Exploring the efficacy of short-term high intensity interval training (HIIT) for improving surgical risk factors in older adults

by

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Declaration

I hereby declare that the work presented in this thesis is my own.

James Blackwell

Statistical support was provided formally within studies in this thesis by Dr Andrea Venn (Honorary Associate Professor in Statistics, School of Medicine, and University of Nottingham) and clinician Dr Brett Doleman (PhD) who in particular guided me through the statistical aspects of meta-analysis.

Thesis Abstract

Purpose:

National cancer waiting time guidelines enforce a limited time period between diagnosis and surgery (31 days). Low preoperative cardiorespiratory fitness (CRF), in particular anaerobic threshold (VO_{2AT}), is associated with poorer surgical outcomes. The optimal preoperative exercise regimes to improve cardiorespiratory fitness (CRF) are not fully understood. High intensity interval training (HIIT) may represent an efficacious means of increasing CRF in a short time period. The effect of advancing age and comorbidity, in relation to the optimal HIIT regime to evoke positive responses are unknown.

Methods:

Systematic review and meta-analyses established that HIIT is more efficacious than moderate continuous exercise, particularly in patients with cardiac pathology, over truncated timeframes. Our 5 x 1 minute (90 seconds rest periods between) HIIT protocol is used throughout studies in this thesis. Cardiopulmonary exercise testing provides objective measurement of CRF parameters.

Results:

HIIT confers greater improvements in CRF over short periods in individuals with chronic disease versus moderate continuous training (MCT). Our HIIT protocol delivers improvements in VO_{2AT} (mean difference (MD)) over short periods (<31 days) in healthy sedentary (MD 2.95 ml/kg/min), comorbid octogenarians (MD 1.21 ml/kg/min) and urological cancer patients (MD 2.26 ml/kg/min).

Conclusions:

Short term HIIT is more efficacious than MCT in cardiac patients. Supervised HIIT delivers greater improvements in CRF than work matched unsupervised HIIT. Certain elderly individuals with comorbidity are able to rapidly improve CRF following HIIT. Preoperative HIIT is efficacious, safe and feasibly delivered within the current clinical framework within urology.

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III. List of abbreviations

6-MWT	Six-minute walk test
ACSM	American college of sports medicine
ADLS	Activities of daily living
ADP	Adenosine diphosphate
ASA	American society of anaesthesiologists
AT	Anaerobic threshold (synonymous with VO_{2AT})
ATP	Adenosine triphosphate
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
CS	Citrate synthase
CSA	Cross sectional area
CT	Computer tomography
CVD	Cardiovascular disease
DASI	Dukes activity status index
DBP	Diastolic blood pressure
DXA	Dual-energy x-ray absorptiometry scan
ECG	Electrocardiogram
EIM	Exercise is medicine
EQ5D5L	EuroQuol 5-dimension questionnaire (English)
ERAS	Enhanced recovery after surgery
FFM	Fat free mass
HbA_1C	Haemoglobin A1C
HDU	High dependency unit
H-HIIT	Home based HIIT
H-IHGT	Home based isometric hand grip training
HIIT	High intensity interval training
HIT	Synonymous with 'HIIT'
HR	Heart rate

HRQOL	Health related quality of life
HRR	Heart rate recovery
HRRv	Heart rate reserve
IL-6	Interleukin-6
IPAQ	International physical activity questionnaire
ITU	Intensive care unit
LMM	Lean muscle mass
LV-HIIT	Low volume HIIT
MABP	Mean arterial blood pressure
MCID	Minimal clinically important difference
MCT	Moderate continuous training
MD	Mean difference
MDT	Multi-disciplinary team
MET	Metabolic equivalent
MICT	Moderate intensity continuous training
MRI	Magnetic resonance imaging
MVC	Maximal voluntary contraction
NACRT	Neo-adjuvant chemo-radiotherapy
NCAT	National Cancer Action Team
NELA	National emergency laparotomy audit
NIBP	Non-invasive blood pressure
PGC-1alpha	Peroxisome proliferator-activated receptor-gamma co-activator-1-alpha
P-POSSUM	The physiological and operative score for enumeration of mortality and morbidity
Q	Cardiac output
QoL	Quality of life
RARP	Robotically assisted radical prostatectomy
RBP	Resting blood pressure
RCP	Respiratory compensation point
REHIIT	Reduced exertion HIIT
RER	Respiratory exchange ratio
RET	Resistance exercise training
RHR	Resting heart rate

