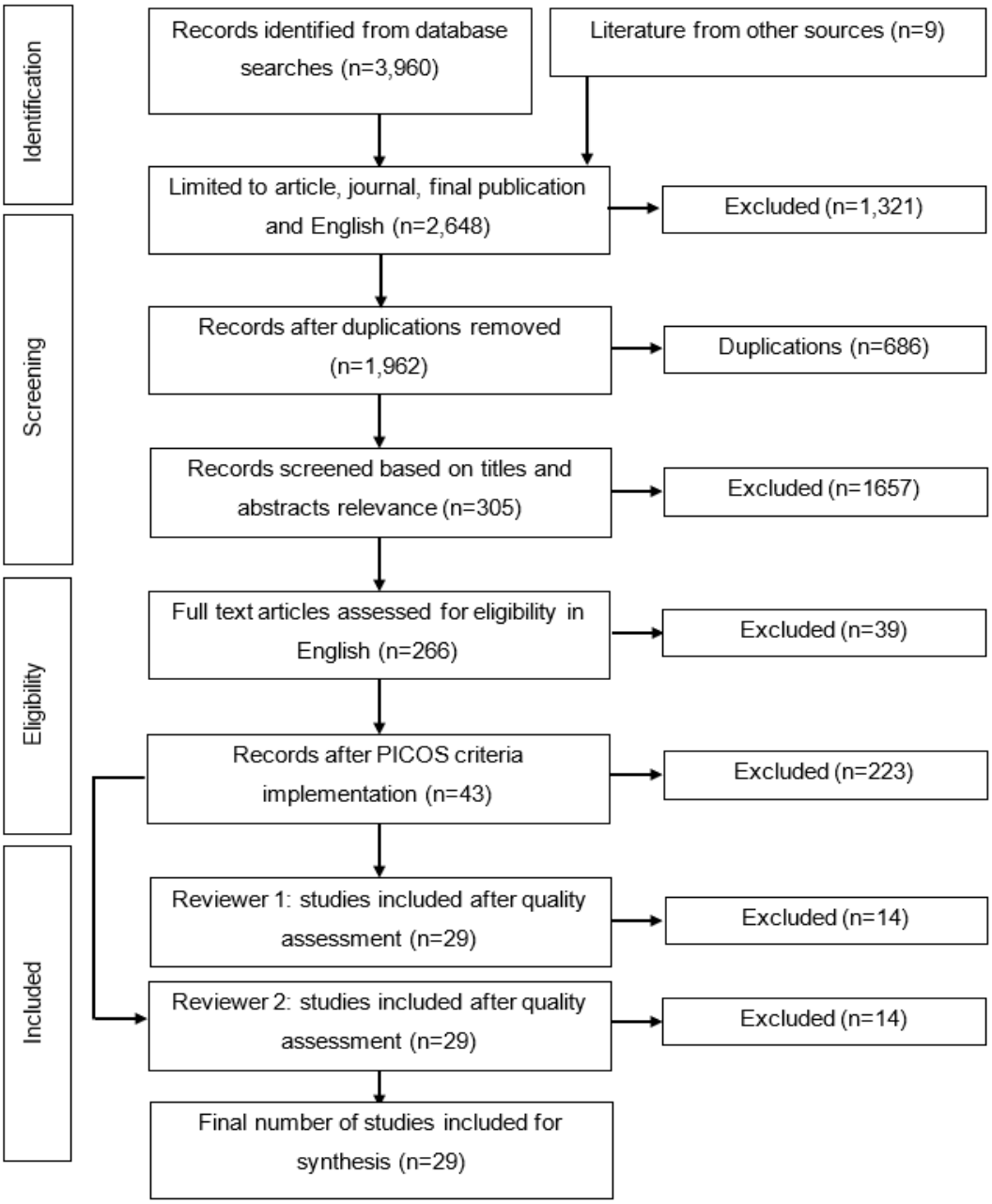


Figure 17. Flow diagram of gene studies. Method of collecting and excluding studies at each stage for this review. Where other sources were from unpublished sources and grey literature. This entire process was repeated twice. Three pearl papers were used as a control method.

4.2.4. Data Extraction and Statistical Analysis

Mean and standard deviations were manually extracted from the studies for synthesis of the meta-analysis. A minimum of two groups were required to have reported the same variable(s) for a conclusive outcome but avoiding duplication of results (Brown, Upchurch and Acton, 2003; Valentine, Pigott and Rothstein, 2010). Meta-Essentials 2018 spreadsheet 1.4 (Microsoft Excel 2016, Washington, USA) was implemented for the meta-analysis (Suurmond, van Rhee and Hak, 2017; van Rhee, Suurmond and Hak, 2015).

Table 17. Extracted variables of interest. List of variables that were measured in all the studies. This also shows the variables abbreviations and the common units of measurement.

Variable	Abbreviation	Unit of measurement
Cardiorespiratory fitness	$\dot{V}O_{2max}$	$ml \cdot kg^{-1} \cdot min^{-1}$ or $l \cdot min^{-1}$
One repetition maximum	1RM	kg or lb
Peak power output	PPO	W or $W \cdot kg^{-1}$
Genetic grouping variables	N/A	N/A

- $ml \cdot kg^{-1} \cdot min^{-1}$ = millilitres per kilogram per minute; $l \cdot min^{-1}$ = litres per minute; kg = kilogram; lb = pounds; W= watts; $W \cdot kg^{-1}$ = watts per kilogram; N/A = Not Applicable.

Pre and post intervention means, SD, pooled SD, SE, variance (s^1), Cohens *d* ES, upper and lower 95% CI and standardised means difference (SMD%) (Harrison, 2011), were calculated. Any genes and genotypes of interest identified were combined to form one group to define the experimental sub-groups and compared.

Post-hoc Statistical Power (ß) was also calculated with the threshold set at ≥0.8 (80%) and alpha level set to .05 (Cohen, 2013; Suresh and Chandrashekara, 2012). Forest and funnel plots were created using Meta-Essentials. IBM SPSS statistics version 24 (SPSS, Chicago, Illinois) was used to compare sub-groups based on genotype and the change in primary variables. Normality and homogeneity of variance was assessed using Shapiro-Wilk test and Levene's test, respectively. A non-parametric Kruskal-Wallis H test, mean ranks and subgroup weight analysis was also implemented for the estimation of gene variability and contribution towards the change in phenotypes.

4.3. RESULTS

4.3.1. Bias assessments

The same two reviewers (chapter 3) scored the 43 studies independently using similar methods, studies were scored from 1-4 on each item in the COSMIN checklist (31 items in total), which were rated high-to-low risk, respectively (Table 18). Any conflicts in scorings were resolved and the mean scores were taken (Mokkink et al., 2010). A Bland Altman plot LoA found the differences in COSMIN scores against the average means within the 95% CI (Figure 18). These results show no systematic differences, fixed bias, or possible outliers between the two reviewers in scoring these studies, classing the method with acceptable inter-ratter reliability and validity. The CI for the 95% LoA (approximate method), were also plotted (Bland and Altman 2010).

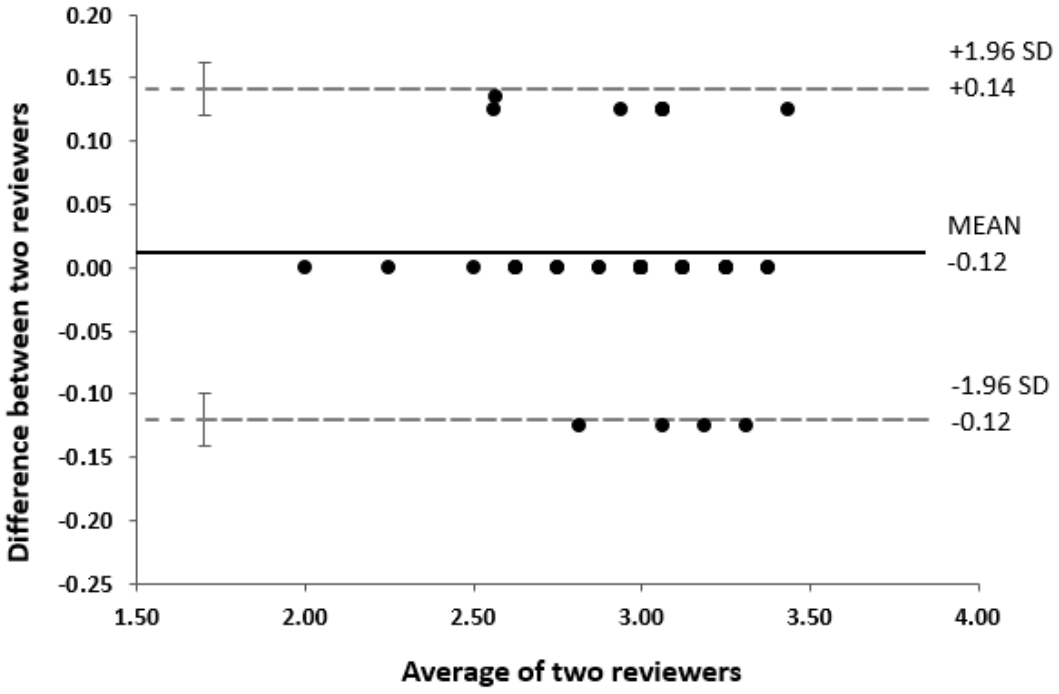


Figure 18. Bland Altman plot of gene studies. The results of both reviewers using the quality assessment tool is mapped as the difference in scores against the average score (Bias). The 95% LoA are also calculated and represented as the upper +1.96 and lower -1.96 dashed lines, showing the variation limits between the reviewers. Bland Altman's approximate method was also used similarly to chapter 3 (Bland and Altman 1986-2010).

Table 18. COSMIN quality control assessment tool and post-hoc power. The 'worst score' threshold of ≥ 3 was used to meet the satisfactory requirement of study quality. The average score between reviewers was taken for the final inclusion (Mokkink et al., 2010; Terwee et al., 2012). Power threshold was based at 0.8 or 80% as recommended by Cohen (1988) and Suresh (2012).

Study	Reviewer 1 COSMIN score	Reviewer 2 COSMIN score	Mean scores of reviewers	Included in review (Yes/No)	Statistical Power (ß) (%)
Ahtiainen et al., 2011	3.38	3.25	3.31	Yes	46.3
Bae et al., 2007	2.50	2.64	2.57	No	81.3
Böhm et al., 2016	3.25	3.25	3.25	Yes	25.4
Bouchard et al., 2010	3.00	3.00	3.00	Yes	89.2
Butcher et al., 2008	3.13	3.13	3.13	Yes	13.6
Caldow et al., 2015	2.63	2.63	2.63	No	98.1
Camera et al., 2010	2.50	2.63	2.56	No	NR
Christiansen et al., 2010	2.75	2.75	2.75	No	53.6
Cięszczyk et al., 2016	2.75	2.75	2.75	No	96
Clarkson et al., 2005	3.00	3.00	3.00	Yes	100
Colakoglu et al., 2005	3.25	3.13	3.19	Yes	100
Davidsen et al., 2010	3.13	3.00	3.06	Yes	78.8
Denham et al., 2018	2.50	2.50	2.50	No	54.5
Dohlmann et al., 2018	3.25	3.25	3.25	Yes	84.3
Egan et al., 2013	3.00	3.00	3.00	Yes	77.4
Erskine et al., 2012	3.13	3.13	3.13	Yes	96.1
Gentil et al., 2011	3.25	3.25	3.25	Yes	85
Gentil et al., 2012	3.38	3.50	3.44	Yes	98.3
Hamel et al., 1986	2.88	2.88	2.88	No	54.7
Harmon et al., 2010	2.88	2.88	2.88	No	100
He et al., 2010	3.00	3.00	3.00	Yes	46.8
Kazior et al., 2016	3.00	3.00	3.00	Yes	99.9
Konopka et al., 2013	3.00	3.13	3.06	Yes	84.1
Lamas et al., 2010	3.00	3.00	3.00	Yes	99.7
Little et al., 2010	3.00	3.00	3.00	Yes	84.2
Lundberg et al., 2014	3.00	3.13	3.06	Yes	75.4
McPhee et al., 2011a	3.13	3.13	3.13	Yes	89.3
McPhee et al., 2011b	3.00	3.13	3.06	Yes	100
Murakami et al., 2002	2.88	2.75	2.81	No	99.9
Nader et al., 2014	2.63	2.63	2.63	No	100
Parcell et al., 2005	2.63	2.63	2.63	No	97.6
Parra et al., 2000	3.00	3.00	3.00	Yes	100
Rankinen et al., 2000a	3.38	3.38	3.38	Yes	100
Rankinen et al., 2000b	3.25	3.25	3.25	Yes	100
Rico-Sanz et al., 2004	3.00	3.00	3.00	Yes	100
Schrauwen et al., 2002	2.00	2.00	2.00	No	19.4
Silva et al., 2015	3.00	3.13	3.06	Yes	90.7
Thomis et al., 2004	3.38	3.38	3.38	Yes	97.1
Thompson et al., 2004	3.13	3.13	3.13	Yes	97.6
Walker et al., 2004	2.88	3.00	2.94	No	99.9
Wilkinson et al., 2008	3.13	3.13	3.13	Yes	100
Yu et al., 2014	3.00	3.00	3.00	Yes	86.8
Zarebska et al.,2014	2.25	2.25	2.25	No	81.1

- NR = not reported (unable to calculate power due to lack of data presented).

22 of the 29 studies met the post-hoc statistical power threshold. A funnel plot was constructed to assess the publication bias and precision of the studies. The asymmetric plot demonstrated signs of bias (t = 3.24, p = .002), as there was a lack of reported studies with low ES and high SE (Light and Pillemer, 1984; Egger, Smith, Schneider and Minder, 1997).

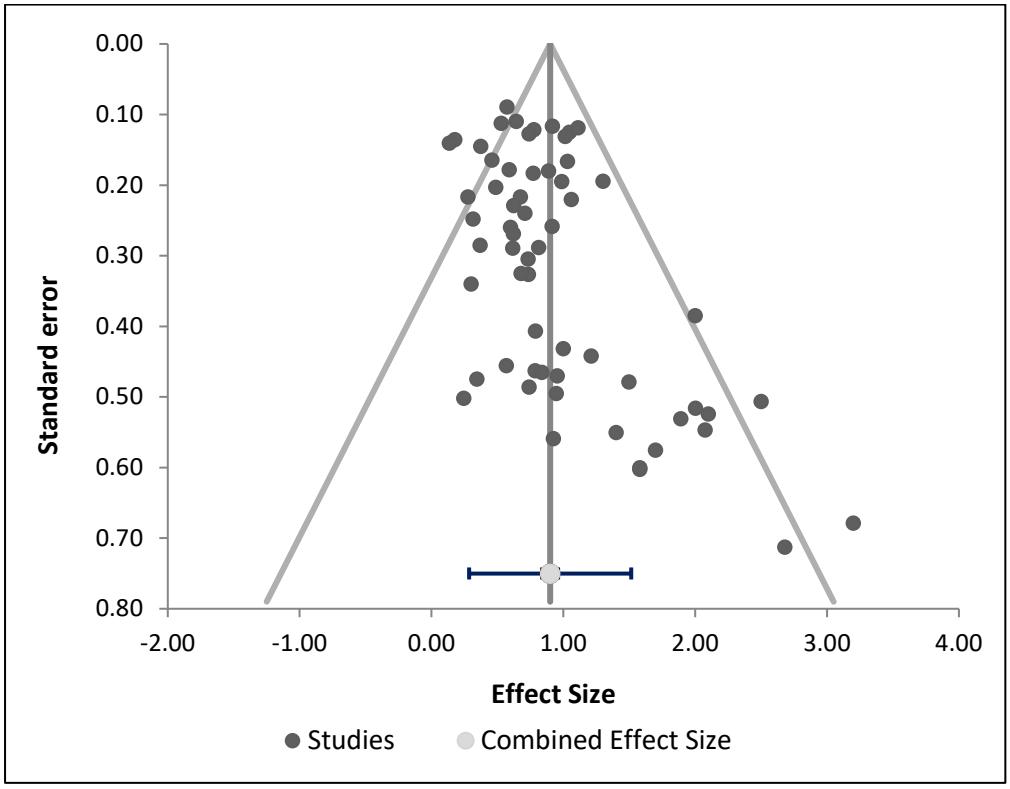


Figure 19. Funnel plot of gene studies. Using effect sizes from standard errors of the studies (Meta-Essentials 2018 spreadsheet 1.4 Microsoft Excel 2016, Washington, USA).

4.3.2. Overview of intervention and genes

Of the 43 studies, 29 were accepted with the COSMIN tool, and 24 of these were included in the final analysis. The remainder were excluded as they did not include a common, comparable genotype. The training intervention for all studies are shown in table 19. A total of 44 different candidate genes were initially associated with training. From this, a final 13 candidate genes were included in the meta-analytical review due to the lack of reported consistency for the data-analysis (Table 20). Any studies with two, or more training groups were included in the meta-analysis, but only if the groups met the specific PICOS criteria and the data was not being duplicated. The 24 included studies resulted in, 43 groups in aerobic training interventions, 29 in strength, and 17 in anaerobic power, which comprised of a total of 3,012 participants.

Table 19. Study training intervention information. These only included studies and groups that met the meta-analysis criteria in-which there was at least two groups that measured the same genetic and phenotype variable. Of the 29 studies 24 were included.

Study	Time-course	Intervention
Aerobic training intervention		
Böhm et al., 2016	8 weeks 3 days per-week	30-min cycling at 80% of $\dot{V}O_{2peak}$ and was not changed throughout the training period.
Butcher et al., 2008	8 weeks 3 days per-week	Self-selected walking speeds of 10,000 steps completed on a treadmill.
Dohlmann et al., 2018	6 weeks 3 days per-week	Seven high intensity cycles of 1-min bouts per-session: session 1: 60, 70, 80, 90, 95, 95, 95%; session 2: 70, 80, 90, 95, 95, 95, 95%: session 3: 80, 90, 95, 95, 95, 95, 95% of $\dot{V}O_{2peak}$. Session 4-6 at 95%, 7-12 increased to 100%, 13-18 ending at 105%.
Egan et al., 2013	2 weeks 7 days per-week	60-min continuous cycle training at 80% $\dot{V}O_{2peak}$, consistent throughout for the 14 consecutive days.
Kazior et al., 2016	7 weeks 2 days per-week	Endurance cycling at 63-65% $\dot{V}O_{2max}$ increasing every 2-weeks. Cadence at 60-65rpm, followed by 10 min rest. Resistance training included leg press at 70% 1RM, increasing by 5–7% every 3-4 training sessions. Sets increased from four on week one to six by week five, number of reps decreased from 12 to 8 with 3-min rest between sets.
Konopka et al., 2013	12 weeks 3-4 days per-week	Progressive aerobic continuous cycling: 20-45 min per-session at intensities of 60-80% heart rate reserve. Last 5-weeks consisting of 45-min cycles at 80%.
McPhee et al., 2011a	6 weeks 3 days per-week	Aerobic cycling at 85 rpm: First at 30-min cycles at 75% HR_{max}, week-2 ended with 2-min at 90%, week 3-6 of 24-min between 75-80%, followed by 2-min at 90%.
McPhee et al., 2011b	6 weeks 3 days per-week	Aerobic cycling at 85 rpm: First at 30-min cycles at 75% HR_{max}, week-2 ended with 2-min at 90%, week 3-6 of 24-min between 75-80%, followed by 2-min at 90%.
Rankinen et al., 2000a	20 weeks 3 days per-week	First 2-weeks at 55% $\dot{V}O_{2max}$ for 30-min continuous cycling and increased to 50-min at 75% and sustained for the last 6-weeks.
Rico-Sanz et al., 2004	20 weeks 3 days per-week	Continuous cycling of 30-min for the first 2-weeks to 50-min which was maintained from week 14 at 55% $\dot{V}O_{2max}$ for 4 weeks to 75% during the last 8 weeks.

Silva et al., 2015	18 weeks 3 days per-week	60-min of running, first half of the running was determined by heart rate at ventilator anaerobic threshold and the second half was slightly above respiratory compensation point.
Thompson et al., 2004	27 weeks 4 days per-week	Treadmill running at intensities between 60-85% $\dot{V}O_{2max,}$ duration at 15-40 min during the first 4-weeks once 40-min was reached it would be maintained.
Wilkinson et al., 2008	10 weeks 2-3 days per-week	G1: cycle endurance training two times per-week for 30-min at 75% $\dot{V}O_{2max.}$ Third week = 45-min and week 6, 1-hour.
Yu et al., 2014	27 weeks 3 days per-week	Progressive treadmill training programme between 60-85% of $\dot{V}O_{2max}$ of continuous exercise.
Strength training intervention		
Clarkson et al., 2005	12 weeks 2 days per-week	Weeks 1-4: 3-sets of 12-rep max. Weeks 5-9: 3-sets of 8-rep max. Weeks 10-12: 3-sets of 6-rep max with elbow flexion, biceps preacher curl, biceps concentration curl, standing biceps curl, overhead triceps extension, and triceps kickback.
Colakoglu et al., 2005	6 weeks 3 days per-week	12–15 RM in the first 3-weeks (first mesocycle). In the second 3-week (second mesocycle), equaled 8–12 RM. 1-5 sets with 20-30 seconds rest between of seven exercises per-session.
Davidsen et al., 2010	12 weeks 5 days per-week	Split-body progressive resistance training: military, bench press, seated chest fly, and triceps extension two times per-week. Lateral pull-down, wide grip row, reverse fly, biceps curl, and a series of abdominal exercises two times per-week. Leg press, knee extension, hamstring curl, and calf raise once per-week. All performed at 80% of 1RM, 3-4 sets of 6-12 reps.
Gentil et al., 2011	11 weeks 2 days per-week	Resistance training consisted of five exercises: leg press, knee flexion, bench press, pull down and sit ups. Initially set at 8-rep maximum and increased to 12 at 2-sets.
Gentil et al., 2012	11 weeks 2 days per-week	Performed the same intervention as their previous study (Gentil et al., 2011), instead with a different cohort of 124 men without previous resistance training experience.
Lamas et al., 2010	8 weeks 3 days per-week	Progressive resistance training: Group 1 between 4-10 rep max. Group 2, intensities from 30-60% 1RM between 6-8 reps and 2-4 sets of lower body exercises.
Thomis et al., 2004	10 weeks 3 days per-week	Progressive 5-sets of biceps curl training. Set 1, 14-reps at 60%; set 2, 12-reps at 75%; set 3, 10-reps at 80%, set 4, 8-reps at 85%; and set 5, 70% 1RM to failure.

Wilkinson et al., 2008	10 weeks 2-3 days per-week	Resistance training three times per-week. 3-sets of 10-12 reps at 80% 1RM, week five, 5-sets of 8-10 reps, week 8-10, 5-sets at 6-8 reps.
Anaerobic power training intervention		
Dohlmann et al., 2018	6 weeks 3 days per-week	Seven high intensity cycling of 1-min bouts per-session: session 1: 60, 70, 80, 90, 95, 95, 95%; session 2: 70, 80, 90, 95, 95, 95, 95%: session 3: 80, 90, 95, 95, 95, 95, 95% of $\dot{V}O_{2peak}$. Session 4-6 at 95%, session 7-12 increased to 100%, session 13-18 at 105%.
Little et al., 2010	2 weeks 3 days per-week	60-seconds of high intensity cycles at 100% $\dot{V}O_{2max}$ with 75-seconds active rest between bouts at 30W. First two sessions at 8-bouts, session 3-4 10-bouts and final two sessions 12-bouts.
Lundberg et al., 2014	5 weeks 2-3 days per-week	Aerobic exercise of 40-min one-legged cycle at 70% max workload at 60rpm, followed by a 15-min rest and 4x7 maximal knee extension reps with 2-min rest between.
Parra et al., 2000	2-6 weeks 2-7 days per-week	G1: seven days per-week for 2-weeks, G2: two days per-week for 6-weeks. 30-second maximum all-out cycling with 12-min rest between bouts. Sessions 1-3: two 15-seconds and two 30-seconds bouts and increased by one bout every two sessions. Flywheel at 0.075 kg body mass.

- 1RM = One repetition maximum; RPM = revolutions per minute; W = Watts; G1 = Group 1; G2 = Group 2; Min = minutes; Sec = Seconds; HRmax = Heart rate maximum

Table 20. Final list of candidate genes. Interactions are only with other included candidate genes in this review.

Gene	Gene description	No. Participants	Associated phenotype	Interactions with listed genes
ACE	Angiotensin-converting enzyme is a central component of the renin–angiotensin system, which controls blood pressure by regulating the volume of fluids in the body. The G-allele (D) is associated with a greater increase in left ventricular growth and cardiac hypertrophy, which benefits overall strength. The A-allele (I) increases maximal heart rate, causing higher maximal oxygen uptake and enhanced endurance performance.	402	$\dot{V}O_{2max}$ 1RM	APOE4 PCG-1α
ACTN3	Alpha-actinin-3 fast-twitch specific isoform, expressed only in type II myofibers. CC genotypes (RR) show higher baseline muscle strength. The TT (XX) allele has shown an overrepresentation among endurance athletes due to interactions with ACTN2 and type I fibres promoting aerobic fitness.	949	$\dot{V}O_{2max}$ 1RM	-
AKT1	AKT1 gene encodes serine-threonine protein kinase. It has been shown to increase testosterone actions, promote muscle hypertrophy, muscle mass, and strength, and regulate cell growth and division by interacting with the mTOR pathways.	39	1RM	AMPK, mTOR, PGC-1α
AMPK / PRKAA2	AMPK or Protein Kinase AMP-Activated Catalytic Subunit Alpha (PRKAA) (Thr172) encodes the enzyme 5'-AMP-activated protein kinase catalytic subunit alpha-1. Restores AMP/ATP balance and triggers transcriptional activators, regulating mitochondrial biogenesis. It protects cells from stresses that cause ATP depletion by switching off ATP-consuming biosynthetic pathways. This gene has been associated with aerobic training and suppresses mTOR.	18	$\dot{V}O_{2max}$	AKT1, HADH, mTOR, PGC-1α
APOE	Apolipoprotein E is a protein involved in the metabolism of fats in the body and is associated with cognitive function that improves during exercise. This gene improves aerobic fitness with fat metabolism in aerobic respiration. T = E2, C = E4, and C/T = E3.	480	$\dot{V}O_{2max}$	-
COX4I1	Cytochrome c oxidase subunit 4 isoform 1, is a nuclear-encoded isoform and couples the transfer of electrons from cytochrome c to molecular oxygen, contributing to a proton electrochemical gradient across the inner mitochondrial membrane, acting as the terminal enzyme of the mitochondrial respiratory chain. COX4 in different conditions has shown to provide benefits in both aerobic and anaerobic training.	1,097	$\dot{V}O_{2max}$ 1RM	-

CS	Citrate Synthase is a protein coding gene and a biomarker for mitochondrial function, increasing intrinsic mitochondrial respiratory capacity and aids the Krebs cycle. Maximal activity of CS reflects the mitochondrial content of skeletal muscle and can increase with endurance or high-intensity interval training.	112	$\dot{V}O_{2max}$ PPO	-
HADH	Hydroxyacyl-Coenzyme A dehydrogenase or hydroxyl-acyl-CoA catalyses the oxidation of straight-chain 3-hydroxyacyl-CoAs for the β-oxidation of fatty acids functioning in the mitochondrial matrix. High levels of HADH are associated with an enhanced involvement of aerobic metabolism and sprint ability. Resistance training has been found to decrease levels of HADH, which increase 1RM.	145	$\dot{V}O_{2max}$ 1RM, PPO	AMPK, PGC-1α PFK
MAFbx	Known as FBXO32 or Atrogin-1 gene, associated with MuRF-1 and myostatin (MSTN). The MAFbx and myostatin mRNA level are reduced post-exercise and protein is highly expressed during muscle atrophy. Therefore, reductions promote hypertrophic responses.	20	1RM, PPO	VEGF-A MSTN
mTOR	The mechanistic target of rapamycin (Ser2448) integrates the inputs of upstream pathways including insulin growth factors (IGF1, IGF2), sense cellular nutrient, oxygen, and energy levels. A central regulator of mammalian metabolism, with important roles in the function of tissues including liver, muscle, white and brown adipose tissue. mTOR maintains energy homeostasis and can also regulate mitochondrial biogenesis through regulation of PPARGC1A pathways.	29	1RM	AKT1, AMPK, PGC-1α IGF2
PFKM	This gene converts fructose 6 phosphate and ATP to fructose 1, 6-bisphosphate and ADP. Glycolysis is the foundation for respiration, both anaerobic and aerobic performance. Three isoforms exist in muscle, liver, and platelet. T increases levels of PFK, while C genotype decreases PFK.	78	$\dot{V}O_{2max}$ PPO	HAD
PGC-1α	Peroxisome proliferator-activated receptor-γ (PPAR) coactivator 1α (PGC-1α) or PPARGC1a (Gly482Ser) is the “master regulator” of various transcription factors and a primary regulator of mitochondrial biogenesis. Endurance exercise activates the PGC-1α gene in human skeletal muscle and unfolded protein response. Ser/Ser (T alleles) favours power and Gly (C allele) favours endurance.	86	$\dot{V}O_{2max}$ PPO	ACE, AKT1, AMPK, HADH, mTOR

VEGF-A	Vascular Endothelial Growth Factor A is a protein-coding gene. When cells are deprived of oxygen VEGF-A increases, mediating the growth of new blood vessels (angiogenesis) through VEGFR1 and 2. Upregulation increases muscle oxygen consumption and number of capillaries with resistance training. Angiogenesis promotes both oxygen and blood availability at the muscle.	17	$\dot{V}O_{2max}$ 1RM, PPO	MAFbx

- 1RM = 1 Repetition Maximum; PPO = Peak Power Output; No. participants = total number of participants assessed for candidate gene; gene description = brief information on the gene and its alleles, all information was cited by www.genecards.org. The list was created from the studies collected in this review

Table 21. Associated alleles and rs numbers for the candidate genes of interest. Using the information gathered from this review and previous research in these genes, the minor allele frequency was obtained using https://www.ensembl.org/Homo_sapiens/Info/Index and https://selfdecode.com (Keiller and Gordon, 2019). Muhdo Health Ltd also referenced the RS numbers in their SNP databases (https://muhdo.com/).

Gene	Alleles	Location	Minor allele frequency (MAF)	rs number
ACE	A/G	17q23.3	G = 0.47 - 0.49	rs4343
ACTN3	C/T	11q13.2	T = 0.40 - 0.49	rs1815739
AKT1	T/C	14q32.33	C = 0.43 - 0.50	rs2494732
AMPK	-	5p13.1	-	-
APOE	C/T	19q13.32	T = 0.08 - 0.17	rs429358
COX4I1	-	16q24.1	-	-
CS	-	12q13.3	-	-
HADH	C/T	4q25	T = < 0.01	rs375717077
MAFbx	A/G	8q24.13	G = 0.46	rs9277534
mTOR	T/G	1p36.22	G = 0.46 - 0.47	rs2295080 rs2275942 rs2295079 rs2536
PFKM	C/T	12q13.11	T = < 0.01	rs121918195
PGC-1α	C/T	4p15.2	T = 0.27 - 0.50	rs8192678
VEGF-A	G/C	6p21.1	C = 0.33 - 0.45	rs2010963 rs833068 rs2146323

The rs number (reference SNP cluster ID) is an accession number commonly used by researchers and databases to refer to specific SNPs. The minor allele frequency is the frequency at which the second most common allele after the ancestral occurs in a population. The MAF is represented as a percentage where 1 = 100%, meaning that an allele at 0.49 is equal to 49% of a random population. This would also mean the ancestral or major allele frequency (most common allele) would be estimated at 51% in this case. This information is important and widely used as this helps to predict and estimate how common and rare a gene variant / allele is and the chances of observing this within a given population. Therefore, the lower the MAF, the higher the major allele frequency should be (Hernandez et al., 2019).

4.3.3. Genes associated with Aerobic Fitness ($\dot{V}O_{2max}$).

1st Author of Study	Gene	SMD (%)	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
Rankinen 2000a II	ACE	14.51	1.06	0.62	1.50	3.00
Rankinen 2000a ID	ACE	13.36	1.03	0.70	1.36	3.52
Rankinen 2000a DD	ACE	13.35	0.99	0.60	1.38	3.24
Silva 2015 RR	ACTN3	10.53	0.46	0.13	0.79	3.54
Silva 2015 RX	ACTN3	9.94	0.37	0.09	0.66	3.72
Silva 2015 XX	ACTN3	7.00	0.32	-0.19	0.82	2.75
Böhm 2016	AMPK	6.32	0.24	-0.94	1.43	1.23
Wilkinson 2008	AMPK	17.14	0.95	-0.11	2.02	1.35
Thompson 2004 E2/E3	APO E	11.88	0.62	0.16	1.09	2.92
Thompson 2004 E3/E3	APO E	4.64	0.28	-0.16	0.71	3.03
Thompson 2004 E4/E3	APO E	11.65	0.71	0.22	1.19	2.82
Yu 2014 E2/E3 Male	APO E	12.12	0.68	0.00	1.36	2.13
Yu 2014 E3/E3 Male	APO E	3.33	0.18	-0.09	0.44	3.82
Yu 2014 E3/E4 Male	APO E	10.85	0.60	0.07	1.13	2.64
Yu 2014 E2/E3 Female	APO E	11.43	0.62	0.02	1.21	2.40
Yu 2014 E3/E3 Female	APO E	2.63	0.14	-0.14	0.41	3.77
Yu 2014 E3/E4 Female	APO E	11.11	0.62	0.07	1.17	2.57
Konopka 2013	COX IV	14.20	0.92	-0.44	2.29	1.04
McPhee 2011a G1	COX IV	12.51	0.67	0.24	1.11	3.03
McPhee 2011a G2	COX IV	9.99	0.79	-0.10	1.67	1.64
McPhee 2011b	COX IV	7.69	2.00	1.19	2.81	1.76
Rico-Sanz 2004 Men G1	COX IV	12.66	0.77	0.40	1.14	3.35
Rico-Sanz 2004 Men G2	COX IV	13.00	0.78	0.54	1.02	3.94
Rico-Sanz 2004 Women G1	COX IV	14.98	0.74	0.49	0.99	3.89
Rico-Sanz 2004 Women G2	COX IV	15.33	0.92	0.69	1.15	3.99
Dohlmann 2018	CS	6.90	1.00	0.05	1.95	1.52
Egan 2013	CS	17.81	1.40	0.09	2.70	1.06
Kazior 2016	CS	7.63	0.34	-0.75	1.44	1.33
Konopka 2013	CS	14.20	0.92	-0.44	2.29	1.04
Wilkinson 2008	CS	17.14	0.95	-0.11	2.02	1.35
Kazior 2016	HADH	7.63	0.34	-0.75	1.44	1.33
Konopka 2013	HADH	14.20	0.92	-0.44	2.29	1.04
McPhee 2011a G1	HADH	12.51	0.67	0.24	1.11	3.03
McPhee 2011a G2	HADH	9.99	0.79	-0.10	1.67	1.64
McPhee 2011b	HADH	7.69	2.00	1.19	2.81	1.76
Dohlmann 2018	HADH	6.90	1.00	0.05	1.95	1.52
McPhee 2011a G1	PFK	12.51	0.67	0.24	1.11	3.03
McPhee 2011a G2	PFK	9.99	0.79	-0.10	1.67	1.64
McPhee 2011b	PFK	7.69	2.00	1.19	2.81	1.76
Egan 2013	PGC-1a	17.81	1.40	0.09	2.70	1.06
Konopka 2013	PGC-1a	14.20	0.92	-0.44	2.29	1.04
McPhee 2011b	PGC-1a	7.69	2.00	1.19	2.81	1.76
Butcher 2008	PGC-1a	7.17	0.30	-0.43	1.03	2.00
Mean		10.97	0.76	0.13	1.39	

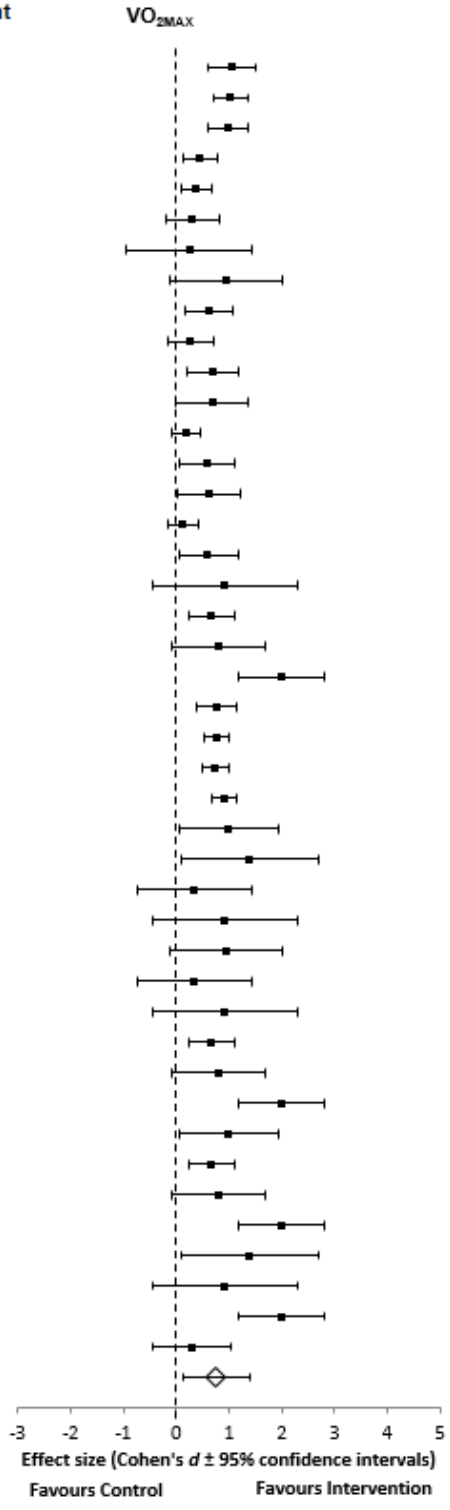


Figure 20. $\dot{V}O_{2max}$ forest plot grouped by gene. ES represents the change in $\dot{V}O_{2max}$ post intervention. For all plots, the 95% CI were calculated, and the overall mean ES is represented with the diamond, whereas the squares are the ES of each study.