ROI	Region of interest
ROS	Reactive oxygen species
RP	Radical prostatectomy
RPE	Rating of perceived exertion
RPM	Revolutions per minute
RT	Resistance training
RT	Resistance training
SBP	Systolic blood pressure
SD	Standard deviation
SIT	Sprint interval training
SPPB	Short physical performance battery
SV	Stroke volume
TPVR	Total peripheral vascular resistance
TUG	Timed up and go test
V	Minute ventilation
VL	Vastus lateralis muscle
VO_2	Volume of oxygen consumption
VO_{2AT}	Volume of oxygen consumption at the anaerobic threshold
VO_{2max}	Maximal volume of oxygen consumption when satisfying maximal effort requirements
VO_{2PEAK}	Volume of oxygen consumption at peak exercise
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale
WHO	World health organisation
WMD	Weighted mean difference

IV. Publications, presentations and awards

Papers

Blackwell, J. et al. (2017) ‘The efficacy of unsupervised home - based exercise regimens in comparison to supervised laboratory - based exercise training upon cardio - respiratory health facets, Physiological Reports, 5(17), p. e13390.

Quinlan, J. I. et al. (2017) ‘Muscle and Tendon Contributions to Reduced Rate of Torque Development in Healthy Older Males’, The Journals of Gerontology: Series A, 73(4), pp. 539-545.

Blackwell, J. E. M. et al. (2018) ‘Short-term (<8 weeks) high-intensity interval training in diseased cohorts.’, Med Sci Sports Exerc, 50(9), pp. 1740–1749.

Blackwell, J. E. M. et al. (2019) ‘The efficacy of "static" training interventions for improving indices of cardiorespiratory fitness in premenopausal females’, European Journal of Applied Physiology. Springer Berlin Heidelberg, 119(3), p 645-652.

Herrod, P. J. J. et al. (2018) ‘Exercise and other nonpharmacological strategies to reduce blood pressure in older adults: a systematic review and meta-analysis’, Journal of the American Society of Hypertension. Elsevier, 12(4), pp. 248–267.

Conference proceedings:

Platform presentations:

Blackwell, J.E.M. et al., 2016. Exploring the efficacy of home-based interventions for improving cardiorespiratory status in the preoperative period. In The Preoperative Association National Conference.

Blackwell, J.E.M. et al., 2017. High intensity interval training significantly improves anaerobic threshold within 28 days in the comorbid elderly. British Journal of Surgery, 105((S3)), p.64.

Blackwell, J.E.M. et al., 2017. High intensity interval training elicits improvements in cardiorespiratory fitness within 31 days in urological but not colorectal cancer patients presenting for surgery. 22nd Annual Congress of the European College of Sport Science, Ruhr, Germany.

Blackwell, J.E.M. et al., 2018. Effect of 4 weeks high intensity interval training (HIIT) on cardiorespiratory fitness and mitochondrial protein synthetic rate, in an older population with co-morbidities. British Journal of Surgery, 105(S1), p.21.

Poster presentations:

Sian, T. et al., 2018. A randomised control trial to assess the efficacy of short-term, home-based, high-intensity interval training (hit) for improving indices of cardiorespiratory fitness. British Journal of Surgery, 105((S3)), p.45.