The average $\dot{V}O_{2max}$ increased (10.97 ± 3.8%) in the intervention groups across the included studies. The forest plot demonstrates that, regardless of gene groups, the results represented a medium to large ES. This was classed as significantly improved ($p < .001$).

Between group analysis showed assumptions were not normally distributed across the nine aerobic gene subgroups (D (43), .876, $p < .05$), a non-parametric Kruskal-Wallis H test found significant differences between groups (H (8), 18.427, $p = .018$). Eta Squared calculated through Pearson's $\chi 2$ tests found 44% of the variability in the increase of $\dot{V}O_{2max}$ post-training intervention was explained by the gene subgroups. Post-hoc analysis indicated the distribution of the variance in $\dot{V}O_{2max}$ scores between the genetic groups (Table 22).

Table 22. Candidate genes for aerobic cardiorespiratory fitness. The lowest mean rank is the group with the lowest scores per-study. Subgroup % shows how much of the 44% variance is accounted from the nine genes and accounts for sample size, SE and within group variation in SMD.

Gene Groups	**No. of Study groups**	**Total Group Sample Size**	**Mean Rank (Not adjusted for sample size)**	**Subgroup (Adjusted for sample size) % of weight**	**Mean Group Effect Size (*d*)**
ACE	3	188	35.33	14.24	1.02
ACTN3	3	206	8.33	14.15	0.39
AMPK	2	18	17.25	7.84	0.62
APOE	9	437	10.44	13.67	0.41
COX4I1	8	591	25.06	13.43	0.85
CS	5	46	28.00	12.12	0.90
HADH	6	106	25.25	10.58	0.96
PFKM	3	78	27.17	6.62	1.12
PGC-1α	4	52	28.25	7.36	1.14
Total	43	1,722			

The combined results show that the ACE gene, regardless of allele has the greatest mean rank, weight, and ES, although having a smaller sample size and low number of study groups. COX4I1, CS, HADH, PFKM, and PGC-1α found non-significant differences between mean rank scores and equally contributed to the increase in $\dot{V}O_{2max.}$ These genes mean ranks were higher than that of ACTN3, AMPK and APOE groups, all showing a large ES.

4.3.4. Genes associated with Muscular Strength

1st Author of Study	Gene	SMD (%)	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
Colakoglu 2005 II	ACE	17.43	1.89	0.69	3.09	2.09
Colakoglu 2005 ID	ACE	18.65	2.10	0.93	3.27	2.13
Colakoglu 2005 DD	ACE	19.35	2.60	1.50	3.69	2.22
Gentil 2012 II	ACE	12.90	0.73	0.10	1.36	3.73
Gentil 2012 ID	ACE	11.90	0.89	0.53	1.25	4.98
Gentil 2012 DD	ACE	16.59	0.91	0.39	1.44	4.18
Thomis 2004 II	ACE	33.29	0.74	-0.38	1.86	2.34
Thomis 2004 ID	ACE	35.27	0.81	0.22	1.41	3.89
Thomis 2004 DD	ACE	32.70	0.73	0.05	1.42	3.53
Clarkson 2005 RR	ACTN3	17.09	0.64	0.43	0.86	5.62
Clarkson 2005 RX	ACTN3	16.23	0.57	0.40	0.75	5.76
Clarkson 2005 XX	ACTN3	16.55	0.53	0.31	0.75	5.59
Gentil 2011 RR	ACTN3	10.02	0.49	0.08	0.89	4.75
Gentil 2011 RX	ACTN3	10.86	0.59	0.23	0.94	5.00
Gentil 2011 XX	ACTN3	8.74	0.37	-0.22	0.96	3.92
Kazior 2016	Akt1	22.75	2.68	0.94	4.42	1.37
Lamas 2010 G1	Akt1	18.60	2.00	0.85	3.15	2.17
Lamas 2010 G2	Akt1	14.22	1.50	0.43	2.56	2.38
Wilkinson 2008	Akt1	40.51	3.37	1.83	4.90	1.48
Rico-Sanz 2004 Men G1	COX IV	22.34	1.30	0.91	1.69	4.84
Rico-Sanz 2004 Men G2	COX IV	21.84	1.05	0.80	1.29	5.49
Rico-Sanz 2004 Women G1	COX IV	22.62	1.01	0.76	1.27	5.44
Rico-Sanz 2004 Women G2	COX IV	21.61	1.11	0.88	1.35	5.54
Kazior 2016	mTOR	22.75	2.68	0.94	4.42	1.37
Lamas 2010 G1	mTOR	18.60	2.00	0.85	3.15	2.17
Lamas 2010 G2	mTOR	14.22	1.50	0.43	2.56	2.38
Wilkinson 2008	mTOR	40.51	3.37	1.83	4.90	1.48
Davidsen 2010 G1	VEGF-A	46.25	1.70	0.34	3.06	1.88
Davidsen 2010 G2	VEGF-A	37.06	0.95	-0.19	2.09	2.29
Mean		22.12	1.11	0.28	1.95	

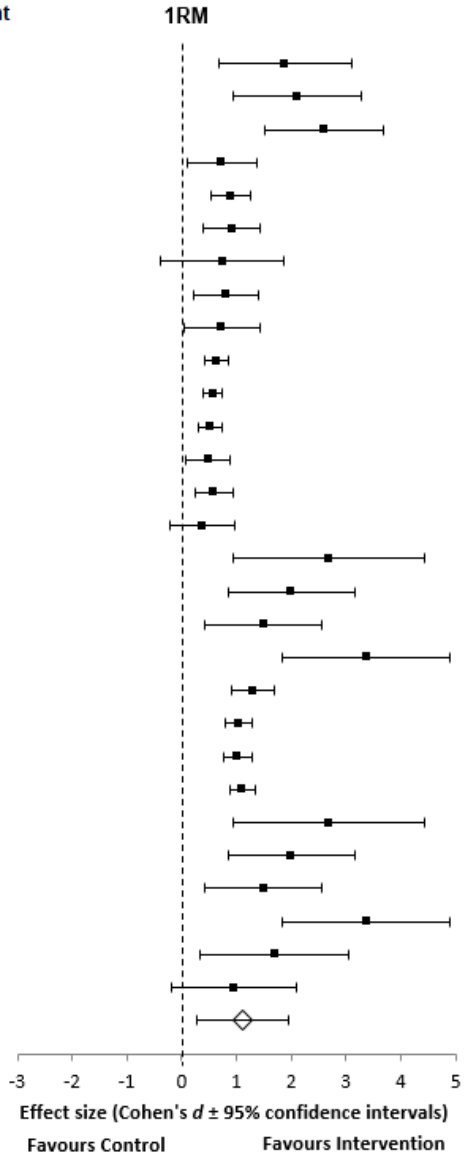


Figure 21. 1RM forest plot grouped by gene. ES represents the change in lower body 1RM post intervention. For all plots, the 95% CI were calculated, and the overall ES is represented with the diamond, whereas the black squares are the ES of each individual study. The weight is adjusted for sample size, SD, and variance.

Strength training interventions in total found a mean increase in 1RM of 22.12 ± 10.08% across the 29 study groups. The forest plot results show that all groups agreed in the increase in 1RM with man exercise intervention. Overall ES for 1RM exhibited a large effect (1.11), which was deemed as significantly improved (p <.001).

The data did not meet the assumptions for normality between the six candidate strength gene groups (D (29), .886, p < .05). Kruskal-Wallis H test found significant differences between the six gene groups (H (5), 20.081, p = .001). Eta Squared uncovered that 72% of the variability in the increase of 1RM post-training was explained by the genetic subgroups.

Table 23. Candidate genes for strength. The lowest mean rank is the group with the lowest scores per-study. Groups with the highest mean rank show greater numbers of high scores. Subgroup % shows how much of the 72% variance is account from the six genes, adjusted for sample size, SE and within group variation in SMD.

Gene Groups	No. of Study groups	Total Group Sample Size	Mean Rank (Not adjusted for sample size)	Subgroup (Adjusted for sample size) % of weight	Mean Group Effect Size (*d*)
ACE	9	194	14.11	18.22	1.12
ACTN3	6	743	3.50	22.96	0.57
AKT1	4	39	24.00	11.71	2.27
COX4I1	4	506	15.50	22.72	1.09
mTOR	4	39	24.00	11.71	2.27
VEGF-A	2	17	16.50	12.68	1.27
Total	29	1,538			

Mean rank scores agree with the forest plot analysis showing that ACE, AKT1, and mTOR genes have a large influence in the variability of 1RM with large ES. When adjusted for sample size ACTN3 and COX4I1 contribute to 45.68% of the 72% variability in the increase in strength. Results show that AKT1 and mTOR are large contributors to the mean rank with a large ES of 2.27, although only having 39 participants per-group out of a total of the 1,538.

The only gene group that did not observe a large ES is the ACTN3, regardless of genotype and allele (RR, RX, XX) as there were no significant differences in genotypes and 1RM within these groups (p > .05). Although RR and RX displayed a greater baseline strength when compared to XX genotype.

4.3.5. Genes associated with Anaerobic Power

1st Author of Study	Gene	SMD (%)	Effect Size Cohens *d*	95% CI for effect sizes Lower	Upper	Weight (%)
Dohlmann 2018	CS	8.70	1.21	0.24	2.18	7.49
Konopka 2013	CS	16.61	1.58	0.11	3.05	4.03
Little 2010	CS	8.95	1.58	0.11	3.06	4.03
Lundberg 2014 G1	CS	13.71	0.84	-0.21	1.89	6.77
Lundberg 2014 G2	CS	15.53	0.79	-0.26	1.83	6.83
Parra 2000 G1	CS	3.00	2.07	0.84	3.31	4.89
Parra 2000 G2	CS	14.01	0.57	-0.46	1.60	7.05
Konopka 2013	HADH	16.61	1.58	0.11	3.05	4.03
Parra 2000 G1	HADH	3.00	0.79	-0.26	1.83	6.83
Parra 2000 G2	HADH	14.01	2.07	0.84	3.31	4.89
Dohlmann 2018	HADH	8.70	1.21	0.24	2.18	7.49
Lundberg 2014 G1	MAFbx	13.71	0.57	-0.46	1.60	7.05
Lundberg 2014 G2	MAFbx	15.53	0.84	-0.21	1.89	6.77
Konopka 2013	PGC-1a	16.61	1.58	0.11	3.05	4.03
Little 2010	PGC-1a	8.95	1.58	0.11	3.06	4.03
Lundberg 2014 G1	PGC-1a	13.71	0.57	-0.46	1.60	7.05
Lundberg 2014 G2	PGC-1a	15.53	0.84	-0.21	1.89	6.77
Mean		12.17	1.10	0.85	1.35	

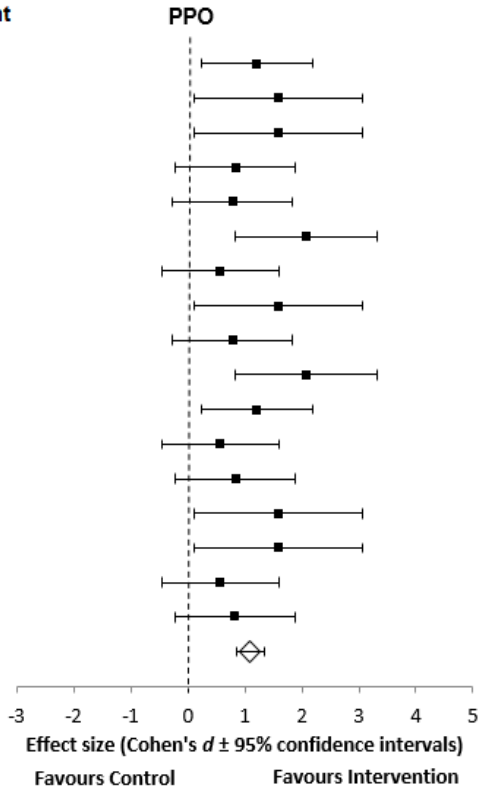


Figure 22. PPO forest plot grouped by gene. ES represents the change in PPO post intervention. For all plots, the 95% CI were calculated, and the overall ES is represented with the diamond, whereas the squares are ES of each study.

Studies included in this review revealed a mean increase in PPO of 12.17 ± 4.4% with power training interventions, irrespective of gene groups. The forest plot established all studies increased PPO with a medium to large ES (range: 0.57-2.07). The mean for all studies equalled a large effect (1.10), which was classed as significantly improved ($p < .001$).

PPO results were not normally distributed for the collective group (D (17), .888, $p < .05$). A Non-parametric Kruskal-Wallis H test found non-significant differences between gene groups (H (3), 1.592, $p = .661$). Eta Squared found that only 10% of the variability in the 12.17% increase, was explained by genetic sub-groups (total = 1.22%).

Table 24. Candidate genes for PPO. Subgroups show how much of the 10% variance is account from the four genes, adjusted for study sample size, SE and within group SD in SMD.

Gene Groups	No. of Study groups	Total Group Sample Size	Mean Rank (Not adjusted for sample size)	Subgroup (Adjusted for sample size) % of weight	Mean Group Effect Size (*d*)
CS	6	66	9.33	26.15	1.15
HADH	4	39	10.88	18.96	1.34
MAFbx	3	27	6.17	34.36	0.70
PGC-1a	4	34	8.75	20.53	1.02
Total	17	166			

Subgroup analysis did not find any significant differences between PPO scores (p = .661). Table 24 shows that although there was no significance, there were still noticeable differences when comparing subgroups. In terms of ES, HADH group was the greatest at 1.34, classed as a large effect and had the largest mean rank score. Conversely, HADH also had the lowest weighting of 18.95% when compared to other genes such as, MAFbx with 34.36%, which explains around 1/3 of the variability in the 10% PPO increase.

4.4. DISCUSSION

The aim of this systematic literature review and meta-analysis was to identify candidate genes associated with cardiorespiratory fitness, muscular strength, and anaerobic peak power in untrained humans, following exercise training. The meta-analysis identified several candidate genes that are significantly associated with the three components of health-related fitness of interest in this review. A major finding of the analysis is that a genetic component for responsiveness to exercise training can explain between 10-72% of the variability in aerobic, strength, and power adaptations. These findings are broadly consistent with previous studies, which reported percentages of up-to 80% (Bouchard, 2012; Del Coso et al., 2018; Hautala et al., 2006; Schutte et al., 2016; Spurway and Wackerhage, 2006). The data extraction from the initial studies in this review found numerous investigated genes (ABCA1, ACSL1, ADIPOQ. AR, CCL3, CD44, CKM, CRY1, FOXO1, GAPDH, HIF1A, HK1, IGF1, IGF2, IL6, IL15, IL18, MDH1, MFN1, MFN2, MIR1-1, MTHFR, MuRF-1, MYF5, MYF8, MYOD1, MYOG, MSTN, NCAM1, PAX7, Per2, SIRT1, TNF). However, these could not be included in in the analysis, due to the lack of reported findings. However, these candidate genes may still have importance and should be considered in future studies (Williams et al., 2017). In this review, a final 13 candidate genes were further examined in the meta-analysis, nine were associated with $\dot{V}O_{2max}$, six with 1RM, and four with PPO. However, it should be noted that some of these studies assessed and grouped the gene, regardless of their allelic composition. Such an omission makes it difficult to compare the exact role of the genes identified as the alternative alleles will almost certainly affect the phenotype differently (Silva et al., 2015; Spurway and Wackerhage, 2006). In this regard, the alleles for some but not all genes were identified using a genome-wide association study (GWAS) catalogue (ebi.ac.uk) and the rs number and primer/assay codes. However due to the studies analysing the gene, as a whole, the allele specific data was not present. Additionally, table 21 outlines that there is a lack of information within the literature and gene databases for the evidence on using AMPK, COX4|1, CS, HADH and PFKM as they are rarely reported. Regardless, these candidate genes do give some knowledge on the associations and variance in the phenotype response.

7 of the 29 studies did not meet the post-hoc power thresholds of 80%. Studies such as Butcher et al., (2008), using a cohort of 34 healthy adults, of which 18 were male and 16 females, equated to 13.6% power. In contrast, Wilkinson et al., (2008) with a sample size of ten healthy males, obtained 100% post-hoc power. This reinforces the observation that power is not a calculation that can be relied on in isolation but rather, in combination with other tests. Therefore, using these separate assessments in a collective manner enabled all studies that met the COSMIN assessment to be included in this review. Such an approach minimises both

levels of publication bias allowing comparisons of studies that may or may not have an effect, rather than just assessing the studies that do have high significance (Light and Pillemer, 1984; Egger, Smith, Schneider and Minder, 1997).

For cardiorespiratory fitness, across all studies, an average increase in $\dot{V}O_{2max}$ (10.97 ± 3.8%) in response to aerobic interventions was observed. The forest plot demonstrated that, regardless of gene groups, exercise interventions resulted in a medium to large ES and was classed as significantly improved. The ACE gene demonstrated the largest influence and ES (MR: 35.33; weight: 14.24%; ES: 1.02), despite having only three groups in the analysis (188 participants out of 1,772). COX4I1, Citrate Synthase and HADH genes also displayed large effect (Range MR: 25.06–28.00; weight: 10.58–13.43%; ES: 0.90-0.96). Thirdly, PFKM and PGC-1α displayed the largest subgroup effect of 1.12 and 1.14, respectively, but only contributed 6.62 and 7.36% of the 44% gene variability. This could be explained by the combination of low study numbers and sample representatives, with only 78 and 52 out of the 1,722 participants. Finally, ACTN3, AMPK and APOE genes showed the lowest scores with low effects.

A possible explanation of why AMPK may not have benefited $\dot{V}O_{2max}$ can be asserted from other genetic influences such as, PGC-1α as the independent master regulator of the mitochondrial biogenesis and aerobic respiration (Popov et al., 2017), it could downregulate AMPK, as there is an associated upstream regulation in the Akt-mTOR pathway associated with PGC-1α, which AMPK activation supresses (Lantier et al., 2014; Metcalfe et al., 2015; Tannerstedt, Apró and Blomstrand 2009). Another reason subgroup analysis contributions were low could simply reflect the small study and sample sizes included. Furthermore, APOE results indicated no advantage of the E3/E3 allele in cardiorespiratory fitness. This is not surprising as the epsilon 3 allele is considered the neutral genotype. Medium ES in E2 and E4 alleles were observed similar to research from Bernstein et al., (2002) and Deeny et al., (2008). In fact, Obisesan et al., (2008) found APOE genotypes explained approximately 33% of the variability in training-induced increases after 24-weeks (p = .002). This could explain why in this study, the observed 44% gene associations with $\dot{V}O_{2max}$ were not as high as previous literature reports (Bouchard, 2012; Hautala et al., 2006; Huygens et al., 2004; Klissouras, 1971; Komi et al., 1977). These included candidate genes and genotypes may not specifically be associated with improved aerobic performance, therefore introduce a negative weighting, decreasing the associated gene variability in subgroup and whole-group analysis (Richardson, 2011). Interestingly, the well-researched ACTN3 gene showed mixed results. In theory the X stop codon allele should promote greater ACTN2 expression and a suppression of ACTN3, leading to improved $\dot{V}O_{2max}$ (Clarkson et al., 2005; Del Coso et al., 2018; Gentil et

al., 2011). Whereas the R allele should promote increases in strength through ACTN3 expression (Keiller and Gordon, 2019; Pickering and Kiely, 2017; Seto et al., 2013; Silva et al., 2015), but this was not observed in this review, rather agreed with that of Gineviciene et al., (2016), which assessed the influence of ACTN3 R577X polymorphism in a wide cohort of 1,524 strength and power athletes. A similar response was found, for the well-studied ACE genotypes, with non-significant differences between alleles. Again, theory suggests that I allele is associated with greater increases in aerobic fitness and endurance due to low levels of ACE and increased maximal heart rate (Colakoglu et al., 2005). D alleles are associated with increased ACE presence, which is associated with strength performance (Montgomery et al., 1997). However, the findings from this review are like those of Bustamante-Ara et al., (2010) and Gineviciene et al., (2016), where non-significant differences were found between alleles.

This review also demonstrated that 1RM had the largest observed genetic variability, which was explained by the six listed candidate genes. Strength training resulted in an increase of 22.12 ± 10.08% across the 29 groups, which equated to a large effect and significant improvements. In terms of MR and ES, ACTN3 resulted in the lowest scores with a medium effect. This was, however, the largest subgroup influence on the weight of the overall 72% variability, such an observation is consistent with findings from Thomis et al., (2004). The low overall ES from strength interventions could be explained by the relatively low data pool from two study groups, and the large subgroup weight could be explained by the high proportion of participants included (743 out of 1,538). Interestingly AKT1 and mTOR display the largest MR and ES. VEGFA also contributing to 11.71 - 12.68% of the variability, yet only having 39 and 17 out of the 1,538 participants, respectively. Here previous studies are consistent in showing associations between AKT and mTOR downstream signalling pathways and regulation, which are activated through resistance exercise (Akt-mTOR pathway) promoting muscle hypertrophy (Léger et al., 2006; Møller et al., 2013). The results also suggest that the ACE and COX4I1 have a combined 40.9% weight and a large effect. From these results, it is evident that listed candidate genes are associated with strength.

Finally, overall mean PPO increased (12.17 ± 4.4%) with sprint power training, equal to a large effect (1.10) which was significant over the 17 subgroups. Of the three measured variables, PPO displayed the lowest genetic influence of 10%. Only one unique candidate gene was reported from the reviewed studies which was the MAFbx (FBXO32), or Atrogin-1 gene. MAFbx has previously been found to be associated with strength genes such as, VEGF-A, AKT and mTOR, this protein is highly expressed during muscle hypertrophy through an up-regulation in exercise (Lagirand-Cantaloube et al., 2008; Lundberg et al., 2014). This review

also found that MAFbx gene explains 34.4% in changes in PPO, although only in 27 out of 166 participants. This may suggest a paucity of investigation in candidate genes for the PPO phenotype, as only five studies were found. The current analysis revealed four potentially associated genes, of which three were also associated with $\dot{V}O_{2max}$. The literature has supported the idea that PPARGC1A gene (PGC-1α) has been associated with power variables (Gineviciene et al., 2016). The results do show that power increases were significant with large ES in PGC-1α groups, although only explaining 20.5% of the 10% variability. It has been stated that there is a large crossover between the interactions of aerobic and anaerobic genes within the human body (Ahmetov et al., 2016; Spurway and Wackerhage, 2006; Williams and Folland, 2008), partly because human performance and improvement is a multifactorial trait. The list of candidate genes that could be associated with inter-individual variance in exercise-related phenotypes is extensive (Rankinen et al., 2000). Reasons why the genes may explain different phenotype changes and low variability rates, especially in anaerobic power may be due to studies mistakenly estimating metabolic power, which reflects a combination of energy sources. Beneke et al., (2002) explained that when assessing power via a 30 second Wingate test (WAnT) energy from aerobic, anaerobic, and lactic acid metabolism were 18.6%, 31.1%, and 50.3%, respectively. Therefore, these studies assess metabolic power, which is the overall amount of energy required, per unit of time, rather than anaerobic power, which is understood as is the greatest possible work done for a given time-period (Bundle and Weyand, 2012; Cometti et al., 2001). Another important factor to consider is the allelic frequencies of the participant groups themselves. Allele frequencies calculated by the Hardy-Weinberg equilibrium are fundamental because particular markers can suggest difficulties with genotyping or population structure in future studies (Wigginton, Cutler and Abecasis, 2005).

4.5. LIMITATIONS

A key limitation to this review was the difficulty comparing study interventions, as the training was not standardised. This meant that all studies that were included used different training methods, which could potentially affect the inter-individual difference. Another limitation was the number of gene studies and groups that were identified. This also meant that other candidate genes were not included in this review, due to the lack of reported consistency, therefore, this list is not exhaustive. The problem with a systematic review is that it solely aims to exploit information already available and genes that have already been explored. On the other hand, the benefit of this review compared to other studies is that the analysis aims to compare multiple genes contribution towards the total variance of the phenotype, rather than independent analysis.

Although in this review all participants were classed as untrained there are still training differences between them which could cause issues when observing differences between participants (Hautala et al., 2006; Peterson, Rhea and Alvar, 2005). Predisposition of the genetic heritability in baseline results shows genes and specific alleles heavily influence adaptations even before training interventions are implemented (Burley et al., 2018), whereas the included studies reflected genetic differences after training. A noteworthy limitation addressed in this review was the lack of identified information in power training, with low study and sample sizes. Future work might benefit from identifying key genes associated with power specific phenotypes separate from strength and endurance.

4.6. CONCLUSION

This systematic literature review and meta-analysis has demonstrated that listed candidate genes explain a significant proportion of the variability and association in the adaptations and responses in health-related components of fitness. Accordingly, the knowledge gained from this review will be useful in future gene studies and investigations in exploring specific candidate genes, their alleles, and how these effect wider and specific untrained populations. Although the results were obtained from a sample population of 3,012 untrained participants, further research is required within this area since most research has focussed on elite, athletic, and well-trained populations. Additionally, the roles of the specific alleles of the genes have not been fully addressed.

In summary, research evidence has shown that both exercise training and genetics play a crucial role in the improvements and adaptations in the health-related components of fitness and phenotypes in the untrained. Additionally, relationships were found between these physiological improvements and the specific training loads governed by training intensity, duration, and frequency (chapter 3). Furthermore, the specific associations uncovered between the sub-group genotypes and the components of health-related fitness, part-explaining the inter-individual differences in these responses, especially for strength and endurance phenotypes (chapter 4). Therefore, using these reviews, it is necessary to attempt to replicate these observations using a standardised laboratory-based experiment, in a sub-set population of UK-based untrained participants. This would in-part justify the use of training loads to inform training programmes and the implications of using genotype information to predict advantageous training adaptations and responses. To achieve this, it is important to consider the equipment, methods, and procedures in collecting and measuring these physiological changes within the participants, before, during and after exercise training. This will be discussed in more detail and outlined in the next chapter.

CHAPTER 5: GENERAL METHODOLOGY AND PRE-EXPERIMENTAL PROCEDURES

This chapter refers to the devices, equipment, and pilot testing implemented for the preparation of the experimental chapter(s). In addition, how the specific devices work and the theory and science that justifies the application, accuracy, and validity of the devices. The specific use of the equipment and the methodological approach in how to use them are addressed within the specific chapter(s) where the devices are employed.

5.1. Haematological collections

Two pieces of equipment were implemented for the collection of Haematological variables. First, Hemo Control (EKF Hemo Control, EKF diagnostic, Germany) to determine Haemoglobin and haematocrit using a 10 µl capillary blood sample collected at the participants fingertip. Secondly, Biosen C-Line Clinic (EKF-diagnostic GmbH, Germany) to determine resting blood lactate (BLa) and Glucose, using a 20 µl capillary blood sample. Again, at the participant fingertip.

5.1.1. Equipment: EKF Hemo Control Analyser

The Hemo Control analyser is a photometer, which measures the solution colour intensity. This is based on the transformation of haemoglobin to a stable-coloured complex, which forms azide methemoglobin (Vanzetti, 1966). Azide-methemoglobin has an identical absorbance spectrum to haemiglobincyanide (HiCN), which is the standard reference method of the International Committee for Standardisation in Haematology (ICSH) when calculating haemoglobin (ISCH, 1996). Haematocrit values are obtained from the Hb result with the factor 2.94, this represents that Hct is 2.94 times the value of haemoglobin. By using the established photometric azide methemoglobin method, EKF diagnostics ensures reliable and high precision results (CV <2%). The three-step protocol provides the results within 25-60 seconds with only 8-10 µl capillary blood required (EKF 2020a).

For the Pilot testing, the Hemo Control was calibrated using a control cuvette. A series of in-house testing was conducted at Anglia Ruskin University, Cambridge to assess the reliability and consistency of the device. The readings from the analyser were tested using a control cuvette at different times within a 24-hour period and showed no sign of equipment/calibration drifts or inconsistencies. The calibration was also within the acceptable range according to the EKF diagnostic manual. In addition, a known control standard of 7.9 $g \cdot dL^{-1}$ was also used to assess the devices' accuracy and drift at low volumes, which was made of bovine hemolysate.

Once opened it has a shelf life of 30 days, if stored in the correct environmental conditions, for this experiment a brand-new sample was opened and then stored in lab temperature, which was 18°C.

The results revealed that all measurements were within the acceptable range to the EKF standards. In terms of the calibration cuvette, out of the six times it was used in the span of 24 hours (CV = 0.00%) as the results did not change, and calibration was consistent (hb = 15.7; Hct = 46%). Similarly, the 7.9 $g \cdot dL^{-1}$ standard observed little to no change over the 24-hour period (CV = 1.03%). This agrees with the reported CV of <2% from EKF diagnostics (EKF 2020a). To ensure the highest reliability and accuracy of the EKF Hemo Control analysis, it should be calibrated with the control calibration cuvette before every trial.

5.1.2. Equipment: Lactate Analyser (Biosen C-Line, EKF diagnostic, Germany)

EKF (2020b) claims that the Biosen C-Line dual channel is the gold standard in testing blood glucose and lactate with the CV imprecision of <2%. The Biosen uses a special chip sensor technology that delivers fast measurements with high degrees of accuracy using the enzymatic-amperometric method. The advantage of this is that it is relatively low cost when compared to other methods and due to the long life of the sensor chip the system requires little maintenance resulting in less human errors. Assessment of the capillary blood is achieved with a 20 µl blood sample. The blood is drawn through a micro-capillary tube, after which the tube tip is carefully wiped to ensure only 20 µl is collected. It is then placed into a 1000 µl EKF pre-filled haemolysis solution, Safe-Lock reaction cup (Eppendorf, Germany) and gently mixed. Samples are then placed into the Biosen for analysis (20 maximum). The measuring range of the Biosen for Glucose is 0.5–50 $mmol \cdot l^{-1}$ and Lactate is 0.5–40 $mmol \cdot l^{-1}$ (EKF 2020b). Amperometric biosensors immobilise oxidase molecules onto an electrochemical interface, the enzyme catalyses a reaction encompassing the analyte with the consumption of an electroactive reactant and the construction of an electroactive product to produce hydrogen peroxide, which is detected by the electrode. The magnitude is directly correlated to the concentration in the enzymatic reaction, once this is known the algorithms can calculate onsets of the results (Artigues, Abellà and Colominas, 2017; Rathee, et al., 2016). Amperometric biosensors can combine the robustness of electrochemical techniques with the specificity of biological recognition processes.

Following the calibration instructions from EKF known standards, a Set-Lin-Test linearity test kit, glucose / lactate, 2, 7 and 18 $mmol \cdot l^{-1}$was implemented to test the reliability, accuracy and consistency of the device and measurements. The in vitro diagnostic of the BIOSEN C-line was conducted over a 24-hour period at Anglia Ruskin University, Cambridge. The chemical

composition within the micro test tubes contained diluted 51-fold measurements of lactate in a phosphate buffered solution (pH 7.2) and further ingredients giving it a known value. According to the calibration instruction kit, when sealed optimal temperature storage is at 2-8 °C and remains stable after opening at 15-25 °C and recommended stability 8 hours after first use. Anglia Ruskin University, Cambridge laboratories meet these storage conditions as samples are taken out of the controlled fridge temperature into the lab environment of 18 - 20 °C.

The pilot results between initial and 8 hours post found that for the 2, 7 and 18 $mmol \cdot l^{-1}$ for both glucose and lactate were 0.91, 0.98, 0.99 and 1.71, 1.47, 1.49 % CV, respectively. This agrees with the <2% stated by EKF. The Biosen analyser automatically calibrates every hour as instructed in manufacturers guide using a known calibration sample that is replaced every 8-hours. Results show small but acceptable drifts in reference to the acceptable range at the initial, 1-, 3-, and 8-hour timestamps. However, at 24 hours the higher solutions become unstable falling outside of the acceptable range. Therefore, it is critical to replace the calibration solution at least every 8 - 24 hours even in stable room conditions once opened.

5.2. PhysioFlow®

The PhysioFlow® (PF05L1, Manatec, Petit-Ebersviller, France), uses non-invasive trans-thoracic bio impedance technology to monitor cardiac functions. To achieve this a series of electrodes are positioned on the skin surface. For maximum accuracy and reliability, it is recommended that the skin is shaved and cleaned with Neuprep abrasive gel for full contact (Alguindy, 2019). Skintact FS50 electrodes must be positioned on the left side of the neck, middle of the sternum, the rib closest to V6 and back left of the mid spine, as instructed and shown on the software (V1.13.05) and operating instructions (Figure 23). A blood pressure reading is also required for the correct software calibration of the PhysioFlow®. For maximum reliability, a two-minute resting-baseline measure should also be taken before any exercise measurements (PhysioFlow software V2 User Manual, 2016).

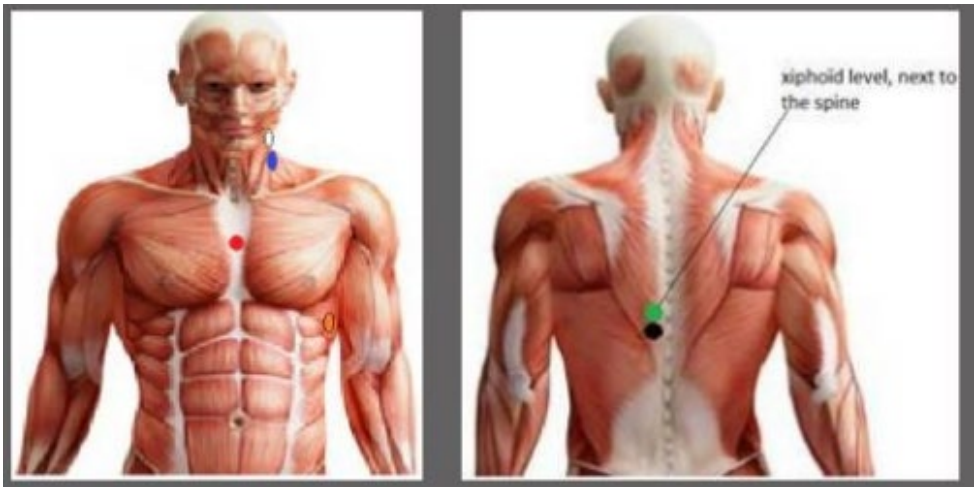


Figure 23. PhysioFlow positioning. This illustrates the placement of the six electrodes on the body. After the skin is prepared. The signal is tested, and a two-minute baseline measure is recorded (Alguindy, 2019; PhysioFlow software V2 User Manual. 2016. pp.26).

The PhysioFlow uses a low magnitude (4.5 mA peak-peak) high frequency alternating current (66 kHz), transmitted and received through the thorax area to monitor functions of the heart, providing heart rate, stroke volume, and cardiac output at a sampling frequency of 1000 Hz. To achieve this, the six electrodes placed around the body create a three-dimensional triangulation monitoring around the heart. This is then relayed back to the software on the PC for a live real-time display, data acquisition, and analysis. The advantage of using PhysioFlow when compared to other well-known methods such as, CO_2 rebreathing, doppler-echocardiography, dye dilution, and thermodilution is that PhysioFlow is a non-invasive technique, relatively inexpensive, robust when measuring multiple variables at the same time, and does not require a highly experienced operator or technician to implement (PF05L1, 2001).

A pilot study was conducted to test the consistency and repeatability on a volunteer at Anglia Ruskin University, Cambridge. Additionally, out of the three variables measured the heart rate measurements were compared using a polar heart rate monitor (Polar 810s, Kemple, Finland). Once the PhysioFlow was setup and calibrated the volunteer was asked to remain seated at rest. Three separate 3-minute readings were taken with a 20-minute gap between measurements, while the PhysioFlow was recalibrated in this time. The raw data was imported into Microsoft office Excel 2016. The PhysioFlow data was collected per heartbeat and a 10-heartbeat moving average was applied recommended in the manual guide (Physioflow® software V2). The results found that the scores for stroke volume (SV), heart Rate (HR) and cardiac output (Q) attained coefficient of variations of 1.56, 1.41 and 1.12%, respectively. In terms of HR, PhysioFlow results were very similar to the Polar heart rate monitor, CV = 1.61 and 1.64%, respectively.

5.2.1. Equipment: Blood pressure cuff

To ensure accurate readings of blood pressure, participants must be seated and rested. Blood pressure measurements result in both a systolic and diastolic pressure value, with the norm values of 120/80 mmHg, respectively (NHS, 2019). High blood pressure is classed as above 140/90mmHg and low blood pressure below 90/60mmHg (NHS, 2019). Systolic represents of the pressure exerted on the vessels during contraction of the heart, whereas diastolic represents the pressure on the vessels during the relaxation phase between beats, when the blood returns to the heart.

The Omron M3 Intellisense (HEM-7051-E) (Omron healthcare, Kyoto, Japan) was implemented. The M3 is a portable non-invasive device that records blood pressure using the oscillometric method, with a pressure range of 0-299 mmHg and pulse rate range of 40-180 beats-per-minute (Asmar, et al., 2010). Systolic pressure, diastolic pressure, and pulse rate are displayed on an LCD display. The automatic controlled inflation / deflation of the cuff eliminates the need for pressure pre-settings or reinflation, as it uses the advance 'IntelliSense' technology (Medaval Ltd, 2020). The oscillatory monitor and the cuff on the upper arm a few inches above the elbow, inflates to ~20 mmHg above the systolic pressure of the individual. Once the cuff reaches the required inflation the blood is restricted. As the cuff deflates moving below the systolic pressure, blood flow is then returned, producing a detectable vibration in the arterial walls. This is then recorded by the transducer. Similarly, as the cuff is still deflating diastolic pressure is detected as blood flow returns to normal and a smooth flow without the vibrations are recorded. These recordings are then converted into an electric signal and displayed on the portable monitor (Berger, 2001).

Asmar et al., (2010) validated the OMRON M3 in a study that included 33 participants (16 men and 17 women) with a mean age of 52 ± 11 years, 144 ± 25 for systolic and 88 ± 18 mmHg for diastolic pressure. In the validation study they compared it to two other blood pressure devices and between two operators. The difference between the two operators was 0.70 ± 1.80 and 0.58 ± 1.40 mmHg for systolic and diastolic, respectively. The study results agreed with the European Society of Hypertension (ESH) International Protocol (ESH-IP) and the US Association for the Advancement of Medical Instrumentation (AAMI) as the numbers of measurements differing from the mercury standard should be ≤5 mmHg (O'Brien et al., 2002; Stergiou et al., 2010). Thus, the OMRON M3 device was acceptable for the validation and accuracy requirements. This agrees to the recent study by Mazoteras-Pardo et al., (2018). In their study, they also concluded that the technology used in the OMRON M3 HEM-7051-E passed in clinical validation studies, between general and specific populations, according to recognised standard protocols, as published in peer-review. Another advantage of using oscillometric measurement and automatic devices, is that it requires far less skill than the auscultatory (manual) technique and may be suitable for use by untrained staff. This also provides time saving opportunities when multiple laboratory protocols are required (Medaval Ltd, 2020).

5.3. PortaMon Near Infrared Spectroscopy (NIRS)

The wireless PortaMon device (Artinis Medical Systems, Netherlands) is a non-invasive method to estimate tissue saturation with Oxy vs Deoxy haemoglobin at the muscle. The PortaMon uses three-channel light emitting optodes that are positioned 30, 35 and 40 mm from the main detector (Figure 24). Continuous infrared light transmits through the skin, disperses back, and is acquired by the receiver allowing the data to be collected in real time. The raw sampling rate was pre-set to 10 Hz as is standard, it is important for a baseline measurement to be taken before any test as recommended by the manufacturer information software.

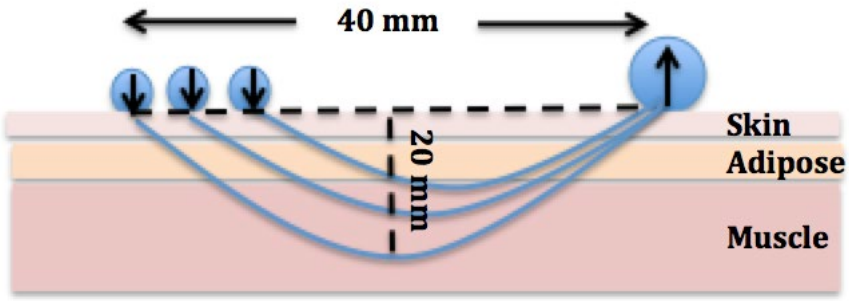


Figure 24. This demonstrated that the NIRS PortaMon using the three-channel light emitting optodes, continuously, sending infrared light and transmitting it through the skin, adipose and muscle where it is then dispersed back and is acquisitioned by the receiver (Artinis, 2020). This was placed on the left vastus lateralis for the measurement of oxy vs deoxy tissue saturation. Measurement at the front display in millimetres (mm) are: 83D X 52W X 20H.

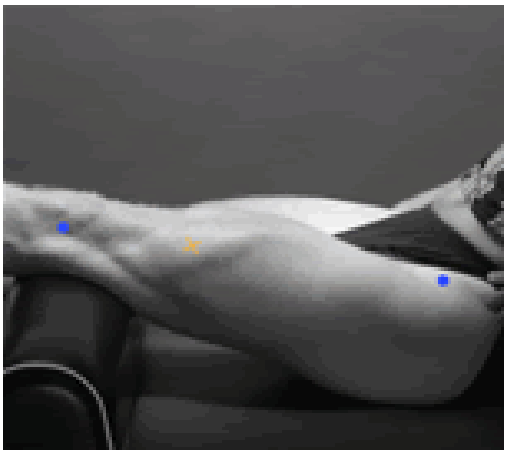


Figure 25. Location of the PortaMon and EMG. Both PortaMon and EMG collected data from the Vastus Lateralis. The location was determined using SENIAM locations and muscle palpation (Seniam, 2020).

Artinis claims the NIRS to be the gold-standard research device for assessing muscle oxygenation. Near-infrared spectroscopy, the technique on which the PortaMon NIRS device is based, relies on two characteristics of the human tissue. One is the relative transparency of the tissue to light in the near infrared region range (770-880 nm). The second is the oxygenation-dependent light absorbing characteristics of haemoglobin. The NIRS uses several different wavelengths to detect the relative changes in haemoglobin concentration from the muscle continuously on the software. The main measurements include, Oxy-, deoxy-, total haemoglobin, and tissue saturation index (TSI %). The advantages of the NIRS PortaMon device are that it is relatively cheap and inexpensive; can record data continuously in the lab and even in the field; there is no need for special infrastructure and specially trained personnel(s). The use of NIRS started with a paper published by Frans Jöbsis in 1977, the paper reported that human tissue is relatively transparent to light in the near infrared spectrum at 700-1300 nm (Artinis, 2020). In this respect, haemoglobin and its two main variants oxyhaemoglobin (O_2Hb) and deoxyhaemoglobin (hHb) exhibit oxygen-dependent absorption and the main chromophore for photons absorption. If the absorption is known, the Beer-Lambert law can be implemented to calculate the absorption, even in a scattered medium with a dimensionless path length correction factor B, "Differential Path length Factor (DPF)". The NIRS system uses a key set of equations and corrections leading to a set of algorithms. A scattering medium is what makes it possible to record the oxygenation and light absorption with the near infrared source in large tissues (Artinis, 2020).

Along with the principles of the NIRS, the spatially resolved spectroscopy (SRS) calculates the absolute concentrations, it is a multi-distance method that uses algorithms to record multiple tissue depths and incorporates the diffusion equation to deliver absolute TSI% calculations. The main limitation, however, is that it is not possible to distinguish between haemoglobin and myoglobin, due to the spectrum overlap not being sufficiently different and the ability of the penetration into the deep tissue. None the less, the chromophores of interest are oxy and deoxy haemoglobin with both showing different absorption characteristics, as does oxy and deoxy myoglobin which can be differentiated. Literature-based evidence suggests that the interference is minimal with myoglobin, and the results are reliable in different groups of muscle tissue using a multi-channel NIRS system (Ferrari, Mottola and Quaresima 2004; Quaresima et al., 2001). Another factor to consider, is that the NIRS location is more reliable on a lean muscle where the light photons do not need to penetrate large amounts of body fat (adipose tissue) (Van Beekvelt, et al., 2001). Therefore, the collection of data will be at the Vastus Lateralis in relation to figure 25 (Seniam, 2020).

5.4. Cortex MetaLyzer® 3B

The MetaLyzer (Cortex MetaLyzer® 3B, MSX 671; Ferraris Respiratory, Middlesex, UK) is a stationary high-resolution metabolic stress test spiroergometry system, with breath-by-breath technology. This allowed the collection of gas variables ($\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$ and RER) and has the capability to measure volume continuously, and simultaneously determines the expired CO_2 and O_2 concentrations. This device allows for visual feedback of live data. This system allows a comprehensive analysis of the functionality of a person's heart, lungs, and metabolism in conditions at rest and under ergometer exercise.

During a CPX test, participants wear an airtight face mask, with the volume transducer and sample line fixed to the end of the mask and the inspired and expired gases are collected. The Triple V® digital turbine (DVT) and sample line relays the information back to the Metalyzer, from which multiple algorithms display the information on the PC. The CO_2 is measured by nondispersive infrared and O_2 with an electro-chemical cell (galvanic fuel cell). The CO_2 sensor absorbs the infrared radiation in a dual beam format. This is passed through a pre-calibrated reference cell and a parallel sample cell contains the test gas at a continual flow rate. The dual beams are then interrupted by a mechanical rotating chopper, which provides an oscillating signal. The magnitude of the oscillations is directly proportional to the differences in concentrations of the test and reference gases. The CO_2 is then calculated and directly relayed from the Metalyzer back to the PC. The O_2 sensor uses a semi-disposable galvanic fuel cell to calculate O_2 by creating a stable current directly proportional to the partial pressure of O_2, giving a response time of < 200 ms in the analysis (Macfarlane, 2001). The calculations of O_2 are based on this and the theory of the Haldane transformation (Poole and Whipp, 1988), which accounts the ratio of inspired to expired physiologically inert nitrogen.

According to the official Cortex operation manual, for the highest absolute accuracy, the Metalyzer needs to be operational for at least 45-minutes to warm up, to run at optimal efficiency (Cortex 2004, manual guide p.28). Both the CO_2 and O_2 analysers reported accuracy is ± 0.1 Vol.% and calibration of the device should be maintained regularly (Cortex 2004 p.9). This breath-by-breath system allows extremely accurate measurements under non-steady-state, changing ambient air conditions and is considered suitable for CPX testing requirements. Therefore, the accuracy and test-re-test reliability were assessed in a pilot study at Anglia Ruskin University, Cambridge. Barometric pressure was recorded and entered into the Metasoft software to calculate the offsets. Known gas concentrations were used for the gas sensor calibrations from, the ambient air (20.93% O_2, 0.03% CO_2) and Cranlea gas (Cranlea, Birmingham, UK), (17.06% O_2, 5.07% CO_2). Finally, for the flow sensor, the volume transducer is attached to a known standard 3 litre syringe pump (TripleV 1). The air is pumped

through the syringe into the transducer and turbine, both inspiration and expiration should equal 3 litres and offsets are adjusted accordingly. Table 25 shows the results completed at different time points to assess any drifts in the calibrations over a 24-hour period.

Table 25a. Pressure sensor calibration.

Time stamp	Barometric pressure (mBar)	Offset
Pre calibration	1002.5	127
30 minutes	1002.5	126
1 hour	1002.1	127
3 hours	1000	124
24 hours	991.9	127

Table 25b. Gas sensor calibration

Time stamp	Fresh Ambient Air (20.93/0.03)	Deviation (Vol.%)	Cranlea Gas (17.06/5.07)	Deviation (Vol.%)
Pre calibration	20.71/0.00	0.22/0.03	16.86/5.08	0.20/0.01
30 minutes	20.83/0.03	0.10/0.00	16.90/5.03	0.16/0.04
1 hour	20.75/0.00	0.18/0.03	16.86/5.11	0.20/0.04
3 hours	20.78/0.00	0.15/0.03	16.89/5.10	0.07/0.03
24 hours	20.72/0.00	0.21/0.03	16.84/5.06	0.22/0.01

Table 25c. Flow sensor calibration

Time stamp	Inspiration	Expiration
Pre calibration	1.001	0.992
30 minutes	0.995	0.992
1 hour	1.002	0.994
3 hours	1.005	0.993
24 hours	0.997	0.990

Results showed that, Barometric pressure of the room changes even in controlled environments. It is important to adjust the pressure sensors of the Metalyzer to account for these atmospheric changes. This ensures that calculations and drifts are to the nearest accurate measurement. In terms of the gas sensor, only when the Metalyzer was calibrated the accuracy was to the nearest ± 0.1% between calibration and 30 minutes post, this agrees to the operation manual claims. The results also established that around 1-hour after initial calibration, there was a drift in both fresh ambient air and Cranlea gas, sensor measurements although the controlled environment was at a constant. The flow sensor results are consistent throughout all time points and the accepted error in the operation manual was equal to 0.03. The results suggest that a calibration is required within 30 minutes to 1 hour of the initial gas sensor adjustments, or if there is a change in barometric pressure. According to the operation manual, the Metalyzer® 3B operating conditions for its intended use, relies heavily on the prevailing altitude of the environment and the mean level of barometric pressure. If either of

these changes significantly (<0.9 bar), it is recommended that a full gas and volume recalibration is performed. Otherwise, if the environmental conditions do not change significantly only a two-point calibration is required at least every 30 days. Although all tests were conducted in a controlled environment, according to the results in this pilot study, because there is a constant change in barometric pressure that cannot be controlled throughout a testing day and hourly drifts in gas sensor precision, it is suggested that the Cortex Metalyzer® 3B should be recalibrated for good practice before every test to ensure maximal reliability and accuracy.

5.4.2. Equipment: Lode Corival Sport

The Lode Corival Sport, Groningen, Netherlands is one of the most popular electronic laboratory-based cycle ergometers worldwide, able to conduct exercise stress tests to a highly reliable and reproducible standard. It has a low start-up load of 7 Watts and is adjustable to 1000 Watts, with an eddy current electro-magnetic braking mechanism. The biggest advantage of this system is the reported accuracy, which uses one of the most important Lode principles. When compared to other cycle ergometers, this specific model adopts a comfortable, upright seating position that is more advantageous for participants that are untrained and not use to cycling in a competitive position, such as, the Lode Excalibur sport (Lode, 2020). This meets the target criteria for the participants of interest, and because of the natural cycling position this ergometer enforces, only the saddle height is adjustable making this piece of equipment more user friendly but also less error and variability can occur in the set-up between tests. This position should be adjusted to participants comfort and noted for future testing trials, to help with test repeatability.

According to the Lode website (Lode, 2020) the accuracy of the Corival at workloads of <100 is equal to a CV of ≤ 3%, 100 – 500 W ≤ 3%, 500 – 1000 W ≤ 5%. Where most untrained individuals will be working between 100 – 500 W during maximal incremental tests to exhaustion. The Corival has multiple user interfaces where it can be connected to a PC and Metasoft software, such as the Cortex Metalyzer® 3B, which is advantageous when setting up exercise protocols.

5.5. TANITA Scales

Tanita scales (Remote display version, Tanita DC-430 S MA, Manchester, UK) estimate body composition, based on the principles of bioelectrical impedance. The advantage with this method, is that it is relatively cheap compared to other methods, such as Dual-energy X-ray absorptiometry (DEXA), as well as easy, consistent, and faster to administer when compared to skin-fold callipers (Jebb et al., 2000). For the greatest accuracy participants are instructed not to consume large quantities of food or water three hours before testing. However, to stay hydrated and only consume small amounts of water two hours before measurements, and ensuring their thighs are not touching during the measurement to allow the impedance to assess the full lower body (Tanita Corporation of America, 2014).

When estimating body fat percentage, Tanita shows higher levels of accuracy when compared to self-administered and digital skinfold methods, outlined in the study by Beam and Szymanski, (2010) and was also comparable to methods such as the DEXA. Tanita uses a Dual Frequency BIA technology and delivers full body composition analysis in < 16 seconds. The Tanita Pro Software uses pre-set calculations to provide a list of variables including, Body Mass (kg), Body Fat (%), Fat Free Mass (kg), Muscle Mass (kg), Metabolic Age (years), and Body Mass Index ($kg \cdot m^2$) (Tanita, 2019).

In the pilot test, a male volunteer preformed measurements using the Tanita scale. They repeated three measures with a 15-minute interval between trials. In all three trials the results were the same for all variables. Body Mass, Body Fat, Fat Free Mass, Muscle Mass, Metabolic Age, and Body Mass Index were equal to, 80.5 kg, 20.3%, 64.2 kg, 61 kg, 30 years, and 25.1 $kg \cdot m^2$, respectively and results in a CV of 0.00% due to all three trails having the exact same scores.

5.5.1. Equipment: Skin-fold callipers

Harpenden skin-fold callipers (Baty International, West Sussex, England) are a hand-held device that use a clamping force to pinch an area of the body to assess the thickness of that area, to predict the total amount of body fat. This method is established on the principle that body fat is equally distributed around the body and that the thickness is a measure for subcutaneous fat. There are numerous methods for the application of skinfolds in specific areas around the body (Pollock and Jackson, 1984). To ensure optimal accuracy of the skin-fold readings, three separate measurements are taken by the same operator to attain a consistent score, with at least a 30 second pause between recordings at the same site. A pinch with the fingers at the site should be held, with the score taken between 1-2 seconds (Beam and Szymanski, 2010). The methods used for this study were similar to that of Leger, Lambert and Martin, (1982) where measurements were taken for the determination of skin and fat thickness only. The pilot testing showed that the repeated collection at 1-site (midpoint between the Inguinal Crease and the top of the Patella), on a male volunteer was equal to 29, 29, 32, 29, 30, 30, 31, 31, mm (mean = 30.1; SD = 1.1; CV = 3.73%).

5.6. Electromyography (EMG)

Surface EMG system (MESPEC 6000, Mega Electronics Ltd, Finland) and the software MEGAWIN, Mega Electronics Ltd, Finland, is a non-invasive electrodiagnostic system for recording the electrical activity produced by skeletal muscles (Kamen, 2004). During muscle contractions, activations of electrical signals are sent from the muscle, controlled by the nervous system via motor neurons which can be recorded. The EMG recordings display the potential voltage difference between two separate electrodes placed on the muscle surface, the raw signal is then converted and displaced on the PC, as this process involves depolarization, the difference in current can be detected (Chowdhury, 2013). This specific system gives live feedback in a visual representation via electromyographs during the muscle actions. An increased amplitude in EMG activity normally reflects the recruitment of additional motor units, ultimately increasing motor unit firing rate, especially those made of fast twitch oxidative glycolytic (type IIa) and fast twitch glycolytic (type IIb) muscle fibres, generating higher muscle forces (Konrad, 2005; Lucia et al., 1999).

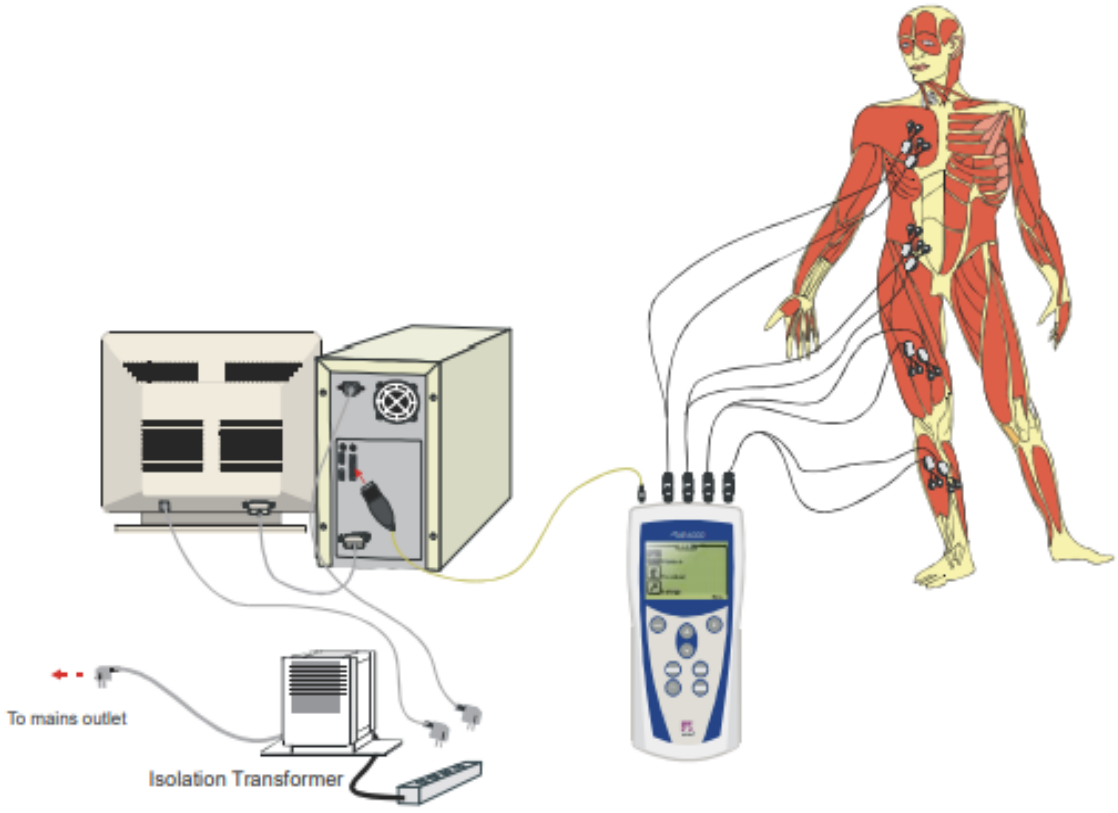


Figure 26. EMG ME6000 example. The portable device is connected to the PC via USB mini-B plug, which has the MEGAWIN software installed to run the device. The PC is connected to an Isolation transformer which is then connected to the mains outlet. Outputs using multi-channel cables (Max 8 channels) can be used for EMG arrays or measuring multiple muscles simultaneously (Mega Electronics, 2004, p.11).

To test the consistency and reliability of the EMG, a pilot study was conducted, where a participant performed five maximal repetitions of seated left leg extension on an isokinetic dynamometer at three different speeds, with 30-second rest between repetitions and 2-minute rest periods between sets. This was repeated on a separate occasion with a 48-hour gap between exercising days (Gleeson and Mercer, 1996). EMG arrays were used on the whole vastus lateralis at the head, mid and proximal points (three channel). These three locations were used to determine the optimal position of the EMG signal (Kamen, 2004). EMG ME 6000 uses MT-M6T4: 2 EMG Pre-amplifier cables with two channels each, type MT-ME6P (Figure 27). The raw data was pre-set to collect at 1000 Hz as instructed in operations manual (Mega Electronics, 2004). At this sample frequency peak calibration accuracy is estimated ± 2%, with operation temperature between 0 – 50 °C and operation humidity under 80%.

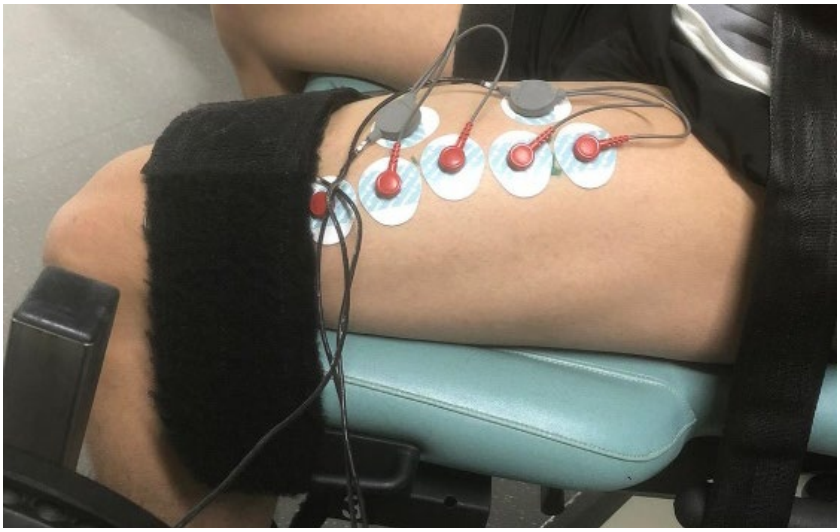


Figure 27. Three channel EMG array. Whole vastus lateralis muscle measured during 5-repetitions at three different speeds. This was conducted at Anglia Ruskin University, Cambridge. Position was determined using the same method as the NIRS (Seniam, 2020).

A high degree of reliability was found between the three EMG placements across the arrays at a speed of 90 degrees per-second. The average measured ICC was .928 with a 95% confidence interval from .877-.953 (F (19,310) = 18.513, p<.000). This suggests that the positioning of the electrodes was equally valid. Similarly, this was the same at speeds of 120 degrees (ICC: .939, CI: .907-.956, F (19,310) = 20.122, p<.000), and 180 degrees per-second (ICC: .945, CI: .925-.958, F (19,310) = 21.157, p<.000). Paired samples t-test found no significant differences in EMG arrays between tests conducted in the same leg on different visits at 90 degrees (t (19409) = .225, p = .822), 120 degrees (t (19469) = .007, p = .995) and 180 degrees per-second (t (15709) = -.008, p = .993). Therefore, concluded that the EMG method used in this study is accurate and repeatable as there were not significant differences between test days in the same measure at all speeds.

5.7. Isokinetic Dynamometer

The Isokinetic Dynamometer (Humac, Norm, USA) is a passive device, which can resist applied forces, and control the speed of human joint actions at a predetermined rate, through a wide range of movements. The dynamometer is known as the gold-standard, test of strength (torque) and power of different muscle groups used within sports and exercise science, as well as clinical testing environments (Hansen et al., 2015).

Depending on the joint action and if it is against gravity, the dynamometer software (HUMAC2009 V.10) weighs the participant's limb, which allows the gravity corrections to be accounted for and zeroed. This is fundamentally important if movements are in the vertical plane, due to the weight of the control arm and the segment (Bartlett, 2007). All movements around the dynamometer axis are recorded by the torque transducer, which is relayed back to the PC unit. Using pre-set angular velocity speeds, the torque sensors adjust the input arm to allow the isokinetic movements to be possible. However, it is important to note that due to the human limbs causing a large acceleration, the resistive mechanism equally activates at the pre-set velocity causing a deceleration phase, the dynamometer moment will be very close to zero for a brief initial period. The resistive mechanism prevents further acceleration of the segment. This means that for a very brief period the movement is not truly isokinetic or at a constant angular velocity, causing 'overshooting'. This becomes more apparent as the pre-set velocity speeds increase, it is recommended to use slower speeds for higher reliability in isokinetic movements, especially for untrained participants that are not familiar with using the device (Humac, C.S.M.I., 2006).

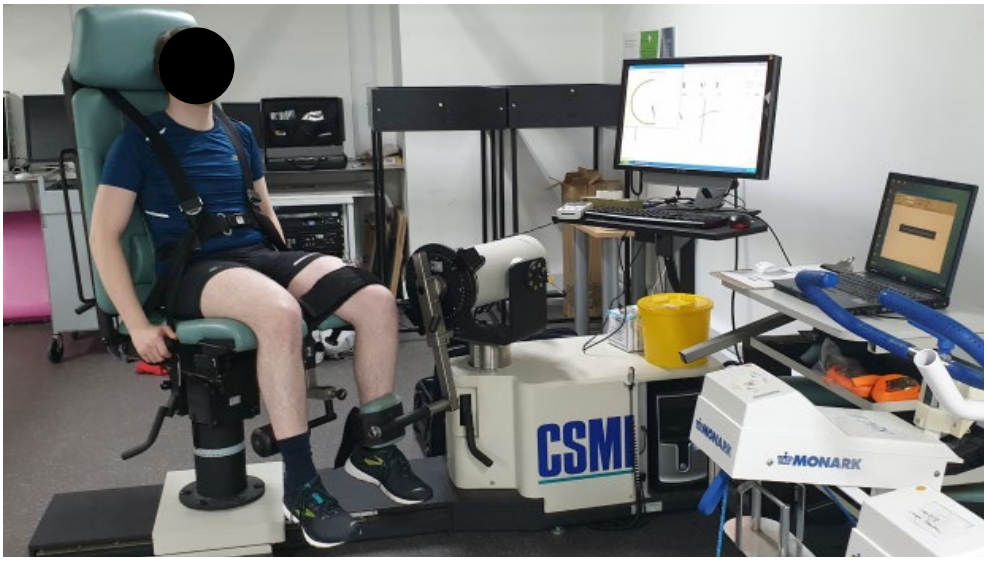


Figure 28. Isokinetic Dynamometer setup. Left leg was tested with the IKD in all participants, the three speeds were randomised for all trials. Calibration and setup were completed in accordance with manufacture's guidelines. Chair dimensions were saved on to the software for future use (Humac, C.S.M.I., 2006).

The dynamometer provides a record of applied force throughout a joint range of motion, and many other variables on a computer system. An advantage of implementing isokinetic exercise includes safety, rehabilitation, accommodating resistance and the ability for muscle force analysis. Isokinetic exercise and movements have become increasingly popular in rehabilitative medicine, due to the assessments in movement, joint actions, and dynamic muscle contractions (Osternig, 1986; HUMAC NORM, 2020). The application of this has been well documented in research within, sport and exercise areas, physical and physiotherapy, Orthopaedic surgery, and more (HUMAC NORM, 2020).

HUMAC NORM torque ranges are from 0.14 N·m and 0.06 degrees per-second to 677.91 N·m and 500 degrees per-second. When compared to other dynamometer like the Biodex, there are a wide range of features available making the HUMAC system more advantageous. These include larger seat area for participant comfort and stability; manual adjustable mechanical ROM stops; 360+ degrees rotational dynamometer shaft; backwards compatible software with all prior generations; high-resolution torque, position, and velocity analogue outputs for incorporation with 3rd party EMG systems. HUMAC published summary reports showing test reliability and accuracy of average peak torques for speeds at 90 degrees per-second displayed a CV of 0.04% in right leg extensor and 0.09% in left leg. Average torque CV of 0.04% in right and 0.06% in left leg, using 5-rep protocols. Similarly, 60 degrees per-second equalled 0.05 and 0.08 for peak torque, respectively (HUMAC®, 2008).

Important note: Due to the restrictions imposed by the UK lockdown, COVID-19, and the closure of universities announced on Wednesday 18th March 2020, the first laboratory study was interrupted. It was not possible to complete the endurance exercise intervention protocols and associated data collection, using the above stated equipment and devices. This was due to commence on the 16th March 2020. Additionally, delaying the second strength intervention study. However, the pre-training methods and results have been reported in chapter 6 and acknowledged that this study is incomplete. Therefore, a reflection and new direction of the work has been outlined in chapter 7, due to accessibility issues with laboratory-based equipment and government guidelines. Nevertheless, chapter 6 was still partly written, and does demonstrate the appropriateness of the methods, data-collection, and techniques applied which still has merit to this thesis.

CHAPTER 6: PHYSIOLOGICAL AND METABOLIC RESPONSES TO AEROBIC EXERCISE TRAINING BASED ON GENOTYPE

6.1. INTRODUCTION

A significant body of evidence relating the improvements in cardiorespiratory fitness from aerobic endurance exercise interventions exists, plus many other positive health benefits (ACSM, 2010; Blair, Cheng, and Holder, 2001; Farrance, Tsofliou and Clark, 2016; Magnan et al., 2013; Ratamess, 2011). Many studies, such as those by Erikssen et al, (1998), Hautala et al., (2006) and Ratamess, (2011) show that even minor (~4%) improvements in cardiorespiratory fitness ($\dot{V}O_{2max}$) can significantly reduce the risk of health problems and increase a person's fitness, wellbeing, and quality of life. It is clear from the results found in the systematic literature review and meta-analysis (Chapter 3), that exercise-training programmes, based on aerobic endurance have positive effects on cardiorespiratory fitness. The review also established that the type of training is important, but only if the stimulus was large enough to trigger adaptive responses to exercise.