Research Grants and Prizes:

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Outreach/ Public Engagement:

Blackwell, J. E. M. and Phillips, B. E. (2016) BBC Trust Me I'm a Doctor - Is there a short-cut to getting fit?, BBC. Available at: https://www.bbc.co.uk/programmes/articles/3nvRZxYFPxHCCvxGwmDt0cC/is-there-a-short-cut-to-getting-fit. (Appendix – Outreach / Public Engagement).

Blackwell, J. E. M. (2018) 'Time for HIIT?' Optimum Nutrition, pp. 48–49. (Appendix – Outreach / Public Engagement).

1 Introduction

1.1 Chapter focus

This chapter discusses the effect of ageing on aspects exercise physiology and related surgical considerations to decrease some of the risks associated with major intra-abdominal operations. It subsequently details the efficacy of exercise interventions for improving physical fitness in different disease groups, and how these interventions may be applied to surgical populations as prehabilitation strategies.

Introduction

1.2 The effects of an ageing population

Across the world people are living longer (United Nations, 2015). In the UK alone, between 2001 and 2011 there was an 11% increase in the population aged over 65 years old (Office for National Statistics, 2017). The median age of the UK population has increased from 33.9 years in 1974 to 40.0 years in 2014 (Office for National Statistics, 2017), with future predictions estimating a median age of 42.8 years by 2037 (Statistica, 2018).

1.2.1 Social effects of an ageing population

The UK population is also increasing in size, rising to its highest ever figure of 66 million at the 2017 mid-year estimate (Office for National Statistics, 2017), suggesting an even larger number of older adults in the future than previously anticipated (Office for National Statistics, 2017). A large, ageing population will have significant social needs, with consequent economic impact. For example, many older adults will lose physical function to the extent that they will be unable to maintain independence (Clegg *et al.*, 2013) and, if adequate family/ at-home care provision is not available, may need supportive housing (care/ nursing homes). The estimated cost to the UK of supported living in 2016 was already approximately £4.12 billion (Blood, Copeland and Finley, 2016). By 2036, over half of local authorities are projected to have 25% or more of their local population aged 65 (Office for National Statistics, 2017). However, the distribution of the ageing population varies markedly between local authorities. For example, in Derbyshire the proportion of individuals aged >65 years is higher in rural areas (Derbyshire dales 26%) than urban areas (Derby City 16%) (Office for National Statistics, 2017), with similar trends across areas of economic affluence/ deprivation (i.e. higher percentage of older individuals in more affluent areas). The population of Derby City centre has 21% of citizens aged 65 and over, with 4% of the population over 85 years old (Office for National Statistics, 2017); both above the national average for these categories (UK: 18% aged 65 and over and 2.4% aged 85 and over) (Office for National Statistics, 2017). Similarly, the local authorities within the catchment area of the Royal Derby Hospital, have slightly higher average percentages of over 65s and over 85s

than found nationally, at 30% and 6% respectively (Office for National Statistics, 2017).

1.2.2 Clinical effects of an ageing population

An ageing population also brings an increased proportion of people living with chronic disease and increasing levels of co-morbidity (Divo, Martinez and Mannino, 2014).

Co-morbidity can be defined as living with two or more chronic diseases (Guralnik, 1996), however, this is a rather simplistic way to summarize the effects of multiple chronic diseases upon a patients' physiological reserve. Instead, there is a growing use of the term 'patient complexity' amongst researchers and healthcare policy makers challenged to risk stratify the effect of multiple chronic diseases upon patient populations (Valderas *et al.*, 2009). Not all comorbidities are equal. For example, an individual with two specific comorbid conditions such as, uncontrolled insulin dependent diabetes and rheumatoid arthritis, may be significantly more complex to manage clinically than a patient with diet-controlled diabetes, hypertension and osteoarthritis, despite having numerically fewer comorbidities. Moreover, people with a diagnosed chronic disease are more likely to have further chronic diseases diagnosed; partly due to selection bias conferred by being routinely monitored for chronic disease, which makes incidental diagnosis of another more likely, but also because many chronic diseases have a causal relationship with another (i.e. hypertension and coronary artery disease) (Fillenbaum *et al.*, 2000).

1.2.3 Economic effects of an ageing population

The financial cost of an ageing population has significant economic impact, which will likely dictate spending and resource allocation within the UK. Europe is distinct from the rest of the world on its reliance on public services (such as health care and long-term care) to support its elderly population, whereas in Asia for example, family support largely provides care for the frail elderly, although this picture is changing with changing demographics in rapidly developing countries with emerging middle classes. With an ageing population comes an imbalance between 'workers' (aged 19 – 65) and social and healthcare 'consumers' (aged <19 & >65), which, if unaddressed, inevitably results in a shortfall in tax revenue required to support the elderly

population (Lee and Mason, 2017). Indeed, the financial impact of an ageing population on healthcare is alarming, with the projected cost of healthcare rising sharply with age over 65 years (Figure 1). Even though allocations for healthcare within government budgets increase each year, the per capita real spending on healthcare is projected to be lower in 2019–20 than in 2009-10 in the UK, with a £1.3 billion pound shortfall even if 2009-10 demands were maintained (Luchinskaya, Simpson and Stoye, 2017).

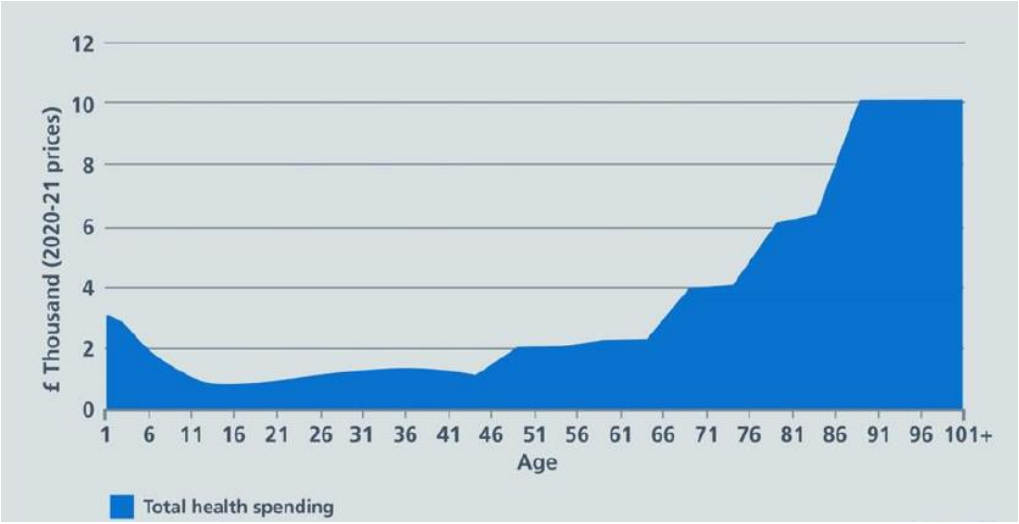


Figure 1 - Projected health care spending to rise sharply with age (England 2017).

These healthcare costs can be attributed to a number of conditions and situations, however not all are based on specific diseases. For example, sarcopenia, the age-associated loss of muscle mass and function (Heard, Ramsay and Hildebrand, 2017), to some degree affects all adults over the age of 40. Sarcopenia is known to be associated with falls, fractures, loss of independence, mortality and morbidity (Cruz-Jentoft *et al.*, 2010; Heard, Ramsay and Hildebrand, 2017), and is associated with an estimated healthcare cost of $18.5 billion per annum in the US (Beaudart *et al.*, 2014). Therefore, given the profound economic impact of ageing and age-associated conditions, including related costs to the individual and wider society, there is a growing need to provide optimal care, not only to prolong life and reduce morbidity, but also to minimise the impact of ageing and age-associated diseases on the states and individuals economic well-being whenever possible.