In this connection, Schutte et al., (2016) and Vancini et al., (2014) showed individuals' responsiveness to exercise training varies significantly depending on the precise exercise-stimulus. Indeed, the results of systematic literature reviews (chapters 3 and 4), found that all studies demonstrated improvements in cardiorespiratory fitness, which were significantly different between participants, even though they were exposed to the same standardised training interventions. Research has revealed that a genetic component for responsiveness to exercise training exists (Bouchard, 2012; Hautala et al., 2006; Huygens et al., 2004; Klissouras, 1971; Komi et al., 1977; Spurway and Wackerhage, 2006; Vancini et al., 2014; Zambon et al., 2003). This is supported by research in elite performers, showing that certain genotypes and their variants influence specific exercise adaptations and responses, due to their influence on energy-pathways, metabolism, tissue and cell growth, storage, hormonal and enzyme interactions etc. (Prud'Homme and Fontaine, 1984; Spurway and Wackerhage, 2006; Vancini et al., 2014). More recent research has revealed several well-studied genes, related to aerobic exercise trainability and positive response outcomes in many phenotypes. Such genes and their alleles have been termed 'candidate genes' (Cieszczyk et al., 2016; Sarzynski, Ghosh and Bouchard, 2017). In theory, these candidate genes may have the potential to predict which individuals will show successful training adaptations and responses, compared with those who do not exhibit these genetic profiles.

Therefore, the aim of this study, was to examine whether these improvements in phenotypes can be replicated in untrained individuals, who are more representative of the general population, using an 8-week aerobic cycling programme. Additionally, genotyping participants for the listed candidate genes and their alleles, as outlined in chapter 4. Finally, using isokinetic torque assessments in muscular strength to evaluate any influences linked with the genotype, as a result of the training. The expectation is that a significant proportion of the variability in aerobic training responses and phenotypes in this standardised intervention, will be explained by the candidate genes and alleles previously identified. Additionally, because the training is aerobic and endurance based, there should be minimal change in muscular strength and again, differences between alleles can be identified.

6.2. METHODS

6.2.1. Participants

Participants were recruited from the local Cambridgeshire area. All aged between 18-50 years old (Mean ± SD; Age 31 ± 10 years, height 171.1 ± 8.5 cm, mass 66.62 ± 9.04 kg, BMI 19.5 ± 2.2 $kg{\cdot}m^2$) and included both males (n=8) (Age 25 ± 7 years, height 177.3 ± 5.2 cm, mass 74.23 ± 6.55 kg, BMI 20.1 ± 1.7 $kg{\cdot}m^2$) and females (n=9) (Age 36 ± 10 years, height 165.5 ± 7.6 cm, mass 59.87 ± 5.21 kg, BMI 18.1 ± 1.6 $kg{\cdot}m^2$). Initial training status was classed as untrained, due to participants undertaking less than the weekly recommended exercise (ACSM, NHS and WHO). Additionally, participants did not perform any cycle training in the past 8-weeks (NHS 2018; ACSM 2017).

Group sample size was determined using an *a*-priori power calculator (https://clincalc.com/stats/samplesize.aspx) and the average baseline variable ($\dot{V}O_{2max}$) data from 32 groups identified in the systematic literature review (Chapter 3). For the calculation, a within group *vs* population was selected, the primary endpoint was set to 'continuous' (means) and the anticipated mean of a known, untrained population equalled 37.16 ± 5.65 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ with a 10.18% anticipated average increase, alpha at 0.05 and power at 0.8 as standard. This estimated a sample size of 18 participants.

6.2.2. Study design

Ethical approval for this study and the pilot studies, were granted by Anglia Ruskin University, Cambridge, SE-Ethics board (FSE/FREP/19/864). Participants visited the Anglia Ruskin University Sport Science Laboratory on two separate occasions for the pre-training baseline collection. All testing was completed between the hours of 9 am–5 pm. Participants booked the same timeslot the following week for the second laboratory visit. This was then to be repeated mid and post-training intervention for a total of six lab-based testing visits (Figure 29). Laboratory visit 1: cycle ergometer $\dot{V}O_{2max}$ test and laboratory visit 2: Isokinetic dynamometer strength test. Upon arrival, basic anthropometrics, such as, height and mass were recorded, additionally room temperature, barometric pressure and humidity were noted and kept the same for every visit. Participants were informed to arrive in appropriate sportswear, fasted for at least 3-hours and well hydrated with water only, avoiding caffeine-containing drinks.

6.2.3. Laboratory visit 1: Cycle ergometer $\dot{V}O_{2max}$ test

For laboratory visits one, three, and five, the $\dot{V}O_{2max}$ tests were to be performed on an electronically braked cycle ergometer (Lode Corival Sport, Groningen, Netherlands). Saddle and handlebar positions were adjusted to participant comfort and noted for future reference. All equipment was serviced and calibrated to manufacturer's guidelines prior to every participant visit.

Pre-test:
Upon arrival, participants provided a 10 µl capillary blood sample for the determination of haemoglobin and haematocrit (EKF Hemo Control, EKF diagnostic, Germany), additionally, a 20 µl sample for resting blood lactate and glucose (EKF-diagnostic Biosen C-Line Clinic, GmbH, Germany). A PhysioFlow® (PF05L1, Manatec, Petit-Ebersviller, France) was applied to monitor cardiac variables during the cycle test (Chapter 5: 5.2.). All procedures were completed in accordance with the operating instructions manual. Participants were instructed to shave areas of the body where the Skintact FS50 electrodes would be stuck onto the skin surface. The skin would be cleaned and wiped with Neuprep abrasive gel until pink for maximal contact and connectivity. Any electrodes that were positioned together in the same location require a small gap between them (PF05L1, 2001. p.3). Once the setup was completed, the participant was then instructed to remain seated, at rest, on the cycle ergometer and three separate blood pressure readings were taken with the OMRON M3 (Omron healthcare, Kyo to, Japan) and entered in to the PhysioFlow® software calibration. The calibration was performed over 30 heart beats and the data was collected for every heart cycle.

Following this, the PortaMon Near Infrared Spectroscopy (NIRS) (Portamon, Artinis, Medical System, Zetten, He Netherlands) for the non-invasive measurement of tissue oxygen saturation was employed (Oueslati, Girard and Ahmaidi, 2018). The skin surface was shaved and cleaned, the NIRS device was placed on the belly of the left Vastus Lateralis, using a mixed method of muscle palpation and anatomical locations from the SENIAM Guidelines (Chapter 5: 5.3. Figure 25). This was two-thirds on the line from the Anterior Spina Iliaca Superior and the lateral side of the Patella, these dimensions were taken with a measuring tape and recorded for each participant, for future positioning (Kime, et al., 2013; Quaresima et al., 2001). The NIRS was then wrapped in cling film to reduce any chance of moisture damage, then covered with a black microfiber cloth, to minimise light interference and positioned securely with bandages to fix and secure the position onto the left leg.

During-test:

Participants were instructed to cycle at a constant cadence, held between 60-70 revolutions per-minute (RPM). The incremental step-test began at 100 W for males and 50 W for females and increased by 25 W, every 3-minutes. This progressive increase was maintained until volitional exhaustion was achieved, or if cadence fell by >5 rpm from the pre-determined rate and could not be maintained (Gordon et al., 2010; Keiller and Gordon, 2019). A further 20 µl blood sample was collected at every stage of the step protocol, at 2-minutes 30-seconds into the stage for the determination of submaximal blood lactate and glucose. During this test breath-by-breath data was collected using the Cortex Metalyzer® 3B (MSX 671; Ferraris Respiratory, Middlesex, UK) (Chapter 5: 5.4.). Additionally, Heart rate data (Polar 810s, Kemple, Finland) was also collected during the entire test. Toward the end of the cycle step-test verbal encouragement was provided to the participant, which was similar for every participant.

Post-test:

Upon completion of the test, a final 20 µl blood lactate and glucose sample was collected at the fingertip. Participants were debriefed and given the option to cool-down at an unweighted resistance of 0 W.

6.2.4. Laboratory visit 2: Isokinetic dynamometer strength test

Pre-test:

On a separate day to the laboratory visit 1, on arrival, participants were instructed to stand barefoot on a set of Tanita scales (Remote display version, Tanita DC-430 S MA, Manchester, UK), for the determination of body composition, using bioelectrical impedance (Chapter 5: 5.5.) and this was repeated three times for an accurate reading. Once completed, participants' left thigh girth was measured, at the midpoint between the Inguinal Crease and the top of the Patella. In the same location, Harpenden skin-fold callipers (Baty International, West Sussex, England) were used to determine skin and fat thickness (Chapter 5: 5.5.1.). This measurement was only taken at one site opposed to the standard 3-7 site outlined by Pollock and Jackson, (1984). The justification for this, was that the skinfolds were not used to determine total body fat scores, neither was it used for any body composition factors. Instead, this measurement was solely to compare pre vs post intervention skin / fat thickness at the quadricep along with leg girth measurements like the study by Leger, Lambert and Martin, (1982). To ensure optimal accuracy of the skin-fold readings, three separate measurements were taken by the same operator to obtain a consistence score, with a 30 second rest between measurements and a pinch held with score taken within 1-2 seconds (Beam and Szymanski, 2010).

Following this, surface EMG (MESPEC 6000, Mega Electronics Ltd, Finland) was positioned on the skin surface, prepared similarly to that for the PhysioFlow. Two Skintact FS50 electrodes were located on the left side of the leg, at the belly of the Vastus Lateralis and one on the medial side of the muscle, as a reference electrode (Beck et al., 2008; Seniam, 2020). Positioned similarly to the PortaMon NIRS device to allow the measurement of neural activity during the isokinetic dynamometer test.

During-test:

An isokinetic dynamometer (Humac, Norm, USA) was used to record the maximum isokinetic muscle torque through a controlled seated concentric leg extension and flexion at 90, 120 and 180 degrees-per-second (Chapter 5: 5.6.). Participants were secured on the dynamometer and performed the set range of motions. The dynamometer was adjusted to participant comfort with respect to their body height, this was recorded on the HUMAC software to keep future positioning consistent, and personal profiles were created. Calibration and setup were completed in accordance with the manufacturer's instruction guide (Humac, C.S.M.I., 2006). Participants were instructed to perform three warm-up repetitions, at each speed, to familiarise themselves with the movements. Following a 30-seconds rest, participants performed five maximal repetitions (maximal extension and flexion) at each speed, with 2-minutes rest between sets (Gleeson and Mercer, 1996). The order of the speeds were randomly generated by the software. During the concentric knee extension phase neural activity was recorded via EMG.

Post-test:

Participants were debriefed, unstrapped, and instructed to safely dismount the dynamometer.

6.2.5. Training intervention

The training intervention was due to take place from the 16th March 2020. Anglia Ruskin University, Cambridge City closed on that date due to the COVID-19 outbreak, indefinitely postponing the study. The training was to consist of 30-minutes of continuous cycling at 70% of $\dot{V}O_{2max}$, at a constant cadence of 60 RPM, with all sessions performed on Monark cycle ergometers (Monark Ergomedic 893 E, Sweden). Once participants reached the stipulated cycle RPM, a magnetic trigger would apply the cycle resistance, at which point, the timer would start.

Participants would train three times a week for 4 consecutive weeks, these would be monitored and conducted at Anglia Ruskin University Sport Science laboratories. Following this, participants would repeat both laboratory visits for the assessment of mid-training adaptations. 4 further consecutive training weeks would then be conducted, for 8-weeks total training, followed by another laboratory block of testing (Figure 29). In total, participants would attend 24 training sessions. This was calculated using information obtained from the systematic literature review (Chapter 3). Participants were required to attend a minimum of 21 sessions, to be included in the final analysis of the study.

Training progression was set to increase every 2-weeks in the endurance group by 2.5% of the $\dot{V}O_{2max}$ wattage, unless participants could not maintain the desired pre-set RPM (Reuter, Dawes and National Strength and Conditioning Association, 2000). Endurance sessions for participants were matched in terms of training load, equal to 2,100 A.U. at the start of the training intervention.

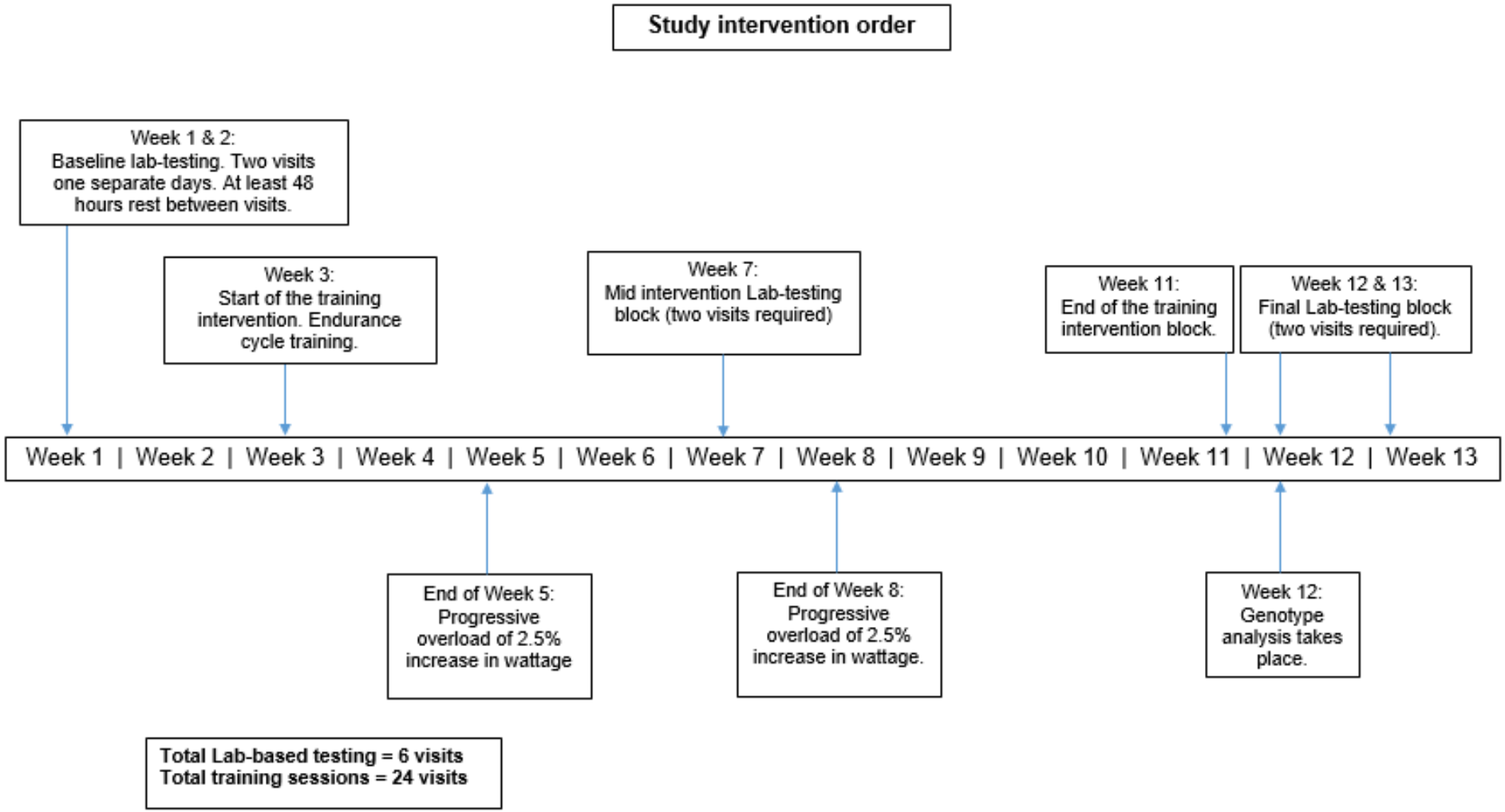


Figure 29. Study intervention schematic timeline. Timeline of the lab-based and training intervention, estimated to be a 13-week period.

6.2.6. Genotyping

An allele specific PCR test was due to take place at Anglia Ruskin University, Cambridge at the end of the training intervention. This was to be conducted in accordance with the methods from Gaudet et al., (2009). A coded sterile plastic tube would have been provided for all participants, including a cotton wool swab-stick (PlayDNA Ltd, DiagnOx Laboratory, 77 Heyford Park, OX255HD, U.K.). The swab-sticks would be used by the participants to collect a cheek cell saliva sample, by rubbing against the inside of the cheek for approximately 1-minute, where the participants will be advised not to brush their teeth, use mouth wash, chew gum, eat or drink 2-hours before the swab as standard. The swab-stick is then sealed in the coded tube for reference and temperately stored on-site in a laboratory freezer (-20 degrees Celsius). Allele-specific-PCR and saliva analysis via ELISA kits sigma in accordance with the Human Tissue Act (HTA) (2004). The analysis should provide the allele specific listed candidate genes outlined and identified from chapter 4. This was to be processed by the Deputy Head of Life Sciences and genetics expert at Anglia Ruskin University, Dr. Donald Keiller.

6.2.7. Data Analysis and Statistical Overview

Respiratory data was converted and normalised (Microsoft office Excel 2016) from the absolute values to the relative participant specific units. Upper and lower SD were also calculated to allow removal of any outliers in the breath-by-breath analysis. A 15-breath rolling average was adopted for $\dot{V}O_2$, $\dot{V}CO_2$, RER, HR and V_E (Robergs, Dwyer and Astorino, 2010). To determine $\dot{V}O_{2max}$ a 1.5 $ml \cdot kg^{-1} \cdot min^{-1}$ Δ $\dot{V}O_2$ plateau criteria was implemented, comparing the final two consecutive 30-second sampling periods (Gordon et al., 2015). In the absence of a Δ $\dot{V}O_2$plateau, secondary criteria were used to establish if a maximum effort was given, heart rate (HR) ≤ 10bpm or 5% of the age-predicted maximum (220-age), blood lactate concentration ≥ 8 $mmol \cdot l^{-1}$, respiratory exchange ratio (RER) > 1.10 and $\dot{V}O_{2peak}$ was defined as the highest single 15 breath average (Poole and Jones, 2017).

Although PhysioFlow® data was collected per heartbeat, a 10-heartbeat moving average was recommended in the manual guide (Physioflow® software V2). To align this data to the $\dot{V}O_2$ breath-by-breath data, each 15-breath average was referenced to the corresponding time at the 10-beat averaged PhysioFlow® time. Maximum arteriovenous oxygen difference (a-vO_{2diff}) was calculated using the reverse Fick principle,

$$a\text{-}vO_{2diff}\,(ml \cdot 100ml) = \dot{V}O_2 \,/\, \text{cardiac output (Q)} \times 100$$

(Lepretre, Koralsztein and Billat, 2004).

Raw NIRS data was processed with Microsoft Excel spreadsheet (2016). This signal was sampled at 10 Hz, as advised in the manual guide. The data was filtered using a 10-cell moving average and the Beer-Lambert law was used to calculate the trace measurements of TSI%, O_2Hb, hHb and tHb per-second. A muscle tissue differential pathlength factor (DPF) of 4.95 was applied (Artinis, 2020; McIntosh et al., 2010; Rissanen et al., 2012; Subudhi et al., 2009). Finally, the averaged data was time-aligned with the $\dot{V}O_2$ data using a similar method from the PhysioFlow® to ensure the correct timeframe.

Isokinetic dynamometer data was sampled at the pre-set value of 100 Hz, using the HUMAC2009 V10 software and exported to Excel. Here an automated spreadsheet was created, allowing visualization of 10 independent peaks, five being quadriceps and five hamstring activations (Figure 30). This represented the 5-repetition maximum of the seated knee extensions and flexions (Gleeson and Mercer, 1996). The movement-arm speed, in degrees-per-second, was used to identify the peaks and the true isokinetic phase, enabling a threshold to be set for these speeds (Bartlett, 2007). Once the peaks were identified the algorithm removed the first two and the last two peaks (first and last repetitions) (Gleeson and Mercer, 1996; Humac, C.S.M.I., 2006). Using the middle three extension and flexions allowed the formula to calculate isokinetic torque (Nm) from the respective speed thresholds. Because of the order of repetitions, the formula was able to differentiate opposing joint actions and separated extension and flexion. These were then averaged over the three peaks and the maximum isokinetic torque was identified for both actions. This was repeated for all three speeds (HUMAC NORM, 2020). The average data is presented in table 27.

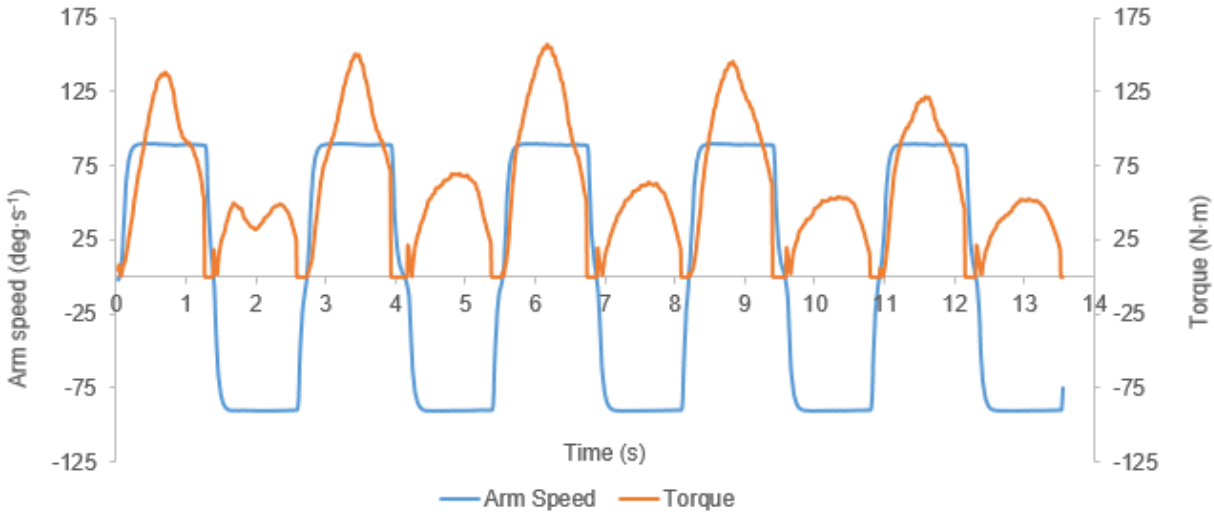


Figure 30. Isokinetic knee extension and flexion at 90 degrees-per-second. Note: Arm speed refers to the speed of the movement lever during the action.

Raw surface EMG was sampled at 1000 Hz and exported to Excel. The data was normalised using a DC bias, a root mean square transformation (RMS) was used to rectify the scores as recommended by Edgett et al., (2013), Lucía et al., (1999), Thigpen et al., (2010) and Wang et al., (2019). All scores were squared and a 100-cell rolling-averaged was completed, where all scores were then square rooted. This procedure transformed the RMS-EMG to 100 Hz and time-alignment with the isokinetic dynamometry data (Figure 31 and 32). Once aligned, the algorithm, was also used to average the peak EMG responses. The mean EMG data is presented in table 27 and an example of how the data was process using one participant's data for an example is shown in figure 31. This process was completed for all participants in this study.

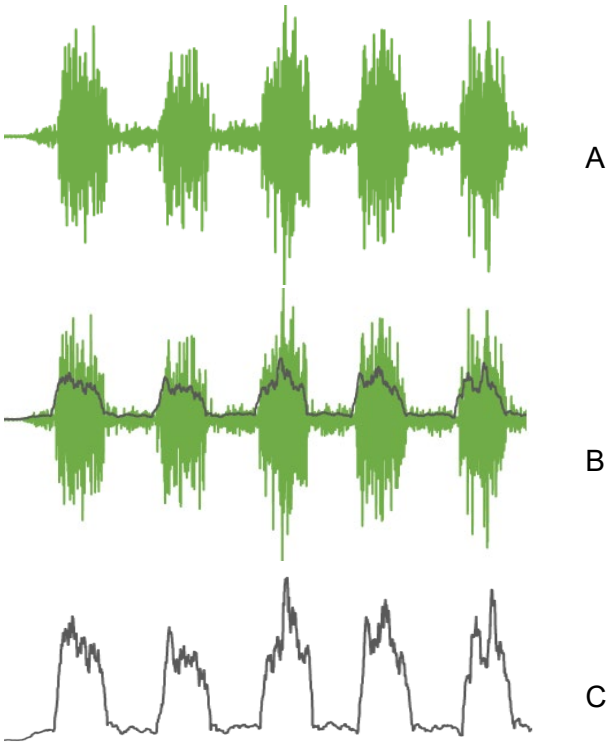


Figure 31. Raw EMG processing using 1 participants data for an example. (a) Raw EMG shows five waveforms that represent all five-knee extension. (b) the DC bias and RMS was applied to the raw waveform, where it then converts the wave into a positive set of peaks and (c) the RMS-EMG absolute values can be used to indicate the level of muscle activation for the action (Konrad, 2005).

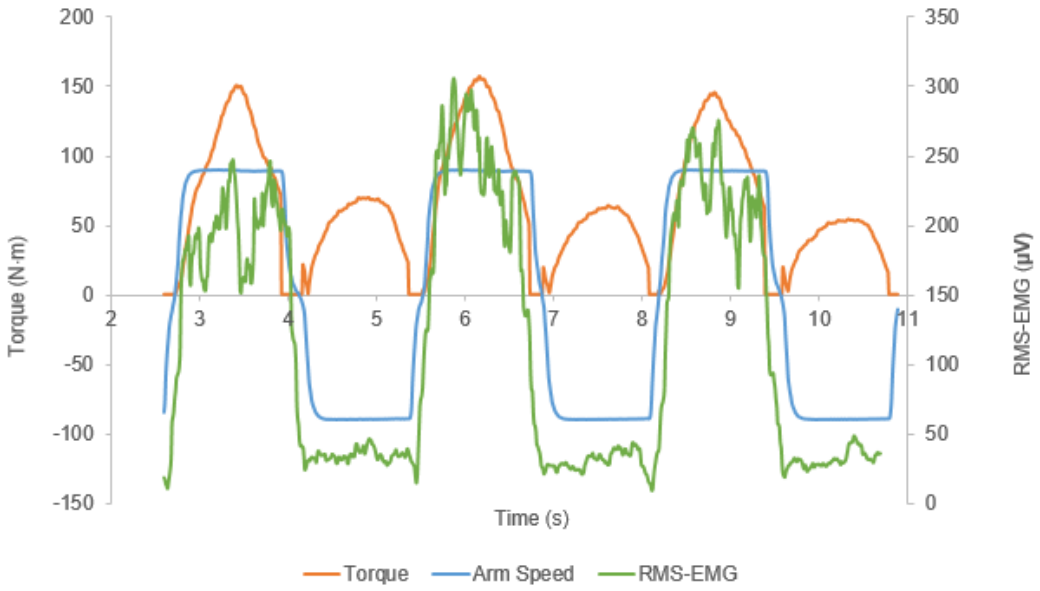


Figure 32. RMS-EMG time-aligned with isokinetic data. The three peaks were aligned, and the RMS-EMG was calculated, based on the period of isokinetic movement outside of the acceleration and deceleration phases. This was where the arm speed was constant and achieved the pre-set threshold of 90, 120 or 180 degrees-per-second.

The results and statistical analysis in this section were limited to baseline data only as no further data was collected. A Shapiro-Wilk test of normality and Levene's test for homogeneity and variance were conducted. For all statistical analyses, the alpha level was set at $p < .05$ using SPSS version 26 (SPSS, Chicago, IL). Additionally, independent samples t-tests for the secondary criteria, where the group was split from achievers and non-achievers of VO_2 plateau were analysed. Pearson's *r* and Spearman's rho correlational tests were used to assess the relationship with the isokinetic torque strength and the neuromuscular activity in the Vastus Lateralis, at the three different speeds. Baseline data for this study was collected from February 24th – March 9th, 2020.

6.3. RESULTS

A final 17 participants completed all pre-training baseline tests (Age 31 ± 10 years, height 171.1 ± 8.5 cm, mass 66.62 ± 9.04 kg, BMI 19.5 ± 2.2 $kg \cdot m^2$). The results indicated that, 13 achieved the $\Delta\dot{V}O_2$plateau criteria (76.5%). The remaining four participants still provided a maximum effort according to the secondary criteria, however, did not achieve $\dot{V}O_2$ plateau (Table 26). Post-hoc statistical power (β) was calculated using the baseline $\dot{V}O_{2max}$ scores, results found that power was accepted in the group of 17 participants equal to 80.2%.

Table 26. Maximum effort criteria. Plateau and secondary criteria for all participants. HR ≤ 10 bpm (220-age), blood lactate ≥ 8 $mmol \cdot l^{-1}$ or respiratory exchange ratio > 1.10

Participant no.	Primary criteria (Yes/No)	HRmax (bpm) Age (years)	Post Exercise Lactate ($mmol \cdot l^{-1}$)	RER
1	Yes	174 (25)	8.98	1.26
2	Yes	174 (47)	6.94	1.21
3	Yes	174 (34)	8.23	1.15
4	Yes	180 (19)	9.38	1.21
5	Yes	193 (24)	15.10	1.27
6	Yes	180 (31)	7.16	1.32
7	Yes	190 (23)	10.11	1.25
8	Yes	156 (46)	5.41	1.15
9	Yes	174 (49)	9.45	1.25
10	Yes	189 (25)	7.71	1.16
11	Yes	176 (42)	8.98	1.22
12	Yes	153 (41)	9.20	1.26
13	Yes	190 (26)	9.86	1.16
14	No	191 (22)	8.63	1.21
15	No	197 (21)	12.52	1.32
16	No	182 (22)	7.02	1.20
17	No	169 (22)	8.85	1.23

Table 27. Variables from laboratory visit 1 and 2. Means and SD all variables.

Variable	**Mean**	**SD**
Cardiovascular measures		
Completed wattage at $\dot{V}O_{2max}$ test	182	52
$\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	33.20	9.03
Stoke volume max (ml)	137.5	39.1
Cardiac output max ($L \cdot min^{-1}$)	24.1	6.6
a-vO_{2diff} max (ml·100 ml)	9.7	2.7
Heart rate max (bpm)	179	12
Respiratory exchange ratio (RER)	1.23	0.05
Time to exhaustion (s)	846.1	270.1
Blood measures		
Pre-exercise lactate ($mmol \cdot l^{-1}$)	1.34	0.36
Post exercise lactate ($mmol \cdot l^{-1}$)	9.03	2.15
Change in lactate ($mmol \cdot l^{-1}$)	7.67	2.11
Pre-exercise glucose ($mmol \cdot l^{-1}$)	4.43	0.66
Post exercise glucose ($mmol \cdot l^{-1}$)	4.11	0.74
Change in glucose ($mmol \cdot l^{-1}$)	-0.21	1.02
Haemoglobin ($g \cdot dl^{-1}$)	14.5	1.6
Haematocrit (%)	43.1	4.4
NIRS measures		
O_2Hb at 100% $\dot{V}O_{2max}$ (A.U)	4.42	3.63
hHb at 100% $\dot{V}O_{2max}$ (A.U)	26.41	6.62
tHb at 100% $\dot{V}O_{2max}$ (A.U)	20.53	7.83
TSI (%)	74.04	14.35
Body composition measures		
Mass (kg)	67.08	9.43
Body fat %	22.4	7.13
Fat mass (kg)	14.74	4.24
Fat free mass (kg)	52.36	10.31
Muscle mass (kg)	49.71	9.79
Left thigh girth (cm)	53.24	3.50
Skinfold mid-thigh (mm)	19.25	7.13
Isokinetic dynamometer Torque		
Peak Quad at 90 $deg \cdot s^{-1}$ ($N \cdot m$)	101.86	33.74
Peak Hamstring at 90 $deg \cdot s^{-1}$ ($N \cdot m$)	60.28	31.53
Peak Quad at 120 $deg \cdot s^{-1}$ ($N \cdot m$)	101.59	30.36
Peak Hamstring at 120 $deg \cdot s^{-1}$ ($N \cdot m$)	59.77	35.68
Peak Quad at 180 $deg \cdot s^{-1}$ ($N \cdot m$)	75.84	30.39
Peak Hamstring at 180 $deg \cdot s^{-1}$ ($N \cdot m$)	44.93	25.66
Electromyograph measures		
Quad RMS-EMG at 90 $deg \cdot s^{-1}$ (µV)	652.04	436.44
Quad RMS-EMG at 120 $deg \cdot s^{-1}$ (µV)	663.45	366.55
Quad RMS-EMG at 180 $deg \cdot s^{-1}$ (µV)	638.65	378.14

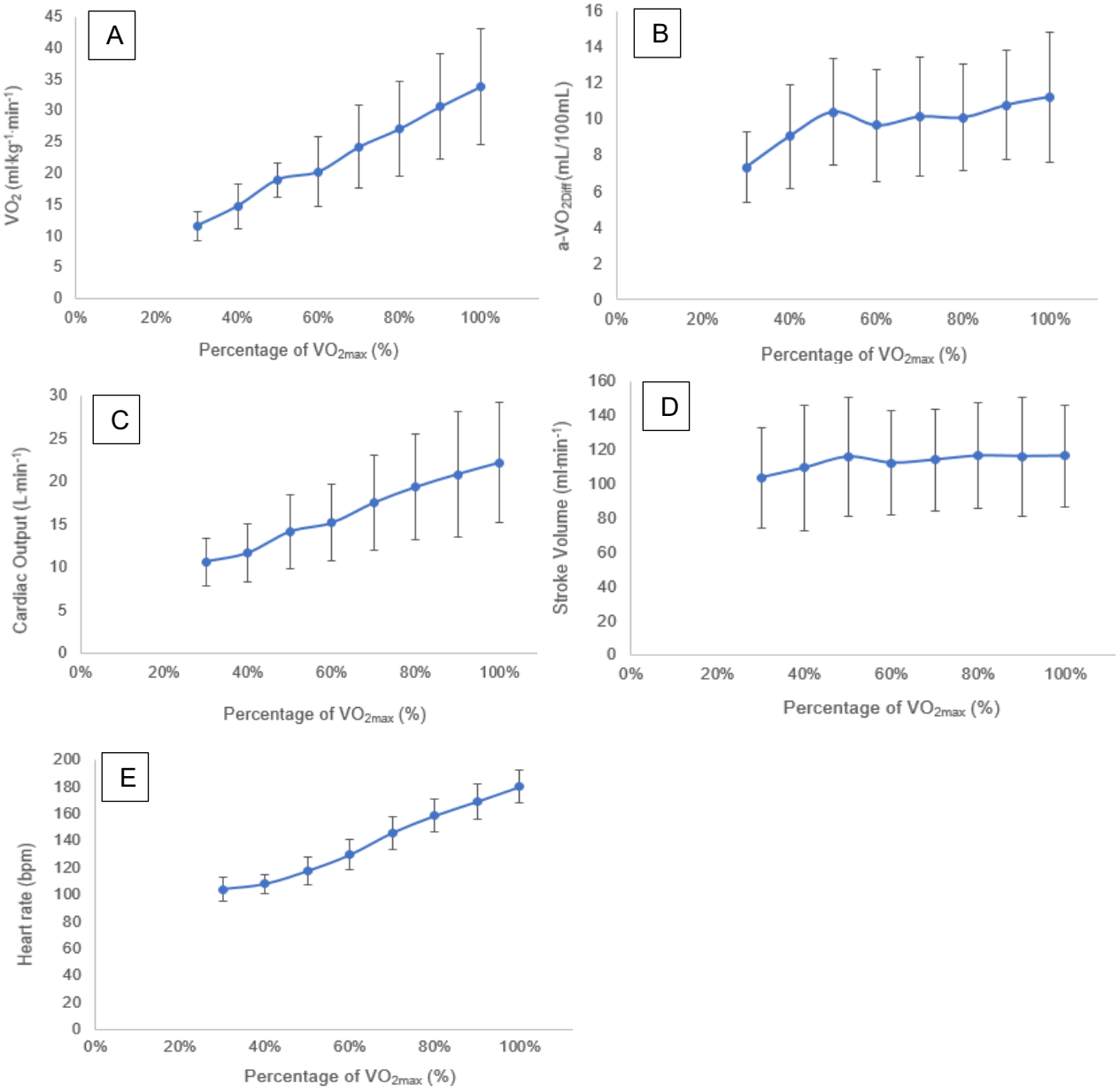


Figure 33. Average change in cardiac variables during the incremental cycle test. VO_2, cardiac output, and heart rate all increase with exercise intensity, whereas stroke volume peaks around 50% on average. a-vO_2 difference continues to increase reaching a maximum around 90-100%.

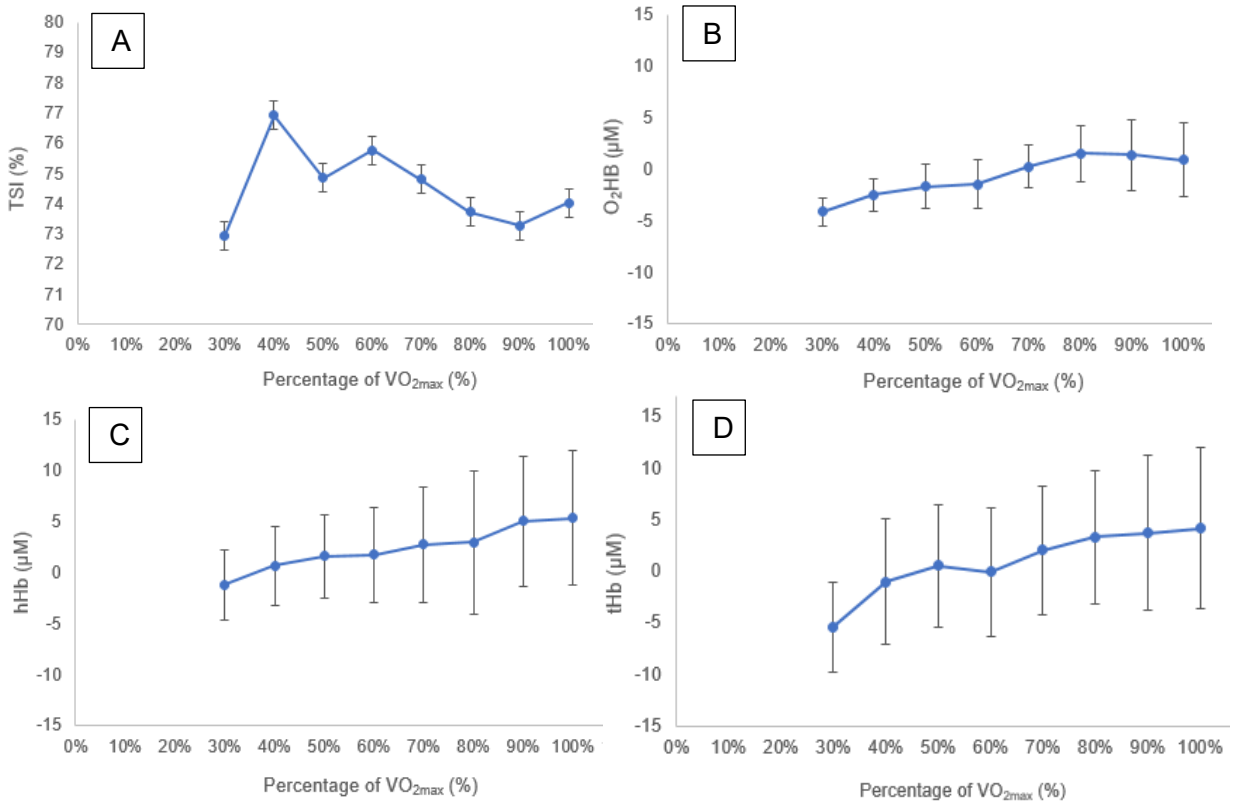


Figure 34. Average change in NIRS readings during the incremental cycle test. Where TSI is tissue saturation index, O_2Hb is oxygenated hemoglobin, hHb is deoxygenated hemoglobin and the tHb is total hemoglobin. During the test, the demand for O_2 increases which causes an increase in the amount of total haemoglobin needed at the tissue.

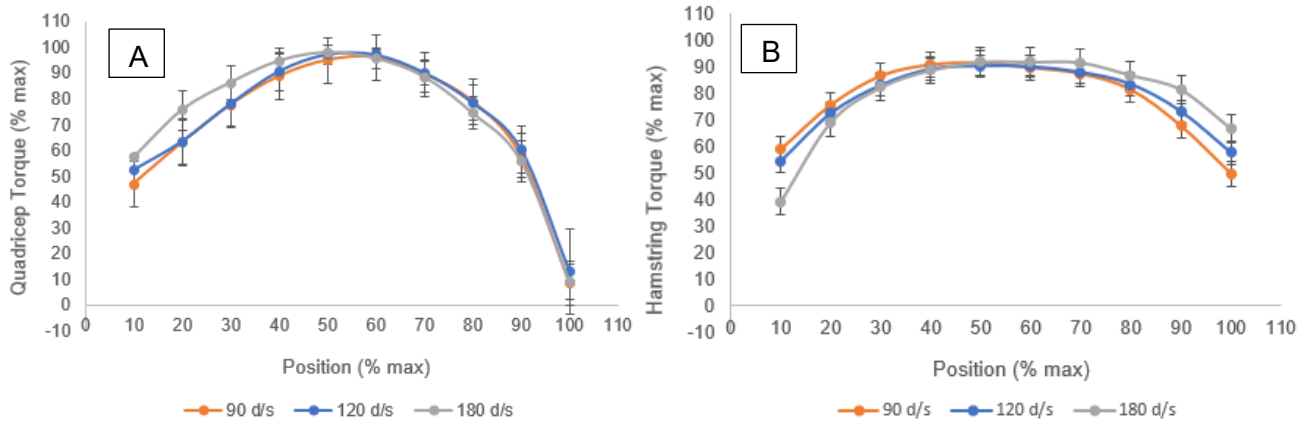


Figure 35. Knee torque vs position curve. For both knee extension (Quad) and flexion (Hamstring) movements. The torque was recorded at three different speeds, where d/s is degrees-per-second. These were all converted to a percentage of the maximum, for both the position of the knee angle and the torque achieved during the movement.

On average, the maximum torque (100%) was achieved at ~50-60% of the knee angle position, for both the concentric knee extension and flexion movements, regardless of speed. 100% of the knee position is equivalent to maximum knee extension or maximum flexion when seated in the range of motion. Results show consistency in torque across speeds.

Four variables (post-exercise glucose, Hamstring Torque at 120 deg·s^{-1}, Quad RMS_EMG at 90 and at 180 deg·s^{-1}) were not normally distributed, however, all variables displayed homogeneity of variance except the post-exercise glucose (p = .001). Participants descriptive characteristics including age, height, mass, body fat, and muscle mass, all met parametric assumptions. Results show that the group of 17 participants were homogenous.

$\dot{V}O_{2max}$, used to determine training status, was normally distributed, D (16), .916, p = .145. When the group was split by sex, Levene's test also found the groups were homogenous, F (1,15) = 4.485, p = .051. Blood lactate, HRmax, and RER were also normally distributed (p = .970, p = .841 and p = .814, respectively). Independent samples t-test found non-significant differences between groups for all variables, t (15) = -1.084, p = .296, t(15) = -.224, p = .826 and t(15) = -.623, p = .543, respectively, confirming group homogeneity, irrespective of whether they achieved a $\dot{V}O_{2max}$ plateau.

Muscle strength assessed by isokinetic torque at all speeds, and for both the concentric knee actions, showed that the group was homogenous and normally distributed. Finally, RMS-EMG at 90 and 180 deg· s^{-1} did not meet parametric assumptions and here Spearman's rho test found a significant correlation between the torque strength and the EMG activity, r_s (16) = .550, p = .027 and r_s (16) = .527, p = .036, respectively. Similarly, isokinetic strength at 120 deg·s^{-1} was correlated to EMG, r (16) = .607, p = .013.

6.4. SUMMARY AND REFLECTION

Due to the restrictions imposed by the UK lockdown, it was not possible to implement the exercise intervention protocols and associated data collection. Nevertheless, this study does demonstrate the appropriateness of the methods, data-collection, and techniques applied. Overall, the key observation was that the preliminary pre-exercise training baseline data of the participants recruited demonstrated group homogeneity and was also normally distributed. This is an important finding as these are the key grouping variables used to determine the training status of the individuals (ACSM, 2010; Ratamess, 2011). Hence, it is reasonable to assume that the study population met the criteria for the target population and agreed with the findings from the systematic literature review (Chapter 3). This is further supported by the homogeneity in baseline secondary criteria and participant group characteristics. Finally, the participant sample size was adequate in terms of post-hoc statistical power.

Isokinetic torque was significantly correlated with RMS-EMG at all speeds, showing that neuromuscular activity contributes to the isokinetic strength of the muscle action being performed. These results are similar to work from, Beck et al., (2008). This outlines the validity and reliability of the methods used within this study and can aid future study methodologies.

It is regrettable that, due to the unique challenge posed by COVID-19, it would appear that this study cannot be fully completed as of this time. In summary, this incomplete chapter has revealed some interesting results from the 17 participants local to the Cambridgeshire area. For further planning and direction of this work a supporting reflective chapter addressing present issues, timescales and future direction of the work will be conducted within the next chapter, in an attempt to support, complete and justifying the current hypotheses for this thesis to be completed.

CHAPTER 7: THESIS REFLECTION

7.1. INTRODUCTION

In December 2019, a novel virus emerged and has since, spread throughout the world, reaching the UK, with the first reported case on January 31st. Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is particularly dangerous due to the relative ease of the spread, as well as several infected people experiencing delayed and little to no symptoms, becoming passive carries. COVID-19 spreads primarily through droplets of saliva or discharge, lasting on surfaces for a prolonged period, which is then touched and transmitted (Gallagher, 2020; WHOb, 2020). The majority of infected people will experience mild to moderate respiratory illness and recover without requiring any treatment. However, people aged 50 year and over, and those with medical conditions such as, cardiovascular disease, diabetes, chronic respiratory disease, and cancers are more likely to develop serious illness and cause death (WHOb, 2020).

The World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) and on the 11th March 2020 officially classed it as a World-wide pandemic (WHOa 2020). Following this declaration and increasing cases, the UK government publicly announced on the 18th March 2020, the closure of all public meeting places, including universities (Stewart and Walker, 2020). The government advised citizens to stay at home, and to only go outside for essentials, health reasons or work only. Always keeping at least two metres (6ft) away from others, and to wash hands as soon as they get home. Additionally, not to meet others, even friends or family outside the current household, and one form of outdoor exercise a day (Gov.uk, 2020; NHS, 2020). Due to this situation, most decided to stay at home and enforce social distancing, this became very important in daily living. As of the updated statistics document from Gov.uk (2020) figures have shown a total of 295,372 lab confirmed cases in the UK and an estimated 15 million cases worldwide. On the 20th July 2020, the UK death toll stood at 45,312, estimated 11 deaths and 581 lab confirmed cases per-day, with theories of a second wave being imminent.

As a result, because COVID-19 is a respiratory disease, it was heavily implied that laboratory based respiratory testing was not possible even if universities were to reopen in the near future. In addition, if the current government guidelines remained, even after a lockdown period, it would also not be possible to continue with participants in close proximity during the laboratory-based tests. Therefore, a reflection process was required to better understand the situation and how to adapt the current thesis to still meet the aims and objectives.

7.2. REFLECTION

There are a variety of theories and models on reflection in research, as part of the continuous learning cycle. Atkins and Murphy, (1993) stated that, although reflective models are useful, they must focus on having a real impact following with an action plan, to ensure the reflection has a suitable outcome. It is noteworthy that explicit frameworks and models may not be appropriate for some reflective situations, due to the varied focus of contexts. Yet, the models are aimed to be critical of knowledge and experience to deepen the understanding of the situation being reflected upon (Mann, Gordon and MacLeod, 2009). The act of reflection and its merit are often overlooked, due to the educational concept and the impact not being easily measured. However, in practise reflection should be difficult, large considerations and debates should challenge difficult issues that may take months to reflect on (Jayatilleke and Mackie, 2013; Kalk et al., 2014). When using reflection there is a wide range of aspects to be considered, for example, perspective, emotional responses, team dynamics, realism, societal impacts etc. In addition, it must be considered if the act of reflection should be completed alone or as part of a team or both. Ultimately, the goal of a reflection process should be to improve, adapt, and learn from relevant past experiences to challenge an idea and evolve future experiences (Jayatilleke and Mackie, 2013).

A number of models were explored, and the literature consensus agreed with the notions that, Jasper's Experience-Reflection-Action (ERA) cycle, should only be used for personal self-reflection due to it being overly simple. This model emphasises using feelings and past experiences, which lead to new experiences to decide on an action (Jasper, 2013). Similarly, to Driscoll's 'What Model' developed in the mid-1990's, asking three main questions (What? So what? Now what?) (Driscoll, 2007). Another consideration was Kolb's Learning Cycle (1984), which implements four stages 1) concrete experience, 2) reflective observation, 3) abstract conceptualisation and 4) active experimentation, however, it has been highlighted to have a high possibility of unrelated outcomes (Kolb, Rubin, and McIntyre, 1984). Gibb's Reflective Cycle builds on these models and Boud's triangular representation model (Boud, Keogh and Walker, 1985) and adds additional levels with a total of six main stages of reflection. The model encourages the user to focus on their feelings about an experience, both during and after, to evaluate and make sense of a situation (Gibbs, 1988). Reflection is a personal and individual process, everyone works towards it in a different way, implementing various models and variations of these (University of Cambridge, 2020). A new plan of action is required during the COVID-19 pandemic. A reflection model will aid the process of proposing a new direction of the current work to make it achievable and realistic but still meeting the current objectives.

7.2.1. Gibb's Reflective Cycle

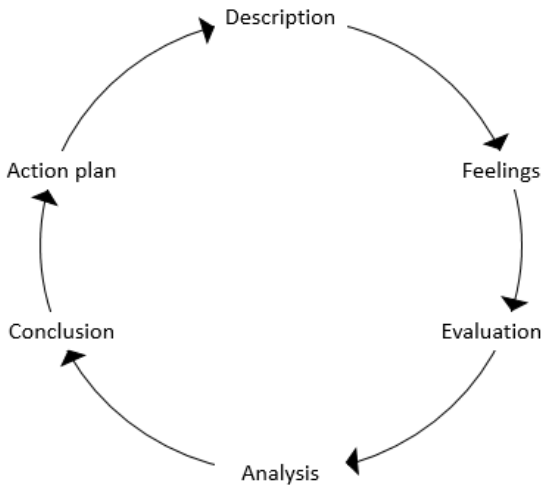


Figure 36. Gibb's Reflective Cycle. This model is used to make the reflector think systematically about the stages of an experience. Stages 1, 2 and 3 are subjective, 4, 5 and 6 are objective (Gibbs, 1988).

7.2.2. Description of what happened

In relation to chapter 3 and 4 and the preliminary laboratory data collection completed in the first group of 17 participants (Chapter 6). The training intervention was scheduled for 16th March 2020. Due to the new UK government guidelines, including the closure of universities, lockdown and social distancing, several critical issues raised. It became uncertain when the university laboratories would be ethically safe to continue physical testing once re-opened, as well as when the social distancing and lockdown would end. In the best-case scenario, the aim was to complete the data collection by November 2020. This would allow approximately 9-months for the genotype analysis and write-up (Figure 37). Initially, it was proposed that the laboratory testing would recommence as soon as the universities re-opened. However, new statements from the government, extended the lockdown period by at least three more weeks with many uncertainties, announced by Dominic Raab on 16th April 2020. The foreign secretary stated that a review had concluded,

"*Relaxing the measures now would risk harming public health and the economy*".

This was due to the UK recording another 861 coronavirus deaths in hospital in a single day (BBC, 2020; England NHS, 2020). Furthermore, on the 10th May 2020 Prime Minister Boris Johnson announced "less strict" lockdown rules with social distancing still in place. Re-opening of schools from June 1st however, universities still having no fixed dates (Peck, 2020). It was becoming more apparent that the university would not re-open until a much later date, with participant interactions and lab testing taking even longer.

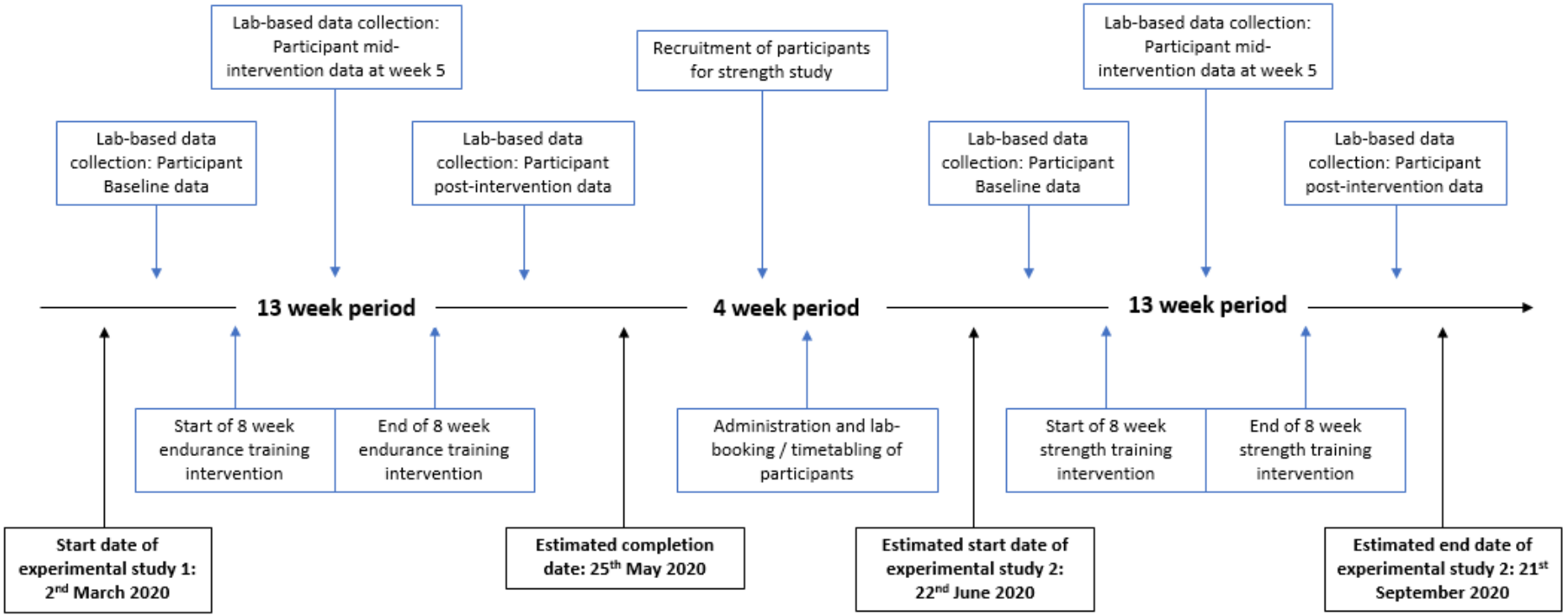


Figure 37. Timeline of initial endurance and strength interventions. In total a 30-week period is necessary for the completion of data collection. 13-week interventions for both endurance and strength protocols.

7.2.3. Feelings (What were you thinking?)

On the 13th March 2020, an email was sent to all postgraduate researchers and staff from the Head of School at Anglia Ruskin University. The email specified that all laboratory work involving human participation cease immediately, following health and safety guidelines. Emotionally at the time, I was anxious about the situation as the laboratory endurance training study was due to commence the following week. Participants had already booked onto the online calendar and scheduled in their training sessions for the next 2-weeks. I felt powerless in this situation. It was agreed that the intervention would have to be postponed until further notice. A large volume of administration work increased, and all participants cancelled all bookings. Not only was I upset, but I felt very guilty, as I had to turn away some very keen and disappointed participants that were looking forward to the training and genotyping. At the time, my main thoughts were,

"*I just hope the participants do not dropout or else I will have to start recruitment all over again*".

During the beginning of the UK lockdown, it was concluded that enough spare time was planned and available, based on the revision of the Gantt chart and timeline, to allow the data collection to still be completed at a later stage. The supervisory team and university fully supported me throughout this stage, where I felt more confident and reassured. However, this was short lived as time passed, it became more apparent that the university was still not planning to re-open and realistically was much longer than anticipated. At the time I was very confused, unmotivated, worried, and anxious for the future of this work. It was clear that the original plan was becoming less achievable as time passed.

7.2.4. Evaluation (What was good and bad about the experience?)

This rare situation is not under anyone's control and because of that there is a certain level of uncertainty, as it has not been experienced before. The delay in laboratory testing has been one of the longest ever recorded at the university. This development has forced a change in the original design, which was initially very well established with clear aims and objectives. With social distancing, lockdown, and a tier system still in place and playing an important role in the near and distant future, this may also impact training, data collection, interacting with participants, and will need to be considered moving forward.

Table 28. Evaluation of the positives and negatives from the experience. What was personally good and bad.

Positives	**Negatives**
• Exploring new and exciting pathways. • Having the opportunity to learn new methods and techniques that would not have previously been used. • Re-evaluate work from a different perspective. • Editing Gantt chart and timeline allows for better time management. • Working closer with members of staff and supervisory team allows me to feel more confident, comfortable, and part of the team. • Due to the closure of the university this has allowed me to work in different environments and settings which is mentally refreshing. • Becoming adaptive and a more well-rounded researcher. • Growth in critical thinking.	• Unwanted and negative emotions such as stress, anxiety, worry. • Loss of initial direction. • Loss of time and effort. • Decreased motivation. • Difficult to understand the situation due to how rare it is, causing confusion and uncertainty. • Unable to complete the current aims and objectives that were initially established. • Increased volume of work that is time consuming. • Uncertainty of the situation causes frustration. • Delay of work and feedback from myself and others. • Increased difficulty to contact individuals.

Upon reflection, it is critical to accept and acknowledge the main problems but also to evaluate them and draw positives from the situation. This experience has shown me how important it is, as a researcher to be flexible and adaptable as situations are constantly changing in the working field of research. I believe these new experiences have positively influenced my critical thinking, building my skills as a researcher and problem solver.

7.2.5. Analysis (What sense can you make of the situation?)

This situation required a revisit of the current methods and strategies in answering the already established aims and objectives, implementing strategies that accommodate these without the use of university laboratories and physical contact with participants in accordance with UK government guidelines. It is imperative that the safety of all participants and the research team are maintained according to university and ethics guidelines. Additionally, it is of high importance that the time in UK lockdown is used efficiently, waiting for the laboratories to reopen and assuming that testing can resume as normal is ambitious, with a high level of risk and many considerations would need to be required.

It was therefore agreed and proposed that an observational study would be made using questionnaire data, identifying training status, training load and training level. The aim of this was to target specific groups, such as endurance athletes, strength athletes, and the general population, to evaluate the differences in training load performed in these groups and how they differ to the findings in chapter 3. Additionally, a sub-sample of the healthy, untrained, sedentary population would be genotyped and complete a field-based training intervention. One main limitation outlined by the systematic literature review (Chapter 4: 4.5.) was that current exercise-based gene studies implement whole gene analysis, rather than an allele specific analysis. This makes it almost impossible to know the exact role of that gene and its contribution to the phenotype. The field-based study using these genotyped participants would be an appropriate replacement for the laboratory-based study examinations and training. The research literature has commonly supported this notion of training, as well as being more representative of day-to-day home-based exercise (Campos et al., 2017; Carling, Reilly and Williams 2008; Jones and Doust, 1996; Puente-Maestu, 2020). The idea would be that participants train, specifically in endurance running/jogging for 8-weeks based on training load recommendations attained from the newly proposed questionnaire and chapter 3. Furthermore, participants would be given an online training diary to track all exercise / physical activity habits to control for the inter-individual variability in training and monitoring in training load outside of the training intervention. Pre, during, and post intervention participants will be required to self-administer a field-based measure of cardio-respiratory fitness, via the Cooper 12-minute run test (Cooper 1968), which can be in-directly converted to $\dot{V}O_{2max}$. The validity and reliability of the Cooper run test has been compared to laboratory-based assessments showing high correlations at $r = .93$, $p < .001$ (Bandyopadhyay 2015) and intraclass correlation coefficient (ICC) of .97 (Anstrén, 2015). The change in $\dot{V}O_{2max}$ over the 8-week training, alongside the genotype data would give valuable and comprehensive results to answer the thesis research question(s).

7.3. CONCLUSION

This reflective chapter was imperative to revise the strategies in answering the research questions, aims and objectives. Adherence to the original research topic was critical in combination with the currently completed work. This does mean a slight change in the research question itself as multiple physiological and metabolic variables may be difficult to measure in the field. Many suggestions have been put forward and many conversations have been made during the lockdown period in preparation for the continuation of this thesis. One suggestion was to continue with laboratory testing on the current 17 participants from chapter 6 and collect the post training data once lockdown ends, in the meantime to administer the training at home and online. However, upon further discussion the health and safety cannot be guaranteed post intervention data collection due to government restrictions and ethical considerations even if the laboratories re-opened immediately after the home-based training were to be completed. Additionally, we did not know when the university would re-open, this meant that these participants could either have a very long training intervention period or a long interim period after the training and before the final data collection, validity of the data would be questionable. New participants could not be recruited into the current laboratory-based study as there was no way of measuring the pre-exercise baseline variables. Laboratory data collection did not seem possible, especially if social distancing rules remained. Another suggestion was to send pieces of equipment to the participants home address for the measurement of physiological and metabolic data. However, this was dismissed as the logistics of this were not feasible. Therefore, the action plan can aid the reflection process, and review whether the future work is realistic and achievable.

In summary, after reflecting on the difficult challenges faced with COVID-19, the action plan and objectives took place immediately during the UK lockdown period and preparations were completed for the deployment of the newly designed chapters 8 and 9. These decisions were made as a research team and were in agreement that this still answered the original aims and objectives of the thesis.

7.4. ACTION PLAN

Table 29. The action plan. This is implemented to the Gibbs model of reflection (Gibbs, 1988).

Objectives	Tasks	Success Criteria	Time Frame	Resources
Revise thesis title, Objectives and aims to suit new government guidelines.	• Adjust Question(s). • Revise, edit and add new aims and objectives. • Create new working title.	These must be agreed by entire research team and exam panel members to an acceptable level.	To be completed before the 2nd year annual review in September 2020.	• Supervisory team. • Doctoral school support.
Create new Gantt chart and timeline for the work to be completed.	• Edit and revise previous Gantt chart. • Create realistic time period for work left. • Outline new sections of the thesis.	Revision from supervisory team and accepted by exam / review panel.	To be completed before the 2nd year annual review in September 2020.	• Microsoft Excel. • Anglia Ruskin University staff support.
Genotype review	• Review method of genotyping. • Look at logistics and costs of sending genotype kits to participant's homes. • Review 3rd party analysis.	Official agreement between the university and any 3rd party company with all payments made.	Agreement and admin must be completed before participant recruitment.	• Laboratory technical support. • University staff. • 3rd party company.
Complete questionnaire and recruit untrained population.	• Review literature on standardised surveys and questions of relevant structure. • Create multiple online questionnaires for different groups. • Apply for ethics. • Recruit participants for the study. • Recruit sample population for next study.	Complete and write the stand-alone chapter to be reviewed by supervisory team.	The final version to be completed by February 2021.	• Library services and database. • JISC surveys for questionnaires. • Anglia Ruskin University support services.

Complete training chapter and genotype.	• Research in-direct methods of assessing $\dot{V}O_{2max}$. • Complete Ethics re-application. • Create online training diaries. • Establish training programme and weekly contact with participants. • Send out genotype kits and collect participant delivery address. • Analyse all data.	Complete and write the chapter as a stand-alone chapter to be reviewed by supervisory team.	The final version be completed by June 2021.	• Library services and database. • Google or outlook docs for online diaries. • 3rd party gene company. • Help by supervisors and their experiences.
Complete discussion and conclusion chapters.	• Write a separate chapter for the sections generated from the information provided in all chapters to establish evidence-based findings and recommendations.	Complete and write the chapter to be reviewed by supervisory team.	The final version to be completed by July 2021.	• Help by supervisors and their experiences. • Online sources and guidance.

CHAPTER 8: THE QUANTIFICATION OF TRAINING LOAD BETWEEN THREE DIFFERENT POPULATION GROUPS

8.1. INTRODUCTION

Training loads, a function of intensity, duration, and frequency are a universal indicator for the measurement of arbitrary “load” and can be used to compare training across studies and groups (Balsamo et al., 2012; Foster, et al., 1996; Foster, Rodriguez-Marroyo and De Koning, 2017). There is a large amount of research examining training loads, the accuracy and reliability in the application for estimating and monitoring exercise performance, progression, recovery, and injury (Drew and Finch, 2016; Foster, Rodriguez-Marroyo and De Koning, 2017; Impellizzeri, Marcora, and Coutts, 2019; Wenger and Bell, 1986).

The findings from chapter 3 estimate training loads, in the anticipation of producing similar improvements in the component of health-related fitness for the untrained, further justifying a research-based training model. This is contrast to many studies using intervention time-courses to predict adaptation, with little justification (Astorino and Schubert, 2014; Daly et al., 2002; Hautala et al., 2006; Herring, Sailors and Bray, 2014; Sigal et al., 2014). Conversely, there are still many gaps in the literature that this study aims to address. Firstly, how the physical activity and exercise levels in a UK-based sample population compares to the research literature that is predominantly USA-based. Secondly, how does a more untrained population that do not class themselves as athletes compare to those who define themselves as endurance and strength-based athletes? More importantly, how does the overall training differ from “real-world” exercise programmes, compared to laboratory study interventions? Another limitation to chapter 3, is comparing endurance and strength loads. This is extremely difficult, although the units are arbitrary, the variable input into the load calculations are different, as strength session durations, time spent exercising, and resting are not often reported. Consequently, accommodating with repetitions and sets as a measurement of volume, instead of time as a measurement of duration, meaning they are not comparable to endurance training even when converting to training load (Balsamo et al., 2012).

This questionnaire-based study aimed to assess the physical activity levels between three UK-based population groups; a trained endurance group, a trained strength group and a mixed general population group. The aim was to establish comparisons of training load limitations with chapter 3 (3.5.) between these population groups using more specific training load measurements, based on intensity, duration, and frequency. The World Health Organisation (WHO), National health service (NHS) and direct.gov draw general population statistics in

health, fitness, and physical activity from questionnaires such as, the Global Physical Activity Questionnaire (GPAQ) and Survey tool, and guidance: behavioural insights on COVID-19 (WHO GPAQ, 2002; WHO Europe, 2020). This study, therefore, will implement a similar strategy for the accumulation of data. This study also aims to derive demographic data to define population groups for the subsequent study (chapter 9) in identifying untrained participants at baseline, to recruit into a field-based training study.

H_0: There will be non-significant differences in training load between groups.

H_1: There will be a significant difference in training load between the three population groups.

H_{02}: Training loads will not be significantly different when compared to that of the literature-based training programmes.

H_2: The average training load will be significantly different compared to loads used within the research literature.

8.2. METHODS

8.2.1. Participants

661 participants were recruited from across the UK and aged between 18-67 years old. Participants were contacted via email, or in response to advertisement of the study via social media platforms (Facebook, Instagram, Twitter etc.). Participants were asked to complete one of the three questionnaires: 1) General population; 2) Endurance population; 3) Strength population. The initial questions in all questionnaires were designed to determine the participants training status by addressing how often they train in the specific component of fitness and at what level. If they did not match the correct questionnaire type, the questionnaire would automatically exclude them, and they would be directed to the general population questionnaire. Additionally, basic anthropometrics such as height, mass and participant information were collected within the questionnaire, participants would self-report these and take measurements at home where possible.

8.2.2. Study design and Questionnaires

All questionnaires were administered online and open to participation from 5th August 2020 – 28th October 2020, taking 10-20 minutes to complete. For the construction of the questionnaire's, JISC (Bristol Online Survey) was implemented. The ethical approval of this study was granted by Anglia Ruskin University, Cambridge (SESPGT10_20). Participant information sheet (PIS) and consent form were embedded at the start of all online questionnaires. Participants were informed that they could skip any questions and withdraw from the study by closing the online browser at any time. Additionally, if participants completed the questionnaire and wanted to withdraw their data they could do so.

The validity and repeatability of the questionnaires, and its origin was from the World Health Organisation survey, GPAQ and Survey tool and guidance (WHO GPAQ, 2002; WHO Europe, 2020), in which physical activity, exercise, and health information are collected from a wide range of populations across the world. The questionnaires were piloted for a period of 2-weeks, in which all sections and mappings were tested, as well as the questions and input functions. The first section of all three questionnaires consisted of 'General demographics', this comprised of six questions: 1) how they would define their training status? 2) How often they trained? 3) sex, 4) age, 5) height, and 6) body mass. These were setup as a 'select from a list of answers' approach (single choice) for ease. The following questions addressed intensity, duration, and frequency of exercise in order to calculate session training load (sTL), weekly training load (wTL), and total training load (tTL).

General population questionnaire (GPQ): https://angliaruskin.onlinesurveys.ac.uk/general-population-exercise-questionnaire. The second section referred to physical activity levels. This included types of exercise and activities, the intensities, durations, and frequencies of these were addressed using rating of perceived exertion (RPE) CR-10 scale (Borg, 1998). This questionnaire included 13 possible responses, which were formulated with multiple choice, single choice, Yes or No, and text box answers.

Endurance population questionnaire (EPQ): https://angliaruskin.onlinesurveys.ac.uk/endurance-population-exercise-questionnaire-henry-phd-2. This focused on personal bests (PB's) of race events, distance, and times if applicable, as well as weekly mileage and the time spent in a particular running zone (Polar ©, 2020) defined below. This questionnaire addressed intensity, duration, and frequency of the training completed. This questionnaire involved 33 possible responses including similar questions as the GPQ, with multiple choice, single choice, Yes or No, and text box answers.

1) 'Recovery runs' or 'easy zone', normally associated with heart rate zone 1. Very comfortable pace and distance to allow recovery, can talk while running with ease.
2) 'Steady runs', between 50-70% heart rate maximum. Long distance and endurance runs.
3) 'Tempo / threshold runs' normally 70-85% of heart rate max (moderate and hard zones), these sessions are not maintainable for long periods.
4) 'Interval running zone' >85% of maximum heart rate. This is classed as a hard-running zone, often associated with heart rate zone 4. This is not maintainable for more than a few minutes, and normally used in interval training.

Strength population questionnaire (SPQ): https://angliaruskin.onlinesurveys.ac.uk/strength-population-exercise-questionnaire-henry-phd. Included PB's of any listed one repetition maximums (1RM), training intensity, duration, frequency, and rest intervals. Specific questions were asked about the types of exercises performed and the time spent in compound, isolated and body weight (BW) exercises as reflected from chapter 4 table 19 (Fisher et al., 2014; Kim and Kim, 2016). This consisted of 46 possible responses including similar questions as the GPQ, again with multiple choice, single choice, Yes or No, and text box answers.

1) Compound: bench press, deadlift, squats etc. this also includes any Olympic lifts. This does NOT include any machine exercises.
2) Isolated: machines that work and assist certain muscle groups, free weights, and cable isolations. This does NOT include compound or body-weight exercises.
3) Body-weight exercise: push-ups, chin-ups, pull-ups, sit-ups, calisthenics etc.

8.2.3. Data Analysis and Statistical Overview

Questionnaires reached saturation when there were no further increases in participation for more than 2-weeks. The data was directly extracted from JISC to Microsoft Excel. Range scale data was transformed into minimum, median and maximal numerical values. Nominal data, such as yes/no and male/female was coded and assigned 1 or 2, and categorical data was left as arbitrary labels for comparisons. To calculate training loads RPE was first converted into estimated exercise intensity as a percentage of heart rate max, as there are many conversion tables for this, these percentages were then converted into a percentage of $\dot{V}O_{2max}$ comparable to the result from previous chapters (Foster, Rodriguez-Marroyo and De Koning, 2017; Haddad et al., 2017; Tibana et al., 2018). The accuracy and reliability of using RPE to calculate training loads has been highlighted through significant correlations with heart rate based methods such as, Banister's TRIMP, Edwards' TL and Lucia's TRIMP in the study by Impellizzeri et al., (2004). They conclude that session-RPE is a good indicator to estimate exercise intensity (r = 0.85, p < 0.01). For this study, all time durations were converted to minutes and the following equations (8.2.4) were used to determine the training loads.

SPSS (Version 26, Chicago, IL) was implemented, alpha set at p <.05. The tests for parametric assumptions included a Kolmogorov-Smirnov test of normality and Levene's test for homogeneity and variance.

A non-parametric Kruskal–Wallis H test was used to assess the differences in scores between the variables in three groups. A Mann-Whitney U test was conducted to assess the difference in variables against each group. To control for the inflation of type 1 errors, a Bonferroni adjustment was calculated to the 5% (0.05) alpha, equivalent to p = .017. Mean-rank was used to identify which group had the higher scores.

8.2.4. Equations List for Endurance sessions

Eq 1.

$$Average\ sTL = \ Running\ duration\ (m) \times Session\ intensity\ (\%)$$

Eq 2.

$$Proportion\ of\ session\ spent\ in\ a\ running\ zone = (Number\ of\ weekly\ sessions\ for\ one\ running\ zone\ \times percentage\ of\ time\ spent\ in\ that\ running\ zone)$$

. Repeated this equation for all running zones.

Eq 3.

$$wTL = (Average\ TL\ in\ recovery\ run\ sessions\ \times Proportion\ spent\ in\ recovery\ zone) + (Average\ TL\ in\ steady\ run\ sessions\ \times Proportion\ spent\ in\ steady\ run\ zone) + (Average\ TL\ in\ tempo\ run\ sessions\ \times Propotion\ spent\ in\ tempo\ run\ zone) + (Average\ TL\ for\ interal\ run\ sessions\ \times Proportion\ spent\ in\ interval\ run\ zone)$$

8.2.4. Equations List for Strength sessions

Eq 1.

$$Time\ spent\ in\ compound\ exercises = (Duration\ of\ training\ sessions\ \times Proportion\ of\ time\ spent\ in\ compound\ exercises) - Total\ rest\ time.$$

Repeated this equation for isolated and body-weighed exercises.

Eq 2.

$$Compond\ TL = (Time\ spent\ in\ compound\ exercises\ \times\ Training\ intenity\ (\%)$$

. Repeated this equation for isolated and body-weighted exercises.

Eq 3.

$$Total\ sTL = Compound\ TL + Isolated\ TL + Bodyweighed\ TL$$

Eq 4.

$$wTL = sTL\ \times Number\ of\ sessions\ per - week$$

8.3. RESULTS

In total, 661 participants were recruited from across the UK aged 18-67 years old (27 ± 7 years; height 173 .9 ± 9.9 cm; mass 74.27 ± 16.39 kg; BMI 24.5 ± 4.5 kg·m^2), of which males (n = 310; 27 ± 7 years; 180.7 ± 7.3 cm; 82.53 ± 15.35 kg; BMI 25.2 ± 4.2 kg·m^2) and females (n = 347; 27 ± 7 years; 167.7 ± 7.6 cm; 66.84 ± 13.45 kg; BMI 23.8 ± 4.7 kg·m^2) and split between the three study groups according to their training status.

8.3.1. General population group (GPG)

548 participants completed this questionnaire (237 males, 307 females, 1 non-binary and 3 not specified). Aged 18-67 years (26 ± 6), height 150 to >192 cm (173.80 ± 10.17), mass <51 kg to >105 kg (74.1 ± 16.0), body mass index (BMI) of 24.6 ± 4.5 kg·m^2. Of the 548, 12 (2.2%) classed as completely 'Inactive'; 36 (6.6%) 'Sedentary' (spends much time seated and somewhat inactive); 135 (24.7%) did less than the recommended weekly physical activity; 175 (32%) thought they met the criteria for the physical activity recommendations; 189 (34.6%) did above the weekly recommended. Further examination found that 93 participants in total (17%), did not report doing any form of exercise, sport, or physical activity and therefore, training load could not be estimated.

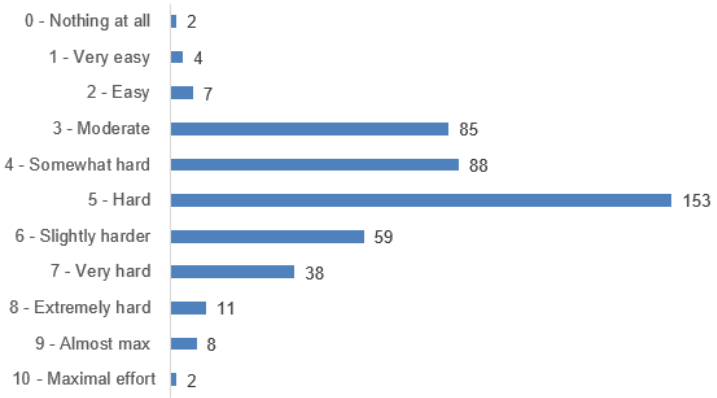


Figure 38. GPG intensity of average sessions using sRPE. Where; 0 = Nothing at all (session was the easiest thing possible); 1 = Very easy (session required very little effort to complete); 2 = Easy (session required little effort to complete); 3 = Moderate (took some effort to complete but can achieve this on a regular basis without fail); 4 = Somewhat hard (Can complete session easily, however, understand that this session causes increased effort); 5 = Hard (session was achievable, but a lot of effort was needed, can complete on a regular basis); 6 = Slightly harder (Ever more effort was needed but should be achievable weekly); 7 = Very hard (Session is sometimes not fully achievable at times and this required a large amount of effort to complete); 8 = Extremely hard (One of the hardest sessions but know you have more to give); 9 = Almost max (One of the hardest sessions you have done but thought you might have had a little bit more to give); 10 = Maximal effort (Cannot possibly do anymore or do better, you are at your maximum effort). The number on the right-hand side shows the number of participants that selected that answer.

For the duration of physical activity completed, 0 participants reported 0-15 minutes; 29 for 16-30 min; 82 = 31-45 min; 176 = 46-60 min; 128 = 61.90 min; 16 = 91 – 105 min; 16 = 106-120 min, and 12 participants reported >120 min per session. In terms of the frequency of sessions, 26 participants reported to train once per-week; 64 = twice per-week; 120 = three times per-week; 94 = four times per-week; 80 = five times per-week; 36 = six times per-week; 13 = seven times per-week and 22 = more than seven times per week (multiple sessions in one day). Overall, 35 different exercises were highlighted, from ball sports to yoga, where 204 reported regular walks, 171 reported going to the gym, 195 performing body-weight exercises and home workouts, and 166 participants were regularly running outdoors.

Of the 183 participants (64 males and 119 females) that did not meet the physical activity guidelines, were classed as untrained. Their average BMI equalled 25.2 ± 5.2 $kg{\cdot}m^2$.

8.3.2. Endurance population group (EPG)

50 participants completed the endurance questionnaire, of which, 23 were males and 27 were females. Aged 18 – 67 years (35 ± 13), height 150 – 193 cm (172.2 ± 8.9), mass 50 – 94 kg (64.76 ± 10.12) and BMI 21.8 ± 2.5 $kg{\cdot}m^2$. Two were classed as recreational runners (physically active but do not train for events or competitions). The remaining 48 participants were classed as amateur athletes (train and compete in race events but are unpaid). The experience level ranged from 2 to >10 years, with 28% >10 years. The weekly running distance ranged from 10 km to 160 km (47 ± 30km). PB times were recorded for marathon, half marathon, 10 km and 5 km events. On average these were 225 ± 38, 101 ± 18, 45 ± 9 and 21 ± 4 minutes, respectively. The remaining information constituted the estimated training load, governed by intensity, duration, and frequency.

The data was categorised into recovery runs, steady runs, tempo runs, and interval runs for the RPE intensity, session durations, and time spent in that running zone. Participants showed mixed results of how much their overall training was spent in each zone as well as the durations of the runs in those types of training sessions.

In terms of the session intensities the 50 endurance participants chose between 1-4 RPE for the recovery runs; between 2-7 RPE for the steady runs; 4-10 RPE on the tempo runs; and between 3-10 RPE for the interval runs. When accounting for how much of the time was spent in each training zone, the results showed an average the overall session intensity equivalent to 55.6 ± 7.7% of $\dot{V}O_{2max}$.

In terms of the session durations, in recovery runs participants reported this could be anywhere from 15-90 minutes with the majority (18 participants) selecting between 46-60

minutes per session; steady runs were between 30-135 minutes; tempo runs were being 15-60 minutes; and interval being 15-45 minutes. Again, when accounting for how much of the time was spent in each training zone, the results showed an average overall session durations were 66 ± 27 min.

For the frequency of sessions, 4 participants trained two times per-week; 11 three times per-week; 10 four times per-week; 16 five times per-week; 4 six times per-week; 2 seven times per-week and 3 participants trained >seven times per-week (multiple sessions per-day), equating to 4.5 ± 1.5 sessions per-week for the group.

8.3.3. Strength population group (SPG)

63 participants completed this questionnaire. 32 (50.8%) were classed as recreational strength athletes (training but not for events or competitions), 25 (39.7%) amateurs (Compete in events but are unpaid) and 6 (9.5%) elite level (competes and are paid). The experience level ranged from 1 to >10 years. 50 were males and 13 were females, aged 18 – 47 years (27 ± 5 yrs), height 156 – 193 cm (175.9 ± 8.3 cm), mass 51 – 128 kg (83.95 ± 18.55 kg) and BMI 26.9 ± 4.5 $kg{\cdot}m^2$ 51 participants reported 1RM values for flat barbell bench press, from 30 – 227.5 kg (115.8 ± 42.2 kg) and 53 for back squat from 86 – 381 kg (173.4 ± 61.4 kg).

The data was categorised into compound, isolating, and bodyweight exercises / sessions. Participants recorded, repetitions, sets, rest intervals, and the intensity (percentage of 1 RM lifted). Of the 63 participants, the intensity for compound lifts ranged from 66-100% 1RM; isolated 44-89% 1RM; and bodyweight between 3-9 RPE. When accounting for the time spent in these types of exercises these was equivalent to an overall intensity of 49 ± 8.4%

Regarding the repetition and set ranges for compounds was 5-20 reps 1-4 sets; isolated 8-20 reps 1-4 sets; and bodyweight exercises between 8->20 reps 1-5 sets, with a rest interval of 1-5 minutes between sets. Participants reported a session duration where 2 performed between 15-30 minutes per-session; 1 undertook 31-34 min; 8 competed 46-60 min; 7 reported 61-75 min; 12 completed 76-90 min; 12 participants reported 91-105 min; 14 undertook 106;120 min; and 7 >120 min in a single session. Participants also reported training frequencies of, once per-week (1 participant); three times per-week (9 participants); four times per-week (19-participants); five times per-week (27-participants); six sessions per-week (6-participants); and seven sessions per week (1 participant). Result found that participants trained for 71.7 ± 29.7 min per-session, 4.5 ± 1 sessions per-week.

8.3.4. Training load

For the GPG, of those that undertook exercise the average session TL equalled, 3,260 ± 1,664 A.U., equivalent to ~12,157 A.U per-week in the 455 participants that reported intensity, duration, and frequency of sessions. Ninety-three participants, however, exhibited no TL data and consequently were classed as inactive. When included, load estimations reduced, the average sessions A.U to 2,706 ± 1,948. In addition, the 183 participants of particular interest, who did not meet the weekly recommended exercise levels were analysed separately as an untrained group and TL estimates were 1,702 ± 1,777 A.U. per-session and 4,952 ± 6,173 weekly A.U. The weekly recommended physical activity guidelines from the ACSM and NHS of 150 minutes of moderate intensity aerobic activity (50-70% heart-rate maximum) or 75 minutes a week of vigorous activity (70-85% heart-rate max), equates to 5,250 – 10,500 A.U per-week (MayoClinic, 2019).

In comparison, the EPG revealed within an amateur running group, which are highly trained and compete in race events, they have a session TL of 3,619 ± 1,524 A,U. and an estimated weekly load of 13,836A.U. Finally, the SPG consisting of 63 participants, reported the highest average load of 5,389 ± 2,466 A.U per-session, equivalent to 24,888 A.U. per-week. The results also demonstrate that weekly TL from additional sessions, contributes to an extra 2,737 A.U for endurance and 3,256 A.U. for strength groups. In total, the load per-week approximates 22,620 and 34,668 A.U, respectively.

8.3.5. Statistical results

Participant characteristics (age, height, mass, and BMI) and TL (Intensity, duration, frequency, sTL, and wTL) were tested for parametric assumptions using Kolmogorov-Smirnov[a] normality test and Levene's test for homogeneity of variance. Results found that no groups to have a normal distribution ($p < .05$), however in most cases homogeneity of variance was accepted ($p > .05$).

Across all variables there was a significant difference between the three groups, at $p < .005$ outlined by the non-parametric Kruskal–Wallis H test. Mann-Whitney-U found that when GPG was compared to EPG, there were highly significant differences between age, height, mass, and BMI, (U = 7,764.500, $p = .000$; U = 10,496.500, $p = .006$; U = 9,180, $p = .000$; U = 9,276, $p = .000$, respectively). This was similar for the average exercise intensity and frequency of sessions per-week (U = 7,385, $p = .000$; U = 7,934, $p = .001$), however, the duration per session was non-significant (U = 10,059, $p = .137$). TL per-session was also non-significant (U = 9,527, $p = .059$). Weekly load when the additional sessions were included was significantly different ($p = .001$), but not in terms of the endurance runs alone ($p = .088$). Mean-ranks concluded that intensity was greater in GPG compared to EPG, however not for duration, and frequency, therefore overall session and weekly load were greater in the EPG.

GPG, when compared to SPG found significant differences in the participant characteristics, except for height (U = 16,620, $p = .778$). Exercise intensity, duration, and frequency were also significant (U = 3,533, $p = .000$; U = 10,409, $p = .001$ and U = 8,397, $p = .000$, respectively), session and weekly training load (U = 6,788, $p = .000$; U = 5,232, $p = .000$). Mean-rank found that mass and BMI were greater in the SPG. The session and weekly load were also significantly greater in SPG, regardless of having significantly lower exercise intensities.

When comparing EPG to SPG the results found significant differences in the participant characteristics, exercise intensity, session and weekly training loads ($p = .000$). However, session duration and frequency per-week were not significantly different (U = 1,303, $p = .189$ and U = 1,422.500, $p = .527$). Mean-ranks found body-mass and BMI to be greater in SPG, and that session and weekly training loads were higher in the SPG. Duration and frequency were higher in the SPG, but intensity was greater in the EPG.

8.4. DISCUSSION

In chapter 3, the aim was to compare multiple studies in an untrained population, to see how the training intervention manipulated the physiological responses and adaptations. Additionally, TL governed by intensity, duration, and frequency was calculated to quantify the amount of training completed across the intervention, in an attempt to standardise studies with differing training protocols. It was further concluded that there were significant relationships between the increase in TL and improvements in the components of health-related fitness phenotypes. This study was designed to collect physical activity and exercise training information from three different population groups reflecting two of the key components of fitness, cardiorespiratory fitness, and muscular strength, in a field-based setting, as the current literature information provided has been heavily laboratory-based. This study aimed to recruit similarly untrained participants to compare the training intensities, durations, and frequencies against those that are classed as endurance and strength trained.

The GPG results demonstrated that, in these UK-based participants there were large variations in grouping characteristics, as well as significant differences in the training each participant completes per-session and week. The results show that the sample population has a combination of fitness levels and a variety of training statuses, resulting in a heterogenous group as supported by statistical analysis. The GPG revealed that, of the 548 participants, 183 (33.4%) did not meet the weekly recommended UK physical activity guidelines, therefore, these results in heterogeneity are not surprising. This untrained sub-group is of particular interest and concern, with an average BMI of 25.2 being classed as just overweight with an average session TL of 1,702 and 4,952 per-week, which are significantly less than all other groups in this study. However, BMI as a measure alone has limitations, due to it being dependent on height and mass without accounting for muscle and fat mass, which may explain higher overweight results (Kok, Seidell and Meinders, 2004).

Interestingly, SPG displayed the largest session load, revealing some worthy findings. Firstly, TL in both endurance and strength groups, in this study, are far greater than those in chapter 3, being an estimated 1,700 A.U. per-session and 5,000-6,000 A.U per-week load for large effect sizes. This is because in the review, the participant training status were classed as untrained and therefore, interventions were not as extreme for those groups to drive the initial training stimulus and adaptations in cardiorespiratory fitness and aerobic ability. However, in this study the participants composed endurance and strength athletes, and as stated previously, where training status is greater, higher loads and volumes are needed to evoke the session stimulus for adaptation (Helgerud et al., 2007; Peterson, Rhea and Alvar, 2005; Wenger and Bell, 1986). Additionally, sTL were complex to calculate, as with all high-level

training. This is because not all sessions are similar and for the majority, they do not follow linear research-based training interventions. For EPG, the results in this study show that most sessions in the week are predominantly spent in the steady running zone, however, average session load is comprised of recovery, tempo and interval runs that constitute to the weekly TL. For this group, an average session load of 3,619 A.U. and estimated weekly 13,836 A.U. was calculated. When compared to the GPG weekly load was significantly greater, this is due to the significantly greater volume of training (duration and number of sessions in a week) (p = .01). Furthermore, when compared to the TL from the literature review, these figures were more than double for the weekly load and the SPG followed a similar trend. Finally, when comparing EPG and SPG, the TL's were significantly greater in the SPG. Interestingly, the results in this study found that intensity is important, however, was not the biggest factor for the increase in load due to the highly reported frequencies and durations. This disagrees with the findings from chapter 3 that the exercise volume, a derivative of duration and frequency per sessions were greater in the athletic groups, suggesting more exercise is being completed over the course of a week leading to greater training loads. This would make sense, as laboratory studies adopt a specific time frame to allowing participants to attend at specified times, whereas the training outside of a study protocol has less time restrictions. In terms of body-mass and BMI, they were higher in the SPG compared to the EPG. A possible explanation would be that endurance athletes maintain a lower body mass, especially for long distance events to stay efficient for the demands of the event (i.e. carry less mass when running). Whereas strength athletes would have far more muscle and total body-mass for weight-lifting events (Blair, 2015; Willis et al., 2012). However, this does not equate to an increased risk of obesity, which is a common limitation of using BMI measurements alone (Davison, Ford, Cogswell and Dietz, 2002; Kok, Seidell and Meinders, 2004).

This study has shown that the estimated training loads in a UK sample population is very complex, with multiple factors and variables that contribute to exercise, fitness, and general physical activity levels, especially as the training status of the individuals increases. It is important to note that, the results only provide a snapshot of the training these participants undertook. The TL, especially per-session is always changing. Athletes show that not only do they participate in competitive, high-level training for their chosen profession but additionally, they also compete in individual or team sports, fitness classes, resistance, strength and conditioning, recovery sessions multiple times per-week, contributing to an increased volume of exercise and frequency creating a greater total training load. Nevertheless, the results do show that the TL differences between athletes, are far superior to those in the general population particularly for those participants that complete less than the recommended guidelines and therefore, H_1 is accepted. Additionally, the training loads in this study were far

greater than those reported within the literature and accepts H_2. Finally, the training load methods used in this study are a good indicator of assessing the exercise done across individuals that do different types of exercises, which is calculated by intensity, duration, and frequency of sessions, where training volumes appears to increase the training loads throughout a week, especially in the athletic groups.

8.5. LIMITATIONS

A main limitation to collecting personal information is the risk of the Hawthorne effect, this is when an individual adjusts their behaviour in response to their awareness of being observed (McCarney et al., 2007). Participants may have over-estimated their exercise training habits in fear of being judged on their actual habits. To control for this, it was stated in the questionnaire to be as honest and accurate as possible, and the choice to submit information anonymously was available. Additionally, a large limitation is that the questionnaire relies on participant honesty and recall of the exercise habits within a normal routine, otherwise, instead of a COVID-19 pandemic routine, where it might have been somewhat altered.

Although RPE has been shown to be both, reliable and valid in the assessment of exercise intensity and conversion to intensity percentages both at heart rate and $\dot{V}O_{2max}$, caution is needed when being implemented, especially to people that are unfamiliar with it (Day et al., 2004; Herman et al., 2006). A limitation when using sRPE is that in research, people train at a fixed pre-determined intensity throughout the session. However, the RPE, especially at the end of the session varies, when participants become exhausted, it is common to report near 100% exertion (9-10-point scale), even if the session percentage was fixed at a certain exercise intensity. Therefore, it is important that participants understood how to use RPE in order to reflect on the entirety of the session, rather than the current feelings of exertion at that moment in time (Atkinson, Wilson and Eubank, 2004; Boutcher and Trenske, 1990).

A common pitfall that must be accounted for, is those that reported exercise duration, tend to include exercise rest-time as part of the overall training session, especially in interval work and strength training. This would mean that the estimated training load would be greater. This study questionnaire aimed to ask questions on recovery times and times that are not spent in exercise. This was accounted for through the durations, in order to control for time spent not exercising. Therefore, the training loads in this study are more potentially more reliable and accurate to the true load of each session. Using the knowledge gained from chapter 3 in combination with this chapter, the training load application and assessments in endurance programmes in both laboratory and field-based scenarios can be applied to chapter 9.

CHAPTER 9: TRAINING RESPONSES IN CARDIORESPIRATORY FITNESS AND THE INFLUENCE OF ALLELE SPECIFIC GENE ANALYSIS: A FIELD-BASED STUDY.

9.1. INTRODUCTION

The findings from the systematic literature review (Chapter 4) uncovered relationships between genes and phenotype responses in the three components of health-related fitness (Bouchard et al., 2012; Keiller and Gordon, 2019; Sarzynski, Ghosh and Bouchard, 2017; Spurway and Wackerhage, 2006; Vancini et al., 2014). More specifically, the candidate genes are responsible for a large percentage of the variance in $\dot{V}O_{2max}$ even with very highly standardised laboratory training protocols, which were explained in-part by the genotype sub-groups. Although this has been uncovered in numerous studies, this is still not fully understood neither has it been explored in much detail, particularly in an untrained population (Ahmetov et al., 2016; Erskine et al., 2012; Rankinen et al., 2000; Sarzynski, Ghosh and Bouchard, 2017; Schutte et al., 2016). More explicitly, chapter 4 shows that the $\dot{V}O_{2max}$ improvements can be explained in-part by whole-gene analysis between untrained participants but indicates a lack of literature in allele-specific analysis and genotypes. Additionally, the results in chapter 4 uncovered 13 candidate genes for this study. However, AKT1, AMPK, COX4|1, CS, HADH, MAFbx and PFKM could not be included. This is due to the lack of evidence-based research regarding these genes in a sport and exercise context. Indeed, here is little supporting evidence of specific allele roles and their frequencies and therefore, are not commonly analysed and would require a much more advanced genome-wide association study (GWAS) analysis to locate these specific SNPs. Although these genes cannot be included, IGF2, which is associated with mTOR, and MSTN associated with MAFbx (Table 20) are supported by research evidence, and commonly assessed in gene analysis chips, therefore, can be included as substitutes (Devaney et al., 2007; Santiago et al., 2011).

In terms of a study training intervention to improve $\dot{V}O_{2max}$, chapter 3 found that across studies, an average session and weekly training load of 1,700 and 5,000-6,000 A.U. respectively were significantly correlated to the improvements in $\dot{V}O_{2max}$ eliciting large effect sizes, equal to one set of 25-30 minutes continuous endurance exercise, between 65-70% of $\dot{V}O_{2max}$ intensity or equivalent. These findings agree with ACSM (2013) recommended intensities of 45–80% $\dot{V}O_{2max}$ or 50–90% HR_{max} as a suitable exercise range to enhance cardiorespiratory fitness, similar to the reported intensities outlined by the previous chapters (chapter 3, 4 and 6). Further, it was anticipated by the linear regression model (Figure 14) that the average intervention load was 48,000 A.U. for significant effects equal to 8-weeks of training. Düking

et al., (2020) found improvements in running performance and adaptation in $\dot{V}O_{2max}$, in as little as 3-weeks training with recreational runners due to a progressive overload of 10% in TL per-week and avoided non-functional overreaching. Running, especially outdoors has been shown to display larger physiological efforts and stress to the body when compared to treadmill running and cycling, where the impact forces and chances of injury are greatly reduced, especially in untrained participants (Jones and Doust, 1996; Smith, McKerrow and Kohn, 2017; Strohrmann et al., 2012). However, due to the UK lockdown, COVID-19 restrictions, and the closure of universities, this study aimed to perform a field-based training methodology as opposed to a classic laboratory-based. Evidence supports the use of field-based examinations in the absence or unrealistic applications of laboratory tests (Carling, Reilly and Williams 2008; Ceci and Hassmén, 1991; Puente-Maestu, 2020). The Cooper 12-minute run test (Cooper 1968) is a common field-based examination to estimate cardiorespiratory fitness, where participants attempt to cover a maximal distance in a 12-minute period and has been presented to estimate $\dot{V}O_{2max}$ with high reliability and consistency across ages (Anstrén, 2015; Campos et al., 2017; Dhara and Chatterjee, 2015; Mackenzie, 1997; Oluwadare and Olufemi, 2018; Poole, Wilkerson and Jones, 2008).

Therefore, the aim(s) of this study were to establish the association between candidate genes and the change in $\dot{V}O_{2max}$ in previously untrained participants, and to observe if the variance can be explained by the genotypes. Additionally, to ascertain if the prescribed training loads are correlated to the improvements in $\dot{V}O_{2max}$. To achieve this, participants performed an 8-week aerobic running programme aimed to meet the loads governed from chapters 3, 6 and 8 in anticipation of increasing cardiorespiratory fitness. The response in $\dot{V}O_{2max}$ and training loads between participants can also be explored in greater detail between exercise vs control groups.

H_0: There will be non-significant associations between the candidate genes and the variations in $\dot{V}O_{2max}$.

H_1: There will be significant associations between the candidate genes and the variations in $\dot{V}O_{2max}$.

H_{02}: There will be non-significant increases in $\dot{V}O_{2max}$ due to the training intervention.

H_2: There will be significant increases in $\dot{V}O_{2max}$ due to the training intervention.

H_{03}: There will be no relationships between the change in $\dot{V}O_{2max}$ and the training loads.

H_3: There will be a significant relationship between the change in $\dot{V}O_{2max}$ and the training loads.

9.2. METHODS

9.2.1. Participants

Participants were initially recruited from the questionnaire study (Chapter 8). 184 participants trained below the recommended weekly physical activity guidelines. Of these, 107 participants provided an email address, showing a potential interest in this study. 57 participants responded, 22 participants started regular training since the previous study and therefore, were ineligible. To increase participant numbers this study was advertised via social media, university links, and local clubs. In total 62 participants were recruited into this study that reported to have undertaken no endurance training for the past 8-weeks. Participants were recruited across the UK, aged between 20-55 years old, including 33 males and 29 females.

9.2.2. Study design

Figure 39 highlights the intervention schematic. The ethical approval for this study was granted by Anglia Ruskin University, Cambridge, Faculty of Science and Engineering (ethical approval number: ESPGR-19). This repeated-measures design aimed to reflect the laboratory-based experimental chapter with a field-based application (Chapter 6).

Participants were contacted, instructed, and advised via email throughout the study, and were sent an updated online consent form and participant information sheet (PIS) (https://angliaruskin.onlinesurveys.ac.uk/endurance-training-pis-and-cf-henry-phd).
Participants were randomly assigned to either an endurance group (EG), performing three outdoor runs per-week for 8-weeks, or control group (CG), who were advised to continue with their normal everyday routines for the 8-week time-course. A Cooper 12-minute run was implemented in week 0, end of weeks 4 and 8. Additionally, variables such as, date of birth (DoB), height, body mass, running times, session rating of perceived exertion (sRPE), session frequency and training diaries were recorded. All participants were provided with an online Excel document to record this information (https://onedrive.live.com/embed?cid=B31ED61CB6B61323&resid=B31ED61CB6B61323%2118627&authkey=APxX7LFanCL1Ruo&em=2). For all training sessions and the Cooper run, participants were instructed to perform in appropriate sportswear, be fasted for at least 3-hours and well hydrated with water. At the end of the intervention period, a MUHDO Health Ltd genotype kit was sent for the self-collection of genetic data via a saliva sample.

9.2.3. Cooper 12-minute run test

All participants performed a self-administered Cooper 12-minute run test (Cooper 1968) and were extensively informed and instructed. Participants were advised to run a familiar route, during daytime, avoid obstructions and pedestrians, congested areas, and traffic. Additionally, to run on flat even surfaces where possible. Participants were also asked to perform a familiarisation trial of the Cooper run in advance, before the first official run, with at least 48-hours rest between. Participants were instructed to run the same route for all tests at the same time of day. During the Cooper 12-minute run test participants were instructed to perform a maximal effort and achieve the furthest distance possible, sRPE was also recorded at 30 minutes after the test (Foster et al., 2001; Uchida et al., 2014).

During the Cooper run, participants used the STRAVA running app (Strava Inc, freemium model) (https://www.strava.com/) to track locations, distance, and speed for the calculation of the Cooper 12-minute run scores and estimated $\dot{V}O_{2max}$. The information provided was then saved and exported to the Excel document, where participants had online access to their own document. STRAVA uses a mobile Global Positioning System (GPS) technology to accurately record real-time positioning and can easily be downloaded from any app store to a mobile device for free. At least five satellites are required for an accurate estimation of positioning, and the data acquisition is every 1 second, equal to a sample rate of 1Hz, allowing accurate measurements of distance (https://support.strava.com/).

9.2.4. Training Intervention

Participants in the EG performed three weekly outdoor runs starting at 20 minutes, increasing to 30 minutes with the exact specified times outlined on the online training schedule for 8 consecutive weeks (Figure 39). The training intensity was fixed at a sRPE value of 6-7 (60-70% $\dot{V}O_{2max}$) using the CR-1-10 Borg scale, with 1 being ‘very easy’ and 10 ‘maximal effort’ (Borg, 1998). Training progression was based on Düking et al., (2020) and followed a periodised manner, where TL was increased by 10% per-week. Weekly training duration was reduced accordingly, when a Cooper 12-minute run was completed at the end of week 4 and 8, ensuring there was still a 10% progression in load accounting for this test. Similar to chapter 6 participants needed to complete a minimum of 21 of the total 24 sessions to be included in the final data analysis. Both groups provided a training diary for any additional exercises and activities completed in the week were converted into additional training loads (Foster, Rodriguez-Marroyo and De Koning, 2017).

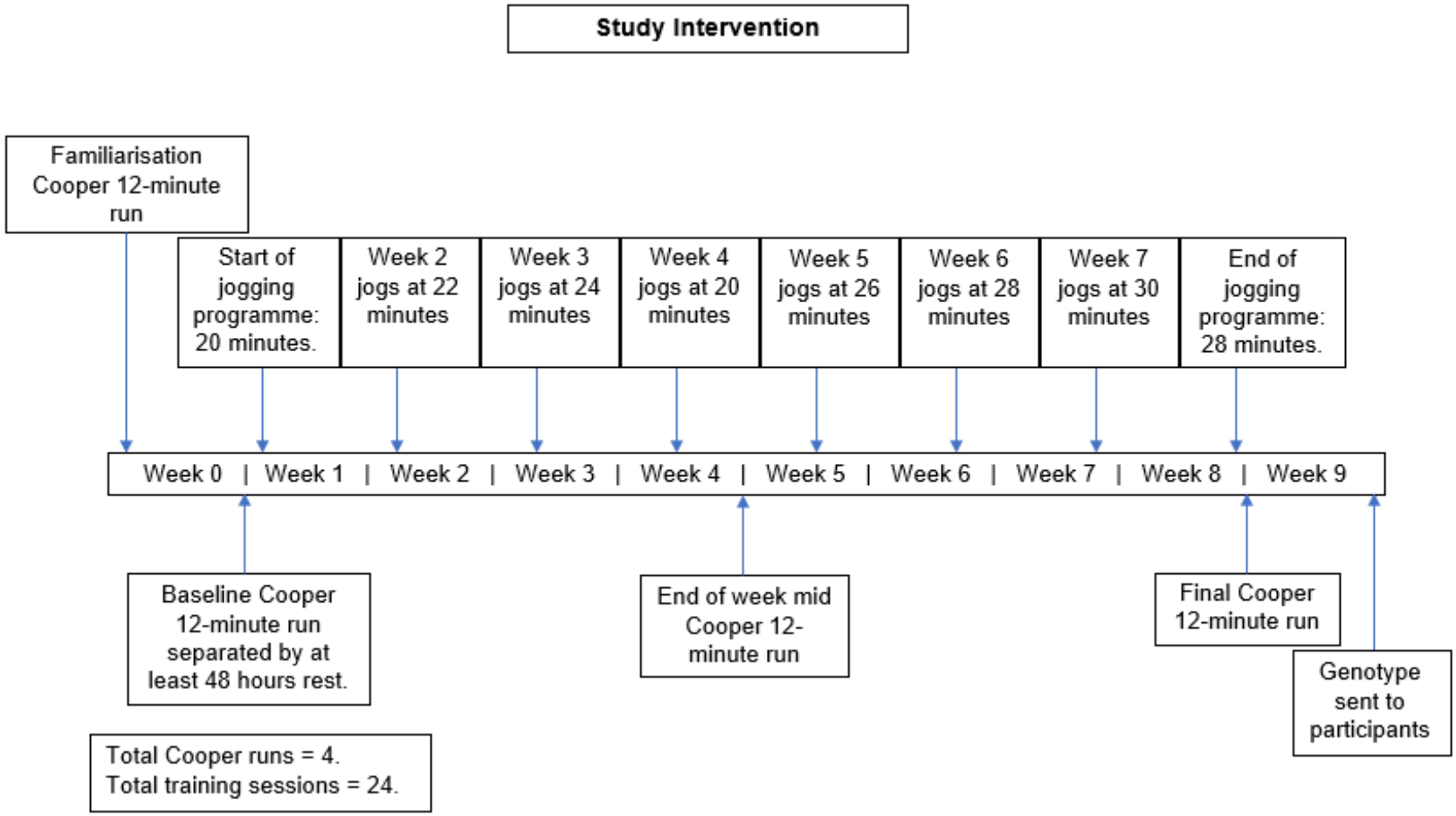


Figure 39. Outdoor endurance training intervention schematic. Training progression was increased by 10% of weekly training load by increasing the duration of the run. Intensity was aimed at an estimated 60-70% $\dot{V}O_{2max}$ throughout. Between all sessions and Cooper runs, participants had at least 24 hours recovery.

9.2.5. Genotype analysis

Muhdo health Ltd genetics company identifies 1000 SNPs to create over 300 reports, which is more than any other DNA profile currently available on the market and uses world-class global Eurofins laboratory facilities (Certification: ISO 17025:2005, ISO 17025:2017) to run the analysis of the genotypes. These laboratory partners are the number one global leader in the bioanalytical testing market, which operate over 800 laboratories in 47 countries (https://muhdo.com/the-science/our-lab-facilities/).

Genotype kits (DNA Health, Muhdo Health Ltd, Ipswich, UK: https://muhdo.com/shop-uk/) were sent via Royal Mail Tracked 48® delivery to all participants. The package included, 1x DNA user-guide, providing instructions on how to perform the saliva test (Figure 40); 1x Royal Mail free return postage guide; 1x Plastic tube with prefilled preservative liquid mix (non-toxic stabilization buffer); 1x Saliva funnel screw-on (unique patented design prevents flow back) and access to an On-Call Doctor for any assistance. Participants provided a non-intrusive saliva sample of 2 ml mixed with the 2ml preservative. The saliva sample (GeneFiX™ Saliva DNA/RNA Collection) was sealed in a uniquely coded tube and sent back to Eurofins lab. The kit is fully specified for sample transport and storage (https://isohelix.com/products/genefix-saliva-dna-collection-device/). Upon analysis completion, the samples were destroyed at the end of the study via incineration in accordance with the Human Tissue Act (HTA) 2004.

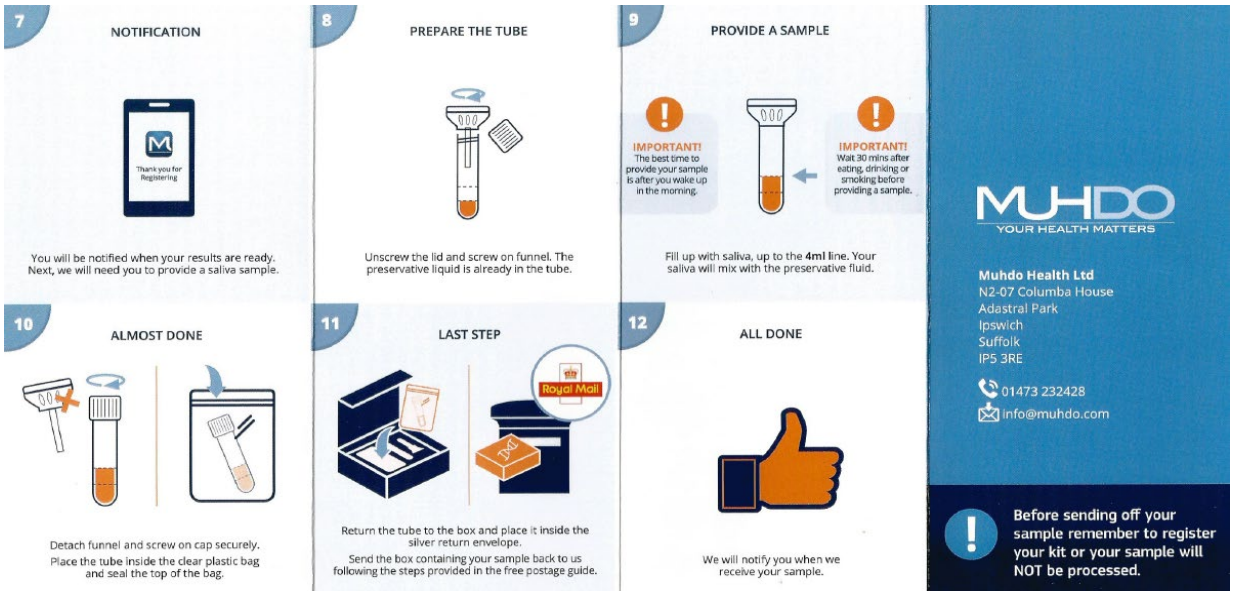


Figure 40. Muhdo DNA user-guide. Steps 1-6 are to download the Muhdo App and register the tube barcode.

Once the saliva samples are retrieved a phosphate buffered saline (PBS) was used to prevent any premature cell rupture and cell recovery was accomplished using standard extraction procedures. Recovered cells and assay medium (Cell Lysis Solution Infinium, GoldenGate)

were loaded into chip wells for Illumina multiplex sequencing. In brief: a custom chip (Illumine® Infimum HumanOmni BeadChip) bound DNA fragments, containing target SNPs, which were scanned using a Microarray Scanner (iScan, Illumina, San Diego, CA, USA). Fluorescence information was collated by Illumina's software (Illumina's GenomeStudio® software). The iScan Control Software automatically normalised the intensity of the fluorescence data to remove technical variation and generated genotype calls (Evans, Hardin and Stoebel, 2018).

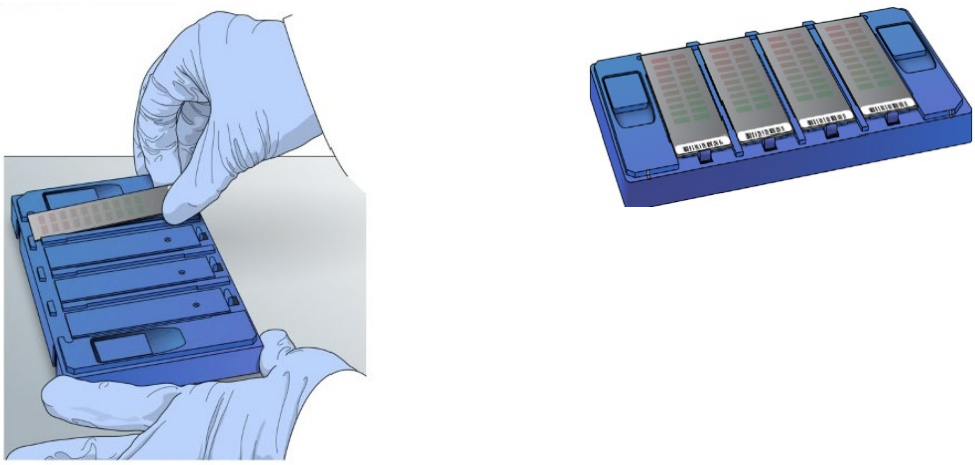


Figure 41a. Loading the BeadChips onto a Carrier for scanning. Using an alcohol wipe or a lint-free tissue moistened with ethanol or isopropanol, wipe the back of the BeadChip to remove the XC4 protective coating. Note: It is very important that all BeadChips are sat flush to the carrier and are straight (illumina iScan System Guide, 2015, pp. 23).

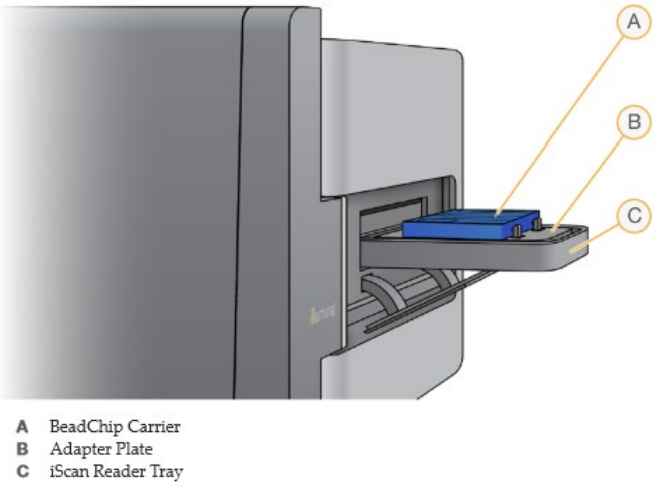


Figure 41b. iScan reader with loaded BeadChip. Note: The adapter plate is calibrated for each individual scan (illumina iScan System Guide, 2015, pp. 4).

The iScan is a laser-based, high-resolution optical imaging system that can rapidly scan and collect large volumes of data from Illumina DNA and RNA high-density BeadChips for gene expression and genotyping applications. The iScan Reader includes red and green lasers for detecting fluorescence information on BeadChips. The barcode scanner allows accurate identity of each BeadChip. The system was integrated with Illumina laboratory information management software (LIMS), assay automation liquid-handling robot (Tecan Group Ltd., Mannedorf, Switzerland) and AutoLoader (AutoLoader 2.x model).

When scanning the BeadChip, the iScan System compiles a virtual representation of a BeadChip (Figure 41c) and exports the data for downstream analysis by Illumina's software tools (Illumina's GenomeStudio® software). Following image scanning and registration, intensities are extracted for every bead type. This is the process by which intensity values are determined for every bead on the image. The AutoConvert feature in the iScan Control Software (ICS) normalises the intensity data and generates genotype calls. This procedure utilises multiple probes to ensure good quality, the sample SNP is then tested three times (illumina iScan System Guide, 2015).

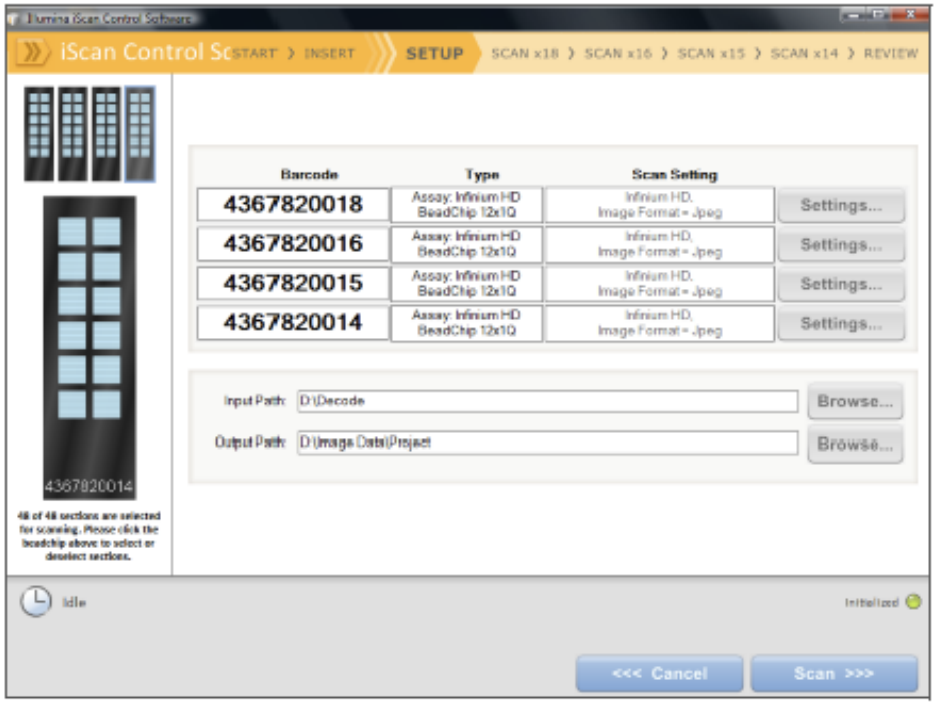


Figure 41c. BeadChip barcodes displayed on the ICS setup screen. A high signal-to-noise ratio, high sensitivity, low limit of detection, and broad dynamic range the scanners produce exponential data quality, with high-call rates of >99% (illumina iScan System Guide, 2015, pp. 29).

9.2.6. Data Analysis and Statistical Overview

Participants self-reported descriptive statistics including, age; mass and height, are reported as Mean ± Standard Deviation. Body Mass Index (BMI) was calculated using the following equation:

$$mass\ (kg) \div height^2\ (m)$$

Cooper 12-minute scores were reported in kilometres (km) and converted to estimated $\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$) scores using the following equation (Cooper, 1968):

$$\dot{V}O_{2max}\ (ml \cdot kg^{-1} \cdot min^{-1}) = (22.351 \times kilometres) - 11.288$$

Where the change in pre-post score = delta (Δ). $\Delta\dot{V}O_{2max}$ scores and percentiles were calculated using methods from Gordon et al., (2015) (Chapter 6: 6.2.6). Additionally, Cohen's *d* Effect size (ES) and 95% Confidence intervals (CI) were calculated. Session training load (sTL), weekly training load (wTL) and total training load (tTL) were calculated for all participants similarly to chapter 8, including any additional session (asTL) and weekly training load (awTL) using methods from Foster et al., (1996) and Foster, Rodriguez-Marroyo and De Koning, (2017).

Upon the 3rd party analyse by Eurofins laboratory the raw data was sent to Muhdo health. The sheet identified 1000 SNPs where each SNP had the unique rs number to identify the candidate gene(s). Three probes were used in different orientations and repeated three times to ensure accurate readings and calls of the alleles. Nucleotides (Adenine, Thymine, Guanine and Cytosine) were listed in the forward-forward orientation, with a reported 99.9% accuracy. If this information was not consistent in all three calls the allele set was not included for the subsequent statistical analysis. All internally consistent genetic data was exported to an Excel spreadsheet (Microsoft Corp, Washington, USA), listing the SNP's by rs number, for statistical analysis. Participants were then grouped by genotype for each gene and sub-grouped accordingly.

For all statistical analyses, SPSS (Version 26, Chicago, IL) was implemented, the alpha level was set at $p < .05$. The tests for parametric assumptions included a Shapiro-Wilk Test of normality and Levene's test for homogeneity of variance. On the basis of parametric assumptions, tests included t-tests and ANOVA's, non-parametric tests included Kruskal-Wallis test as well as Mann-Whitney U test with post-hoc rank means, and correlation Spearman's rho test.

9.3. RESULTS

9.3.1. Participant characteristics

17 participants dropped out of the study due to commitment and loss of interest, with a final 45 completing the 8-week training intervention. All participants who undertook the 8-week training intervention completed 100% of assigned sessions. Participants were aged between 20-55 years old, males (n = 25; 29 ± 7 years; 180.5 ± 7.8 cm; 85.93 ± 14.98 kg; BMI 26.31 ± 4.07 kg·m^2) and females (n = 20; 29 ± 7 years; 168.1 ± 5 cm; 66.51 ± 11.34 kg; BMI 23.46 ± 3.56 kg·m^2). Participants were randomly split into an endurance training group (EG: n = 21; 31 ± 9 years; 178.8 ± 8.5 cm; 82.06 ± 17.08 kg; BMI 25.5 ± 4.0 kg·m^2) and a control group (CG: n = 24; 28 ± 5 years; 171.8 ± 8.4 cm; 73.13 ± 15.38 kg; BMI 24.7 ± 4.2 kg·m^2).

Shapiro-Wilk test of normality found that participants, regardless of group were normally distributed for characteristics in baseline mass (D(45), .957, p = .096) and BMI (D(45), .953, p = .064), but were not for age (D(45), .772, p = .000) and height (D(45), .941, p = .023). When participants were split into EG and CG all characteristics were normally distributed (p>.05) apart from age (EG = D(21), .788, p = .000, CG = D(24), .823, p = .001). Levene's test for homogeneity of variance found that all participant characteristics were homogenous (p>.05) except for age (F(1,43) = 7.058, p = .011). Non-significant differences were found in baseline characteristics between participants in both groups (p > .05), except for height (F(1, 43) = 7.653, p = .008).

After the 8-week intervention the mass for EG decreased by 1.03 ± 2.40 kg (-1.07 ± 2.86 %) and increased in the CG by 0.27 ± 1.06 kg (0.42 ± 1.52%). One-sample t-test found the within group changes in mass were not significantly different (EG = t(20) = -1.963, p = .064; ES = 0.06; CI = -0.67-0.54; CG = t(23) = -1.237, p = .228; ES = 0.02, CI = -0.55-0.58). However, independent samples t-test found that the Δmass was significantly different favouring the EG compared to CG (t(43) = -2.394, p = .010; ES = 0.49, CI = -0.11-1.08).

Additionally, ΔBMI from baseline to post 8-weeks decreased by 0.32 ± 0.72 kg·m^2 in EG (25.18 ± 3.77 kg·m^2) and increased by 0.09 ± 0.35 kg·m^2 in CG (24.74 ± 4.10 kg.m^2), these within group changes in BMI were not significant (t(20) = -2021, p = .057, ES = 0.08, CI = -0.69-0.52; t(20) = 1.267, p = .218; ES = 0.01, CI = -0.56-0.58, respectively). Between group analysis found significant differences, EG decreased more than CG (t(43) = -2.466, p = .018; ES = 0.11, CI = -0.47-0.70).

9.3.2. Training loads

Training load per-session, week, and total intervention for both groups, including any additional sessions outside of the intervention were calculated. EG sTL = 2,421 ± 861 A.U., wTL = 6,321 ± 1,251 A.U. and tTL = 50,810 ± 10,346 A.U. CG training diaries found sTL = 1,460 ± 1025 A.U., wTL of 3,285 ± 2,598 A.U. and tTL of 23,512 ± 20,470 A.U.

The total training loads for sTL, wTL and tTL were not normally distributed for both groups (p < .005 for all cases). However, were all homogenous according to the Levene's test (F(43) = .010, p = .992; F(43) = 1,356, p = .251; F(43) = 1.081, p = .304, respectively).

For sTL, wTL and tTL EG demonstrated greater loads compared to CG (Δ 960; 3,036; 27,298 A.U. respectively), confirmed with the sum of ranks. Equivalent to 65.7, 92.4 and 116.1% more throughout the study time-course. Non-parametric testing, Mann-Whitney U found this to be highly significant (U = 75.000, p = .000, ES = 1.01, CI = 0.39-1.63; U = 50.000, p = .000, ES = 1.46, CI = 0.80-2.11; U = 43.000, p = .000, ES = 1.65, CI = 0.98-2.33, respectively).

9.3.3. Cooper 12-minute run and $\dot{V}O_{2max}$ scores.

Groups were normally distributed for both Cooper run distances and $\dot{V}O_{2max}$, which reported the same results, (EG = D(21), .972, p = .779, CG = D(24), .200, p = .724). Equally, groups were shown to be homogenous (F(1,43) = .941, p = .337). There were non-significant differences between baseline scores across groups (F(1, 43) = 1.623, p = .209). The average Cooper 12-minute run distance was 2.13 ± 0.43 km at baseline, equal to an estimated 36.34 ± 9.56 ml·kg^{-1}·min^{-1}. EG and CG baseline Cooper distances were 2.22 ± 0.48 km and 2.06 ± 0.37 km (38.27 ± 10.75 and 34.65 ± 8.25 ml·kg^{-1}·min^{-1}) respectively.

In the first 4-weeks EG increased $\dot{V}O_{2max}$ to 41.42 ± 10.17 ml·kg^{-1}·min^{-1} ($\Delta\dot{V}O_{2max}$ 3.15 ± 4.26 ml·kg^{-1}·min^{-1}) this was significant (t(20) = -3.392, p = .003, ES = 0.31, CI = -0.31-0.91). Increasing $\dot{V}O_{2max}$ further by 2.09 ± 2.49 ml·kg^{-1}·min^{-1}, in the second half of the study (p = .001). 8-weeks of training improved $\dot{V}O_{2max}$ scores to 43.50 ± 10.49 ml·kg^{-1}·min^{-1} ($\Delta\dot{V}O_{2max}$ 5.24 ± 3.80 ml·kg^{-1}·min^{-1}) equal to a 15.62 ± 12.83% increase (t(20) = -6.315, p = .000, ES = 0.50, CI = -0.12-1.11). CG showed little improvements. First 4-weeks increased by 0.96 ± 2.96 (35.61 ± 9.01 ml·kg^{-1}·min^{-1}) however, was non-significant (t(23) = -1.589, p = .126, ES = 0.11, CI = -0.46-0.68). In the second half it decreased by -0.30 (35.31 ± 8.78 ml·kg^{-1}·min^{-1}) (t(23) = .473, p = .641). For the control group across the 8-week intervention they increased $\dot{V}O_{2max}$ by 2.15 ± 9.21% (Δ = 0.66 ± 3.41 ml·kg^{-1}·min^{-1}) but was non-significant (t(23) = -.952, p = .351, ES = 0.08, CI = -0.49-0.64).

Between group analysis found the $\dot{V}O_{2max}$ scores at 4-weeks mid-training was significant ($F(1, 43) = 4.127$, $p = .048$; ES = 0.62; CI = 0.01-1.21) with greater scores in the EG. Similarly, the post 8-week scores were highly significant ($F(1, 43) = 8.118$, $p = .007$, ES = 0.85, CI = 0.24-1.46). Within-group analysis confirmed that there were inter-individual differences between participants in the EG ($t(16) = 5.594$, $p = .000$, CI = 10.42-23.12), showing that people respond differently to the same training programme. Additionally, this was non-significant in the control group ($t(20) = 2.095$, $p = .337$, CI = -2.35-6.54). Finally, there were non-significant correlations between the $\Delta\dot{V}O_{2max}$ and participant age ($p = .671$, $r = .098$).

Spearmen's rho correlation and correlation coefficient found that in the first 4-weeks of the intervention, sTL, wTL and tTL were significantly correlated with changes in Cooper distance and $\dot{V}O_{2max}$ ($r_s = .308$, $p = .010$; $r_s = .399$, $p = .007$; $r_s = .406$, $p = .006$). Even more so at 8-weeks ($r_s = .535$, $p = .000$; $r_s = .587$, $p = .000$; $r_s = .593$, $p = .000$). This was in-part explained by the significant correlations with the $\Delta\dot{V}O_{2max}$ and exercise sRPE intensity (%) ($r_s = .301$, $p = .031$). Eta Squared through univariate general linear model found TL explained 20.3% of the variance in the interindividual differences between participants in the change in $\dot{V}O_{2max}$ and Cooper scores.

9.3.4. Genotypes

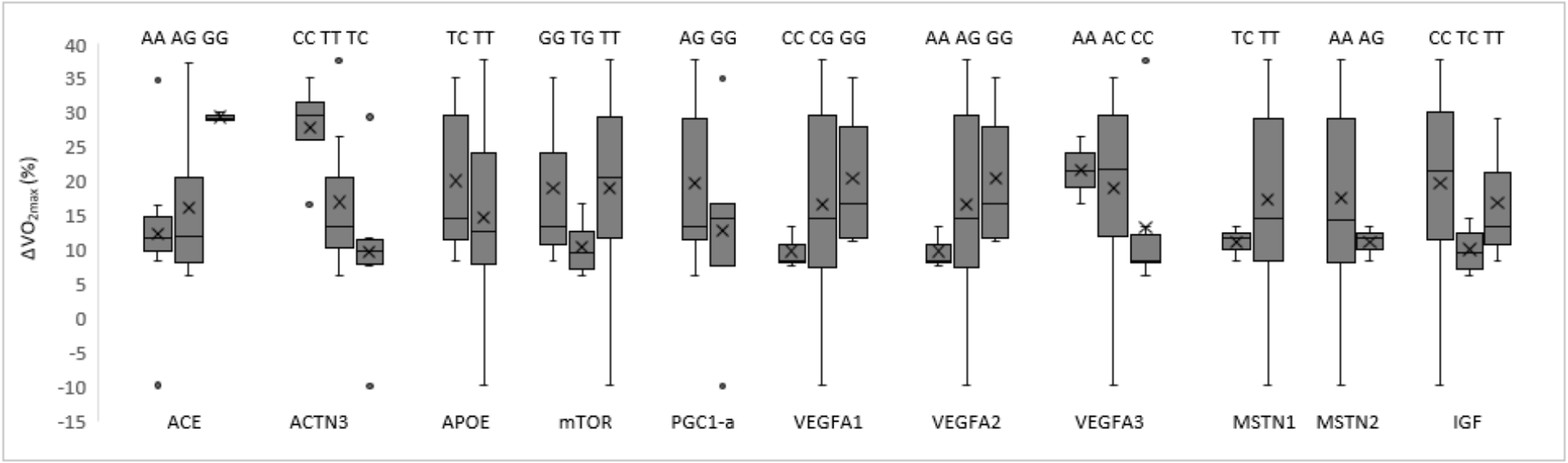
The final list of eight candidate genes and a total of 16 polymorphisms are outlined in Table 30. Due to allele frequencies in mTOR rs2536 and VEGFA rs1805086, rs35781413, rs397515373, and rs3791782 in this study population all exhibiting the same genotype, they were therefore excluded, as there would be no differential results.

Participants were then separated into allele subgroups, and initial observations showed trends in the change in $\dot{V}O_{2max}$ scores (Figure 42). Subgroup analysis showed different $\Delta\dot{V}O_{2max}$ results (mean ranks) even though participants completed the exact same exercise intervention, allele specific analysis showed that genotypes could explain a proportion of the improvements in $\dot{V}O_{2max}$. For example, the average improvement in ACTN3 CC genotype subgroup improved $\dot{V}O_{2max}$ by 27.45 ± 7.77%, whereas TT was much lower at 9.65 ± 12.39% and these were significantly different ($p = .033$). Kruskal-Wallis H and follow-up Mann Whitney U tests found significant differences in allele subgroups (ACTN3 TC, mTOR TT, VEGFA3 CC and IGF2 CC) for $\Delta\dot{V}O_{2max}$ (%) in accordance with Warton and Hui, (2011) as non-normal percentage data was used (Table 31).

There were non-significant correlations with any genotype subgroups and the amount of sTL, wTL or tTL (p > .05), additionally, there were non-significant differences in training load performed based on genotype subgroups for all genes within this study (p > .05). Finally, One-way ANOVA and post-hoc Tukey HSD were used to compare the genotype subgroups for Δmass and ΔBMI. ACE; ACTN3; APOE; mTOR; PGC-1α; VEGFA rs2010963; VEGFA rs833068; MSTN rs3791783; MSTN rs7570532; IGF2 showed non-significant differences in subgroup analysis, however, VEGFA (rs2146323), AC genotype was significantly different compared to AA, showing that AC subgroup had overall larger decreases in mass (p = .024, CI = .233-3.788) and BMI (p = .018, CI = .095-1.195).

Table 30. List of candidate genes and RS numbers. Allele specific genes and the common frequencies of these genes reported by the literature (https://www.nlm.nih.gov/; https://selfdecode.com/; https://www.snpedia.com/). Alleles are listed in pairs of either A, C, G, and T (Adenine, Cytosine, Guanine, and Thymine).

Gene	Rs number	Allele	Frequency (in all populations)
ACE	rs4343	A/G	A/A = 43.9%, G/G = 15.3%, A/G = 40.9%
ACTN3	rs1815739	T/C	C/C = 38.2%, T/T = 18.3%, T/C = 43.5%
APOE	rs429358	T/C	T/T = 72.8%, C/C = 2.8%, T/C = 24.4%
IGF2	rs680	T/C	T/T = 12.8%, C/C = 52.1%, T/C = 35.1%
MSTN	rs1805086	A/G	A/A = 87.3%, G/G = 1.4%, A/G = 11.3%
MSTN	rs35781413	A/G	A/A = 0%, G/G = 98.6%, A/G = 1.4%
MSTN	rs3791783	T/C	T/T = 45.8%, C/C = 21.6%, T/C = 32.5%
MSTN	rs7570532	A/G	A/A = 58.5%, G/G = 12.3% A/G = 29.2%
MSTN	rs397515373	A/G	A/A = 0%, G/G = 100% A/G = 0%
MSTN	rs3791782	T/C	T/T = 89.8%, C/C = 0.7%, T/C = 9.5%
mTOR	rs2295080	T/G	T/T = 36.8%, G/G = 29.3%, T/G = 33.9%
mTOR	rs2536	T/C	T/T = 81.6%, C/C = 1%, T/C = 17.4%
PGC-1a	rs8192678	A/G	A/A = 56.8%, G/G = 9.9%, A/G = 33.3%
VEGFA	rs2010963	C/G	G/G = 45.4%, C/C = 10.7%, G/C = 43.9%
VEGFA	rs833068	A/G	A/A = 14.6%, G/G = 38.3% A/G = 47.1%
VEGFA	rs2146323	A/C	A/A = 8.9%, C/C = 52.3% A/C = 38.8%



- mTOR = rs2295080; VEGFA1 = rs2010963; VEGFA2 = rs833068; VEGFA3 = rs2146323; MSTN1 = rs3791783; MSTN2 = rs7570532

Figure 42. Boxplot of Endurance group when split into the allele specific genotype subgroups. Boxplots show the average change in $\dot{V}O_{2max}$ for all genes and the respected genotype (allele variant of that gene). For example, on average the participants that had the CC allele genotype for ACTN3 showed to improve greater than those with the TT and TC variants.

Table 31. Subgroup scores for $\dot{V}O_{2max}$. 21 participants in the endurance group are split into genotype specific subgroups.

Gene	Allele genotype	$\Delta\dot{V}O_{2max}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	$\Delta\dot{V}O_{2max}$ (%)	Frequency (%)	Sig. ($p \leq .05$)
ACE	AA	5.62 ± 1.37	15.88 ± 9.56	37.50	AA>AG (p = .731)
	AG	5.68 ± 2.71	15.97 ± 11.58	43.75	GG>AA (p = .167)
	GG	9.36 ± 1.00	29.28 ± 0.68	18.75	GG>AG (p = .087)
ACTN3	CC	8.19 ± 1.77	27.45 ± 7.77	25.00	CC>TC (p = .089)
	TC	5.82 ± 2.72	16.77 ± 11.08	43.75	CC>TT (p = .033)*
	TT	5.60 ± 2.06	13.54 ± 8.86	31.25	TC>TT (p = .372)
APOE	CC	-	-	0.00	TC>TT (p = .634)
	TC	6.52 ± 2.40	19.85 ± 10.85	43.75	
	TT	6.22 ± 2.60	17.33 ± 10.99	56.25	
mTOR	GG	5.61 ± 1.62	18.70 ± 14.00	18.75	GG>TG (p = .289)
	TG	4.58 ± 1.76	10.32 ± 4.61	25.00	TT>GG (p = .644)
	TT	7.38 ± 2.52	21.94 ± 10.41	56.25	TT>TG (p = .044)*
PGC-1α	AA	-	-	0.00	GG>AG (p = .896)
	AG	6.73 ± 2.76	19.40 ± 10.88	75.00	
	GG	5.99 ± 0.98	18.28 ± 11.56	25.00	
VEGFA1	CC	4.88 ± 1.26	9.67 ± 3.01	18.75	CG>CC (p = .302)
	CG	6.93 ± 3.54	20.81 ± 12.87	37.50	GG>CC (p = .087)
	GG	6.48 ± 1.54	20.14 ± 9.71	43.75	CG>GG (p = 1.00)
VEGFA2	AA	4.88 ± 1.26	9.67 ± 3.01	18.75	AG>AA (p = 3.02)
	AG	6.93 ± 3.54	20.81 ± 12.87	37.5	GG>AA (p = .087)
	GG	6.48 ± 1.54	20.14 ± 9.71	43.75	AG>GG (p = 1.00)
VEGFA3	AA	7.04 ± 0.47	21.37 ± 6.97	12.5	AC>AA (p = .909)
	AC	7.36 ± 2.04	22.89 ± 9.87	43.75	AA>CC (p = .053)
	CC	5.13 ± 2.74	13.13 ± 10.88	43.75	AC>CC (p = .001)*
MSTN1	CC	-	-	0.00	TT>TC (p = .386)
	TC	5.28 ± 1.45	11.00 ± 2.42	25.00	
	TT	6.27 ± 2.41	19.32 ± 11.18	75.00	
MSTN2	AA	6.35 ± 2.51	19.76 ± 11.62	75.00	AA>AG (p = .484)
	AG	5.28 ± 1.45	11.00 ± 2.42	25.00	
	GG	-	-	0.00	
IGF2	CC	7.13 ± 2.59	22.79 ± 10.93	56.25	CC>TC (p = .045)*
	TC	4.72 ± 1.59	9.91 ± 3.81	25.00	CC>TT (p = .309)
	TT	6.18 ± 2.42	16.72 ± 10.64	18.75	TT>TC (p = 2.89)

- VEGFA1 = rs2010963; VEGFA2 = rs833068; VEGFA3 = rs2146323; MSTN1 = rs3791783; MSTN2 = rs7570532; > = Greater mean ranks; * = significant (p ≤ .05).

The top 25 percentiles in $\Delta\dot{V}O_{2max}$ exhibited similar genotypes. For mTOR all participants had the TT genotype, PGC-1α AG, VEGFA3 AC and IGF2 CC genotypes. Whereas, ACE had GG and AG, and ACTN3 CC and TC genotypes. APOE, VEGFA1 and VEGFA2 were mixed.

Table 32. Genes and the allele frequencies for whole cohort. The 45 participants are equal to 100% of the study population, the distribution of genotypes is shown respectively and can be compared with the frequencies in table 30.

Genes	**Genotype 1 (%)**	**Genotype 2 (%)**	**Genotype 3 (%)**
Ace (AA, AG, GG)	40.54	35.14	24.32
ACTN3 (CC, TC, TT)	35.14	37.84	27.03
APOE (CC, TC, TT)	2.70	29.73	67.57
mTOR (GG, TG, TT)	21.62	40.54	37.84
PGC1a (AA, AG, GG)	18.92	54.05	27.03
VEGFA1 (CC, CG, GG)	10.81	48.65	40.54
VEGFA2 (AA, AG, GG)	10.81	51.35	37.84
VEGFA3 (AA, AC, CC)	13.51	43.24	43.24
MSTN1 (CC, TC, TT)	5.41	21.62	72.97
MSTN2 (AA, AG, GG)	72.22	22.22	5.56
IGF (CC, CT, TT)	45.95	32.43	21.62

Univariate Eta Squared revealed that up-to 53.5% of the inter-individual variance in the improvement in $\dot{V}O_{2max}$ and Cooper run scores were explained by the specific genotypes in subgroup analysis. Four of these genotypes were significant (Table 31).

9.4. DISCUSSION

The aim of this study was to determine if any of the listed candidate genes could explain in-part the variance of change in $\dot{V}O_{2max}$ following an 8-week endurance-based training intervention, in a previously untrained population. It was anticipated that $\dot{V}O_{2max}$ would improve due to the recommended training loads of the study and that there would be a significant relationship between these. Additionally, the genotypes and alleles would in-part explain the inter-individual differences in the change of $\dot{V}O_{2max}$, establishing the importance of exercise genetics and training.

In terms of the average age group of this study (29 ± 7 years), the baseline data before the intervention period showed that the Cooper 12-minute scores in both groups were just within the range (2.13 ± 0.43 km) when compared to the normative values of 1.8 - 2.4 km (Cooper, 1968; Mackenzie, 1997; McGonigal, 2019). Participants completed a pre-health and training questionnaire that suggested they perform little to no aerobic training or exercise in the past 8-weeks (Chapter 8). This suggests that the participant pre-training status was that of the targeted group.

The results show that an 8-week endurance programme based on training loads and a 10% increase in weekly training load elicited significant improvements, with an average increase in $\dot{V}O_{2max}$ by 15.62%. This is reinforced when compared to the control group that had a non-significant change of 2.15%. These results are larger than previous literature findings from Chapters 3 of a 10.18% and 1.71% increase in $\dot{V}O_{2max}$ after training, respectively. These improvements in the health-related component of fitness phenotype were explained by the sTL (p = .000), wTL (p = .000) and tTL (p = .000), which supports the findings from chapter 3 and would appear to support the methodology of using TL to improve cardiorespiratory fitness. However, the results confirmed that the within-group comparisons were significantly different in the $\Delta\dot{V}O_{2max}$ response to training between participants in the endurance group, suggesting some participants improved more than others. Eta squared analysis found that 20.3% of the inter-individual differences were explained by the reported differences in training loads over the 8-weeks from the training diaries. Moreover, the results show that the genotypes play a key role in the improvements in $\dot{V}O_{2max}$ scores as well. The Eta-squared results in this study concluded that a further 53.5% of the variance in scores between participants were explained by the genotypes. This is very similar to the study by Schutte et al., (2016) and Williams et al., (2017) that both reported ~50% variability, and agrees with findings from chapter 4, where multiple studies showed an average 44% in $\dot{V}O_{2max}$ phenotypes. The results in this study estimate 73.8% of the variability in $\dot{V}O_{2max}$ improvements are explained by the training programme and candidate genes. The supporting literature states that, the resulting variability

in the pre-to-post changes would be attributable to random within-subject variation and measurement error or noise (Atkinson and Batterham, 2015). Additionally, sample population, sample size, environmental factors, and statistical methods play a part in this variability (Williamson, Atkinson and Batterham, 2017).

The subgroup analysis revealed that four specific genotypes (ACTN3 rs1815739 CC, mTOR rs2295080 TT, VEGFA rs2146323 AC and IGF2 rs680 CC) out of the 11 genes were significantly more advantageous and over-represented in participants with the highest improvements in $\dot{V}O_{2max}$ scores. Interestingly, the commonly reported roles of ACTN3 CC (RR) genotype have previously been found to be associated with power and sprinting performance, encoding muscle protein alpha-actinin-3 and the TT (XX) genotype is associated with aerobic fitness, lacking the expression (Roth et al., 2008; Yang et al., 2003). Conversely, studies such as Rankinen et al., (2016) failed to repeat these results and evidence does support mixed findings. The study by Silva et al., (2015) implementing an 18-week endurance training programme, agrees with the findings in this study, that CC genotype displayed greater improvements in aerobic improvements compared to its' TT genotype. They suggest that this could be due to a 'ceiling-effect phenomenon', with trained individuals already having high baseline scores, making it difficult to improve and may not constitute an adequate population to explain associations between phenotypic variability and gene variations. Although this would not explain why this response occurred in the untrained population in this study. Similarly, with mTOR genotypes where T allele carries are overrepresented in power-oriented athletes and G allele in endurance-based athletes (Drozdovska and Oleshko, 2016). Again, both IGF2 CC and TC genotypes have been shown to be advantageous in growth and performance, especially in greater strength and power, whereas the TT genotype does not express the gene (Ben-Zaken et al., 2017; Itaka et al., 2016). Evidence supports this, as mTOR mechanistic target of rapamycin (Ser2448) integrates the inputs of upstream pathways including IGF2 and sense cellular nutrient, oxygen, and energy levels, to maintain energy homeostasis and can also regulate mitochondrial biogenesis. mTOR functions as a serine/threonine protein kinase that regulates cell growth, cell proliferation, protein synthesis and transcription (Kazior et al., 2016; National Centre for Biotechnology Information, 2021; Watson and Baar, 2014).

Finally, carrier of the VEGFA A allele and even AC heterozygous genotype have been significantly related to aerobic performance, which agrees with the results in this study (Pokrywka et al., 2013). VEGFA AC was also the only gene to show significant associations with the decrease in mass and BMI scores in the sub-group analysis. This can be explained in part by the interaction between VEGFA and the oxidative pathways, especially fat oxidation

in the presence of endurance-based exercise (Pokrywka et al., 2013). When cells are deprived of oxygen (hypoxic condition) VEGF-A increases, mediating the growth of new blood vessels (angiogenesis) promoting both oxygen and blood availability at the muscle, which is most-likely due to an increase in blood flow response to exercise and oxidative phosphorylation, benefiting endurance, strength, and power performance (Carmeliet, 2005; Prior et al., 2006; Wagner, 2011). This genotype would be beneficial from an exercise and health perspective, especially in the untrained and particularly to populations looking to lose weight and decreasing BMI. When examining the 25th percentile of the most improved participants to that of the least improved, trends of genotypes emerged where, mTOR (rs2295080) TT, PGC-1α AG, VEGFA (rs2146323) AC, IGF2 CC, ACE GG and AG, and ACTN3 CC and TC genotypes were overrepresented in this study. Again, ACE GG genotype was shown to be associated with greater improvements in strength, rather than its AA endurance counterpart, however, it has also been found to be linked with greater left ventricular growth and cardiac hypertrophy, which is advantageous to exercise performance (Gayagay et al., 1998; Pan et al., 2007; Shenoy, 2010 Tsianos et al., 2004; Yamin et al., 2007). PGC-1α has been reported to be important for physical fitness and magnified in endurance and powerlifters, due to its central role in the regulation of cellular energy metabolism, mitochondrial biogenesis, and promotion of the remodelling of muscle tissue (Eynon et al., 2010; Gineviciene et al., 2016). Therefore, those that exhibit the GG variant where there is lower PGC-1α and less efficient coactivation of transcription factors, would be disadvantageous compared to the AA variant (Chomistek et al., 2013; Ruiz et al., 2009).

The lack of consistency in defining the exact allele's role are not surprising. Throughout this thesis it has been shown that previous literature and knowledge of these exercise candidate genes are based on observational studies in athletic populations, twin studies and knockout mice studies (Bouchard and Rankinen, 2001; Bouchard et al., 1998; Ghosh and Bouchard, 2017; Nimmo, Wilson and Snow, 1985), mainly in the frequencies and distributions of the alleles in certain exercise populations (Hernandez et al., 2019; Spurway and Wackerhage, 2006; Wigginton, Cutler and Abecasis, 2005). Whereas this study used untrained participants and based on these findings, any improvements in athletic ability whether, endurance, strength or power related, would be advantageous in improving Cooper running ability, consequently improving aerobic capability. Evidence suggests that most candidate genes and their genotypes are a better indicator of overall performance, rather than specific aerobic, strength, and power phenotypes (Cieszczyk et al., 2016; Sarzynski, Ghosh and Bouchard, 2017; Spurway and Wackerhage, 2006; Vancini et al., 2014), as the association between muscle mass and efficiency and availability with oxygen have previously been established, where an increase in oxygenated muscle blood-flow and more efficient muscle fibre recruitment may aid

in improvements in aerobic fitness (Liguzinski and Korzeniewski, 2007; Miyatani et al., 2008). Interestingly, the studies by Kim et al., (2016) and Fle and Lakatta, (1988) state that active individuals observe a slower rate of decline in $\dot{V}O_{2max}$ gains when compared to sedentary individuals, this was significantly correlated with muscle mass. Thus, $\dot{V}O_{2max}$ can be influenced by other types of training, such as strength if there is an increase in muscle mass. Kim et al., (2016) explain in their study that increased lean muscle mass and strength influence muscle recruitment, neuroactivational force production which is advantageous in exercise, especially in cycling and rowing, where large muscle groups and the ability to transport blood and oxygen to the working muscles are required. However, this could also negatively affect $\dot{V}O_{2max}$ due to the increase in overall body mass which is more prevalent in running modalities. Further, improvements in running technique, pacing, motor unit recruitment patterns, lower-body strength, and power would help in improving overall performance and tolerance (Buckner et al., 2017; Mujika, Rønnestad and Martin, 2016; Vasenina, Kataoka and Buckner, 2020). None the less, this study supports the notion that there are significant associations between exercise genetics and the improvements in health-related fitness components, specifically the $\dot{V}O_{2max}$ phenotype.

In conclusion, this study supports the associations between candidate genes, more specifically the alleles and genotypes with the improvements in Cooper running scores and $\dot{V}O_{2max}$. Additionally, these genes explain up to 53.5% of the variability in scores. The training loads implemented in the 8-week training programme were significantly correlated with the increases in $\dot{V}O_{2max}$, explaining 20.3% of the variability. Therefore, accepting the alternative hypotheses (H_1, H_2 and H_3). In terms of existing research knowledge, this study supports that gene influence aerobic responses ($\dot{V}O_{2max}$), similarly to the reported figures within the literature. Where this study is unique and original is how research information in training and genotyping was used and applied to a field-based scenario during a COVID-19 pandemic, uncovered similar consistent result. The findings, methods, and protocols employed in this study can specifically contribute to the body of knowledge and inform future studies.

9.5. LIMITATIONS

The main limitations within this study are firstly, not being able to conduct this experiment within a controlled environment. Thus, it was not possible to completely control or standardise the training, and not being able to record certain physiological and metabolic variables. It should be noted for future research implementing similar studies, to consider a laboratory-based environment and assessing cardiac and metabolic responses such as, the ones outlined in chapters 5 and 6. This field-based study has merit and represents a 'real-world' scenario where people may not have access to laboratory equipment and can complete the training and tests locally at home and unsupervised (Anstrén, 2015; Mackenzie, 1997; Poole, Wilkerson and Jones, 2008).

Secondly, another limitation is that because this was not conducted in the laboratory, this study relied on the participants being able to report intensity, duration, and frequency of sessions and Cooper runs accurately and honestly, which could lead to error. Participants were instructed and familiarised on how to use the Borg RPE CR1-10 scale to estimate intensity of the sessions and how to use the STRAVA app to record distance and time of the runs. Participants were given a training schedule and were instructed to follow it strictly. Participants were also asked to familiarise themselves with the Cooper 12-minute run test, where instructions, weblinks and videos were sent to them. Although the Cooper run test has been shown to be both valid and reliable, equally. Studies have also questioned the repeatability and accuracy over time and the calculations of estimating $\dot{V}O_{2max}$ (Weisgerber, 2009). Finally, a limitation is the sample representation, the genotype frequencies are shown in table 32, however, this does not necessarily mean that in this small sample population the genotypes will be shown accordingly. Variant SNPs, APOE rs429358, MSTN rs1805086, rs35781413, rs3791783, rs7570532, rs397515373 and rs3791782, VEGFA rs2010963 and rs833068 showed no advantages or associations with improvements, this though does not mean that in larger samples they are not beneficial to exercise performance. SNPs such as MSTN rs1805086 GG genotype are very rare, only seen in 1.4% of all populations, it showed non-significance in this study. Nevertheless, is still a very highly warranted genotype, especially in strength phenotype improvements, and therefore, should not be excluded from future gene listings (Fuku et al., 2016; Santiago et al., 2011).

CHAPTER 10: RESEARCH SYNTHESIS AND CONCLUSIONS

10.1. DISCUSSION

This thesis aimed to address the influence of specific candidate genes in response to the improvements in components of health-related fitness. The objectives of these were to first establish suitable exercise training programmes to improve the three components of health-related fitness, which were, cardiorespiratory, muscular strength, and anaerobic power, and understand how training effects the improvements of these. Specifically, what factors need to be considered when implementing a training strategy to maximise the time spent training (chapter 3). Secondly, it was proposed to identify a list of commonly researched and reported candidate genes and provide evidence that there are associations between the genes of interest and the improvements in the same components of health-related fitness in the untrained population (chapter 4). Thirdly, following these literature-based findings, to apply and implement a repeated-measures training study formulated from this research knowledge into a real-world practical experiment on previously untrained participants, to improve the components of health-related fitness (chapter 6 and 9). Additionally, assess the genetic variability and associations on these components of fitness phenotypes, to better understand the importance of exercise genetics in training, health, and fitness (chapter 9). These findings have demonstrated both originality, contribution to the research area, and new knowledge.

To achieve these, two systematic literature reviews with meta-analysis were conducted in accordance with the PRISMA guidelines to answer the first two objectives. The third objective was in the form of a highly standardised laboratory training study informed by the first systematic literature review. However, due to COVID-19 restrictions, UK lockdown, and social distancing guidelines, the study was postponed indefinitely. After a reflective period and action plan, it was decided that an additional questionnaire-based study was required. The objectives of this study were to gather mass data on a UK based population to compare different population groups to the systematic literature review outcomes. This study also served to inform and recruit untrained participants for the training study. The training study was altered to an outdoor field-based endurance training programme, with the intention of improving cardiorespiratory fitness in a group of untrained participants. The final objective was achieved by genotyping these participants, to assess the individual differences between participants and how the genotypes influence the training responses. The findings in this thesis have established results, which are both statistically significant, as well as clinically important. Even slight improvements in the health-related fitness components are beneficial to overall health.

Moreover, the specific genetic alleles that constitute a genotype heavily affect the response to training in cardiorespiratory fitness.

10.1.1. Training load

The findings suggest that, to improve a component of fitness one must perform training relevant to that component, whether it be endurance, strength, or power-based, or a mixture of approaches (chapter 3 and 4). An important consideration should also be the specific intensity, duration, and frequency implemented in the training programme, the progression of training, which contributes to the training load and therefore, stimulus to drive the adaptations and responses to training (Hautala et al., 2006; Laursen, Blanchard and Jenkins, 2002; Peterson, Rhea and Alvar, 2005; Schutte et al., 2016; Vancini et al., 2014). Training loads were recorded in chapter 3, so that all training interventions gathered from the literature that implemented different intensities, durations and frequencies could be standardised and compared in arbitrary units (Balsamo et al., 2012; Foster, et al., 1996; Foster, Rodriguez-Marroyo and De Koning, 2017). The results from the systematic literature review agree with these statements, the R^2 correlation coefficient found a significant positive association between the improvements in the three components of fitness and the training load implemented (R^2 = 0.86; 0.50; 0.90, respectively). Additionally, the length of the intervention time-course alone was not responsible in adaptation rates. The results in this chapter further revealed that from the combination of 43 untrained study groups to achieve a significant improvement in cardiorespiratory fitness ($\dot{V}O_{2max}$) an estimated session training load of at least 1,700 A.U. would need to be implemented in a single training session and repeated equal to 5,000-6,000 A.U. weekly training-load. Muscular strength and anaerobic power were more difficult to estimate, due to the lack of consistency in how studies reported the training variables. Therefore, a limitation of calculating training load was revealed and this was addressed and corrected for in chapter 8, by evaluating the duration and categorising the exercise of the strength sessions and the time spent at rest. However, although training load may be important, it was recognised that these loads may not represent the real-world application of training and that programmes and regimes are very different to that of a laboratory-based versions.

In chapter 8, 548 participants from the UK completed the training load questionnaires and reported that 2.2% were classed as ‘Inactive’; 6.6% ‘Sedentary’ (spends much time seated and somewhat inactive); 24.7% did less than the recommended weekly physical activity set by the ACSM, NHS and WHO; 32% thought they met the criteria for the physical activity recommendations and 34.6% did above the weekly recommended. Further examination of the data found that, 17% did not report doing any form of exercise, sport, or physical activity and

therefore, training load could not be estimated. The results revealed, the average training load in this study was greater than that reported in the literature. However, 183 participants of particular interest, did not meet the weekly recommended exercise but still preformed an average 1,702 ± 1,777 A.U. of training load per-session and 4,952 A.U. per-week, this is reflected by the lower durations and frequencies, ultimately reducing training loads and volumes. This is far less in comparison, to the endurance athlete group, having a sTL of 3,619 A.U. and estimated weekly load of 13,836 A.U. and strength athletes displaying 5,389 A.U. per-session, equivalent to 24,888 A.U. per-week. The results also demonstrate that wTL from additional sessions, contribute to an extra 2,737 A.U. for endurance and 3,256 A.U. for strength groups. Thus, for athletic groups exercise intensity, session durations and frequency of sessions per-week were much greater than those classed as untrained and explains why training loads are far greater in these groups.

Because it was not possible to conduct exercise training in a laboratory-based setting, field-based assessments were used. Specifically rating of perceived exertion (RPE) was employed to estimate exercise intensity, which has been well documented in the research literature and supported by the methods from chapter 8. In the study by Day et al., (2004) they found that the using RPE (Borg, 1998) as a measure of monitoring intensity was accurate and reproducible with an ICC of 0.882 over different training intensities. This agreed with findings from Gearhart et al., (2002) in which they repeated exercises in both high and low intensity protocols to evaluate the test-re-test reliability of sRPE (ICC 0.73-1.00). Similarly, Herman et al., (2006) found significant relationships between sRPE and $\dot{V}O_2$peak (R^2 = 0.76), %HRpeak (R^2 = 0.74) and %HRreserve (R^2 = 0.71), with non-significant differences in test-re-test in two intensity groups at 60-70% and 80-90% $\dot{V}O_2$peak. Finally, Faulkner, Parfitt and Eston, (2007) reported a RPE of 13 on the 20 scale (equal to 6.5 on the 10 scale) was equivalent to intensities of 66% $\dot{V}O_{2max}$ in sedentary male and female participants. This is very similar to the findings of Lambrick et al., (2009) a RPE score of 13 was approximately 64% of $\dot{V}O_{2max}$ and therefore, was implemented in this thesis as a way of estimating exercise intensity.

Applying this information into a real-world scenario, for the field-based study in chapter 9 the initial training loads were based upon the findings from chapter 3. However, a progressive overload model was implemented to increase the training loads to better match the loads seen in chapter 8 without causing an excessive training load. The exercise group performed a sTL of 2,421, wTL of 6,322 and tTL of 50,811 A.U. The results in chapter 9 found that after 8-weeks endurance training there was a significant correlation between sTL, wTL and tTL and the improvements in $\dot{V}O_{2max}$ results (r_s = .535, p = .000; r_s = .587, p = .000; r_s = .593, p = .000). Due to the duration and frequency of sessions being constant between participants, RPE

intensity was the changing factor reported 30 minutes after every session. The results show that there was a significant correlation between the Δ $\dot{V}O_{2max}$ and exercise sRPE intensity (%). Further the training load differences explained 20.3% of the variance between participants in the change in $\dot{V}O_{2max}$. Therefore, this study confirms that a well-designed outdoor training programme, targeting cardiorespiratory fitness, based on training loads can significantly improve $\dot{V}O_{2max}$ scores in an untrained population.

10.1.2. $\dot{V}O_{2max}$

Chapter 3 outlined that in the 16 study groups that performed exercise training, significantly improved $\dot{V}O_{2max}$ from baseline results by 10.18 ± 3.95% compared to the control group that only increased scores by 1.71 ± 4.21%. Similarly, the chapter 4 (literature review) also found that in the 43 study groups $\dot{V}O_{2max}$ significantly improved by 10.97 ± 3.8%. This shows that the research-based literature agrees with the improvements of $\dot{V}O_{2max}$ following an exercise training intervention in previously, untrained participants. This also agrees with literature findings from Hautala et al., (2006) Nummela et al., (2016) of a 10% increase in $\dot{V}O_{2max}$ in sedentary participants. The findings from the field-based experiments in chapter 9 used the combination of the literature-based evidence and questionnaire-based results to govern the training and improvements in $\dot{V}O_{2max}$. These results were replicated in a group of untrained participants. Following an 8-weeks outdoor endurance study, the exercise group significantly increased $\dot{V}O_{2max}$ by 15.62 ± 12.83%, whereas the control group showed little improvements of 2.15%, which was non-significant (Chapter 9: 9.3.3.). The between-group analysis found this was significant (p = .007; ES = 0.85, CI = 0.24-1.46). Within-group analysis confirmed that there was inter-individual variance between participants in the exercise group (p = .000, CI = 10.42-23.12), showing that untrained participants respond differently, even to the same training programme. Additionally, the improvement in $\dot{V}O_{2max}$ of 15.62% was significantly correlated to the higher training loads applied in this study. This explained 20.3% of the variance in the results and conforms with numerous reports that these variances in $\dot{V}O_{2max}$ exist even with highly standardised programmes (Hautala et al., 2006; Sarzynski, Ghosh and Bouchard, 2017; Schutte et al., 2016). Furthermore, these variances have been shown to have a genetic component, which may explain the differences in scores between participants (Keiller and Gordon, 2019; Landen et al., 2019; Spurway and Wackerhage, 2006; Vancini et al., 2014).

The findings from the literature review in chapter 4 support the notion that $\dot{V}O_{2max}$ is associated with exercise genetics, the results concluded that 44% of the variability in the increase of $\dot{V}O_{2max}$ post-training intervention was explained by the nine gene subgroups across the 43 studies. The results from chapter 9 heavily support the literature-based evidence and

association between exercise genetics and the improvements in the components of fitness. A final list of eight candidate genes and a total of 16 polymorphisms were associated with exercise performance. Participants were then split into allele subgroups and initial observations showed trends in the change in $\dot{V}O_{2max}$ even though participants completed the same exercise intervention. Unsurprisingly, there were non-significant correlations with any genotype subgroups and the amount of training load performed, additionally, there were non-significant differences in training load performed based on genotype subgroups for all genes within this study. However, there were slight differences in training load as participants performed sessions outside of the programme, but this distribution was random and was not significant. Further, allele specific analysis showed that genotypes could explain a proportion of the participants improvements in $\dot{V}O_{2max}$. In fact, the results found that four specific genotypes were directly responsible for the significant increases in $\dot{V}O_{2max}$ in the subgroup analysis. These were, ACTN3 CC genotype, which was significantly greater than the TC and TT (p = .033), achieving a 27.45% increase in $\dot{V}O_{2max}$ compared to 16.77 and 13.54%, respectively. mTOR TT genotype, which was significantly greater than GG and TG (p = .044), displaying 21.94% increase compared to the 18.70 and 10.32%, respectively. VEGFA AC genotype was significantly superior to the CC genotype (p = .001), equal to 22.89% compared to 13.13% and finally, IGF2 CC genotype was significantly more advantageous compared to TC and TT genotype (p = .045), showing a 22.79% increase in $\dot{V}O_{2max}$ after training compared to 9.91% and 16.72%, respectively.

Furthermore, the top 25 percentile of participants in relation to $\Delta\dot{V}O_{2max}$ exhibited similar genotypes. For mTOR all participants had the TT genotype, PGC-1α AG, VEGFA3 AC, and IGF2 CC genotypes. Whereas, ACTN3 had both CC and TC genotypes and ACE had GG and AG. ACE GG group on average found the largest improvement of 29.28% and was superior compared to the 15.88% in AA and 15.97% in AG genotypes, however, was not statistically significant (p = .087). These results agree with that of Silva et al., (2015), who also found that the specific allele genotypes did not observe any significant differences in $\dot{V}O_{2max}$ and disagrees with previous literature findings, suggesting that ACE GG genotype has been shown to be associated with greater improvements in strength, rather than its AA endurance counterpart. However, the literature does support that the GG genotype has also been found to be linked with greater left ventricular growth and cardiac hypertrophy, which is advantageous to overall exercise performance, as the underlining mechanisms support improvements in oxygen delivery to working muscles (Gayagay et al., 1998; Pan et al., 2007; Shenoy, 2010 Tsianos et al., 2004; Yamin et al., 2007). Additionally, the results in chapter 4 agree with the mixed results in the genotype role and found that the allele differences were not significant but still noticeable in this respect. Nevertheless, the results in chapter 9

revealed, when including all candidate genes in the analysis that 53.5% of the inter-individual variance in the improvement of $\dot{V}O_{2max}$ were explained by the specific genotypes. Conclusions can be made, that the genes, specifically the alleles are heavily associated with the components of health-related fitness, which supports previous literature findings. These findings are applicable to groups of previously untrained males and females and have the potential to aid the rate of training improvements and adaptation when compared to those of other genotypes.

10.1.3. 1RM and PPO

The results from the literature revealed that over the 12-study groups in chapter 3, strength training significantly improved lower-body one repetition maximum. The average increase in strength across all studies was equal to 19.40%, whereas the control groups exhibited a decrease in strength of 1.26%. Similarly, the results from chapter 4 found that a further 29 study groups significantly increased 1RM by 22.12%. These findings compare favourably with the findings in cardiorespiratory fitness previously discussed. Similarly, in terms of peak power output, four study groups in chapter 3 found significant improvements post-training of 11.84%, where the control groups improved by 1.52% but was non-significant. In agreement chapter 4 highlighted significant increases in anaerobic power across 17 study groups of 12.17%, which was significant, again, similar to previous findings. It can be concluded that in the untrained, these increases in performance phenotypes as a result of training are repeatable and heavily supported by literature-based evidence.

Additionally, chapter 4 supports that there are associations between the improvements in 1RM and six exercise genes across 29 studies. Eta squared found that 72% of the variability increase in 1RM was explained by the genetic subgroup. Conversely, for PPO, 10% of the variability was explained by the exercise genes. This could be due to the lack of research literature on PPO and the associated genes, as only four genes were highlighted as well as inconsistencies in how anaerobic peak power is estimated. Nevertheless, this thesis failed to repeat these findings in the field-based examination for these two sub-components of fitness, due to the cancellation of the laboratory study (chapter 6). Subsequently, only cardio-respiratory fitness was examined in chapter 9 and the association between these components of fitness and genetics could not be established.

10.1.4. BMI and Body fat percentage

BMI is a measure used to define mass against height and is commonly calculated from a person's height in metres and mass in kilograms (NICE, 2014a). In chapter 3, seven study groups from the literature review assessed body mass index scores in the untrained following an exercise intervention. BMI in the exercise groups decreased by 1.22% while the control groups showed slight increases of 0.21 ($p > .05$). BMI scores collected in this thesis from baseline revealed the participants as overweight. After the 8-weeks a similar decrease of 1.03% was observed, whereas the control group increased by a similar 0.27%, again these changes in BMI were non-significant ($p = .057$, ES = 0.08, CI = -0.69-0.52; $p = .218$, ES = 0.01, CI = -0.56-0.58, respectively). However, the between groups analysis was significant when comparing groups ($p = .018$, ES = 0.11, CI = -0.47-0.70), showing the importance of comparing results against the control group. This is explained by the reduction in body mass following the 8-week intervention. The average change in mass for the exercise group was a decrease of 1.07% and increase in the control group by 0.42%. The change in mass was significantly different when comparing the exercise and control groups ($p = .010$, ES = 0.49, CI = -0.11-1.08).

In terms of body fat percentage (chapter 3), it would appear from the 14 exercise groups that exercise in either endurance, strength, or power reduces body fat scores (4.0, 5.3 and 6.0%, respectively). However, these were non-significant, but did all show a large effect size (1.25, 1.96 and 1.96, respectively). Although these results might not be statistically significant this does not mean that they are not clinically significant, as a reduction in both BMI and body fat percentage in this specific population and in obese and overweight populations would be advantageous towards living a healthier lifestyle. Body fat, muscle mass and fat free mass data collection were initially planned and implemented with Tanita scales outlined in chapters 5 and 6. Unfortunately, due to COVID-19 this could not be conducted in the field-based study and the logistics of sending equipment to the participants was not feasible and therefore, this thesis failed to measure these important variables.

The genotype subgroups also revealed that the change in mass and ΔBMI may have had a genetic component. ACE; ACTN3; APOE; mTOR; PGC-1α; VEGFA rs2010963; VEGFA rs833068; MSTN rs3791783; MSTN rs7570532; IGF2 showed non-significant differences in subgroup analysis and the change in these two variables, however, VEGFA (rs2146323), AC genotype were significantly different compared to the AA and CC genotype, showing that the AC subgroup exhibited the largest overall decrease in mass ($p = .024$, CI = .233-3.788) and BMI ($p = .018$, CI = .095-1.195). Interestingly, this was the only gene to show an association with improvements in mass and BMI. A possible explanation is the interaction between VEGFA

and the oxidative pathways, particularly fat oxidation in the presence of endurance-based exercise (Pokrywka et al., 2013). When cells are deprived of oxygen, VEGFA increases, facilitating the growth of new blood vessels, promoting both oxygen and blood availability at the muscle, stimulating lean muscle mass development and fat oxidation (Carmeliet, 2005; Prior et al., 2006). These findings suggest that more attention is required on the association between training and weight loss, and how exercise related genotypes might be beneficial for improving this adaptation rate in weight management, fat loss, and increase in lean muscle mass.

10.1.5. Important endnotes

As outlined by the introduction section, there is a rise of inactivity leading to increased obesity and people becoming overweight, which is a serious concern, not just in the UK but world-wide (Chen et al., 2016; NHS, 2018). The understanding of exercise from the literature has provided numerous indications that improvements in the health-related components of fitness help in tackling inactivity, weight management, well-being, and general physical fitness (ACSM, 2017; Blair, 2015; Lofrano-Prado et al., 2012; McGuigan et al., 2009; Sarzynski, Ghosh and Bouchard, 2017; Shamim et al., 2018). Yet, there are many factors which contribute to exercise and the improvements in the health-related components of fitness. This research expresses a specific interest in the genetic components that influence adaptations and phenotype responses to the components of health-related fitness. Evidence suggests that up-to 80% of the variability in the adaptation to training are dependent on the genotype, even when performing the exact same training regimen (Bouchard, 2012; Hautala et al., 2006; Huygens et al., 2004; Klissouras, 1971; Komi et al., 1977; Spurway and Wackerhage, 2006). This is supported by the findings from chapter 4 that there is an influence of exercise genetics on the components of health-related fitness, in the order of 72%, further supported through the findings in chapters 8 and 9.

The literature focusing on elite performance has consistently shown that genotypes are important to the development of the athlete, especially when having advantageous allele frequencies predominantly matching the desired component of fitness phenotypes. However, where the findings in this study differ, is that the results show that in the untrained population, a genotype that leads to improvements in overall performance of any health-related component of fitness is advantageous to the individual and improves aerobic fitness and overall health in the presence of exercise. Therefore, these candidate genes should be termed and categorised as exercise performance genes. Thus, this thesis has achieved the aims and objectives of the research and has provided valuable information on exercise genetics, exercise training, and improvements in the health-related components of fitness.

The reliability and validity of the methods, equipment, and techniques have been addressed throughout this thesis. The methods employed have previously been shown to have both high reliability and precision. However, critical considerations are still required when employing these methods. Arguably, the reliability of these methods used have also been stated to only be as good as the person implementing the procedure. The research literature has shown mixed results in both laboratory and field-based measures. Therefore, to ensure the highest possible accuracy of the measurements, it is imperative to follow the manufacturers guidance, calibration, and setup, and for both practitioners and participants to fully understand the protocol and measurements being employed.

An important consideration when reporting these findings are the statistical or clinical significance of the results (Atkinson and Batterham, 2015). Where results may not be statistically significant but still important, especially in untrained participants that show even small improvements in health-related components of fitness can improve someone's health, well-being, and quality of life. Here the smallest worthwhile change (SWC), known as the minimum (clinical) important difference can be relevant. Hopkins, (2004) reported the SWC as 0.3% of the CV, and similarly Peltola, (2005) reported this between 0.3 – 0.5% in the CV difference between groups. The findings in this thesis have provided evidence that there is both statistical significance and clinical importance in implementing training load to improving health related fitness, as well as the advantages of applying allele specific genetic knowledge.

10.1.6. Recommendations and future work

The findings have provided valuable results and evidence between the associations with genetics and cardiorespiratory fitness improvements in the untrained. The findings also provide literature-based evidence of this being applicable to the other components of fitness in the untrained, inactive, and sedentary population. However, these were not tested in a controlled environment. Recommendations would be to apply similar strategies in strength and power specific training which is highly warranted. Additionally, how these affect other variables that were not recorded, such as body fat percentage and muscle mass, cardiac, respiratory, and hemodynamic parameters. In terms of training, another area of interest briefly reflected upon in this thesis is concurrent training, the combination of both aerobic and anaerobic exercises, which is more representative to real-world strategies as shown in chapter 8. There is currently very limited information on the genetic influence on concurrent training, as this work mainly focused on endurance, strength and power as separate outcomes and has shown that genetic pathways may negatively affect each other in terms of endurance and strength.

The work conducted in the genetic analysis has highlighted a major inconsistency and error within the current exercise genetic field. Therefore, it is recommended that for future and ongoing studies that are concerned with gene specific outcomes to employ an allele-specific analysis, rather than the mistake of using whole gene analysis which is a limited measure. Finally, this work has focused heavily on the physiological and metabolic responses to exercise training and genetics. However, research evidence has shown that an increase in exercise and physical activity is also exhibits positive associations with psychological benefits, and well-being. Therefore, in contrast to this work, future studies should explore how psychological parameters such as, mood states and enjoyment of exercise may be affected when participants perform the same standardised exercise and how the allele-specific genetics may impact how people perceive exercise differently. This will provide any trends the genes might have on the physiological aspects, as well as the psychological ones, which current literature has not yet explored.

10.2 LIMITATIONS

The main limitation within this thesis is the absence of a standardised laboratory protocol for the collection of multiple physiological and metabolic variables, meaning adaptations were hard to distinguish and the exact reasons to why there was an adaptation are unclear. Additionally, this made it difficult to outline any further responses that may have had clinical significance outside of the components of fitness, such as the variables from chapter 3 (for example, body fat percentage and muscle mass) that supplement the results. Therefore, it is recommended that future work apply the findings of this research and employ more comprehensive data collection on specific physiological and metabolic variables.

Another limitation of the two systematic literature reviews and meta-analyses were the strict inclusion criteria and the lack of research-based evidence in the untrained populations. Therefore, the genes used in this thesis are not exhaustive. There are many more exercise associated genes that could contribute to the variability in performance phenotypes and a limitation will always be, how to select from the vast list of these candidate genes and SNPs. In addition, the lack of power training studies on peak power output adaptations were present and therefore, no clear results were established for this phenotype response.

A limitation that must be noted is the potential participant error, due to participants reporting training and test outcomes. This was highlighted in both chapter 8 and 9. Firstly, the Hawthorne effect may be relevant as participants know that they are being monitored and may report incorrect or inconsistent results. Secondly, a placebo effect, because participants have been recruited into a study group, they may perceive that they should provide better results and therefore, try harder in the training or do other exercises that improve the test outcomes. Lastly, there may be a lack of understanding from the participants when reporting outcomes. This is especially relevant for rating of perceived exertion, as inexperienced users may not understand how to use the scale and the differences between scores. Although, throughout this thesis the general reliability and validity of these measures have been shown to be high, these limitations can question the reliability and accuracy of these measures. Therefore, for the highest possible accuracy, repeatability, and reliability it is critical participants and practitioners understand how to use and implement these measures.

10.3. CONCLUSION

In this thesis titled, ‘Genotypes and phenotypes: Implications of exercise on the inter-individual differences in biological responses’, it has been concluded that the human allele-specific genotypes in the presence of exercise significantly impact the individual and the inter-individual differences in phenotype and biological responses in previously untrained participants. This thesis has contributed to research knowledge and the practical applications of training and exercise genetics. These chapters have successfully answered the aims and objectives of the thesis and how it relates to the research literature. Firstly, how, and what types of exercise are beneficial to improving the health-related components of fitness phenotypes and the larger implications of this in the untrained. Secondly, how exercise genetics effect this and the role they play within exercise responses and adaptation in the untrained to maximise performance outcomes. The significance of this work demonstrates that theoretical and lab-based studies can be replicated in a field-based setting and has real-world applications. These results in participant adaptations and responses in the phenotypes question the application of generic exercise training within certain populations, especially as that population becomes more trained. Finally, the work provided here has informed and outlined a major flaw in current exercise-genetic research. Moving forward it is now essential and this thesis recommends using allele-specific analysis, rather than whole-gene analysis to distinguishing what the genes do. Therefore, contributing to science and informing future studies.

There were however, two main shortcomings within this work. Firstly, the lack of literature-based evidence included within the reviews in the untrained population and the exercise genetics specifically in the three components of health-related fitness. Secondly, due to COVID-19, changes in the experimental chapters were made, which may have given better insights to the physiological and metabolic responses to the training and genetics. Therefore, future research and avenues are required where this thesis fell short. Nevertheless, the bigger picture of the thesis suggests that using exercise genetic information to govern training programmes are more advantageous compared to randomly selected generic programmes to improve one’s component of health-related fitness.

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