1.2.4 Consequences of age-associated comorbidity

Reduced functional ability leads to increased dependence upon others (Clegg *et al.*, 2013). Independence is defined as 'the ability to make choices and to exercise control over your life, including being able to live independently with or without support' (NICE, 2015), and it is independence which is seen as paramount to maintain older people's mental wellbeing. Elderly individuals with comorbidity have reduced functional reserve across a wide range of parameters including immunity, strength and muscle mass, cognition, endocrine, cardiovascular, respiratory and renal function (Clegg *et al.*, 2013) which makes them susceptible to disproportionate impairment in functional ability should any physical insult occur. Figure 2 illustrates how individuals with a lower functional reserve prior to an insult are more likely to experience loss of independence. Equally a larger physiological insult (as represented by the red line in Figure 2) increases the chance of loss of independence and prolonged return to baseline functional status. Surgery represents such a significant physical insult, posing a unique physiological challenge to the elderly patient whose ability to respond is dependent upon the interaction of comorbidities and the natural ageing process.

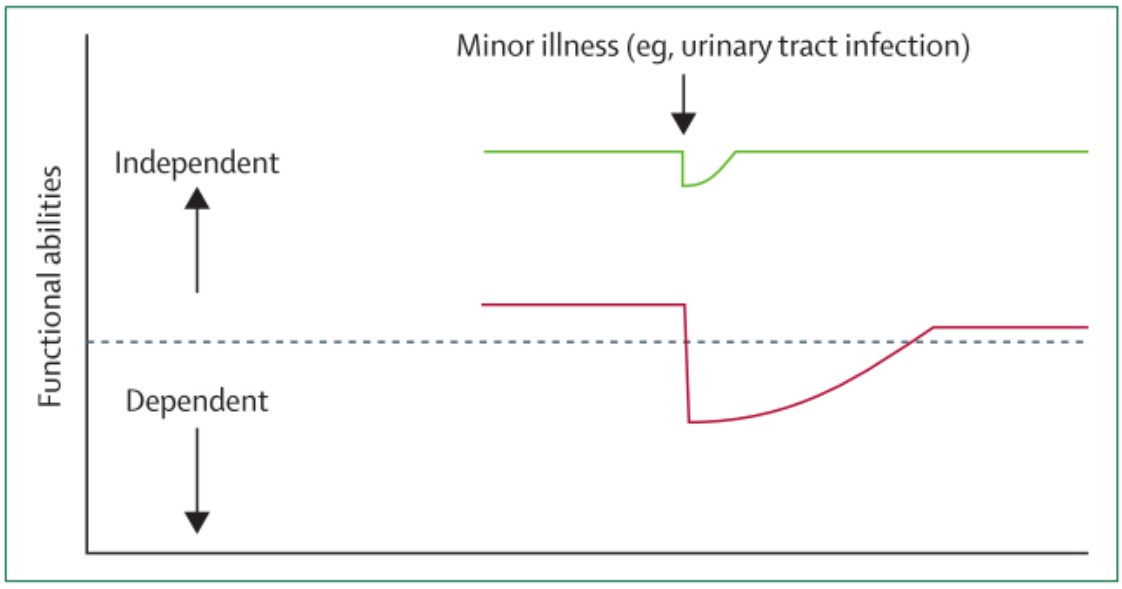


Figure 2 - Vulnerability of frail elderly people to a sudden change in health status after a minor illness (Clegg et al. 2013).

1.2.4.1 Frailty

One condition that is often considered in the context of ageing and comorbidity is that of frailty. Defined as 'a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes' (Fried *et al.*, 2001), frailty can be estimated as the proportion of deficits older adults accumulate over time (Mitnitski *et al.*, 2002). In relation to Figure 2 above, older frail adults have reduced baseline functional abilities, with every physiological insult having a large detrimental impact and a slower return to baseline.

1.2.5 Cancer

Cancer is a disease state which has increasing prevalence with age. The age group most commonly affected by cancer in 2013 – 2015 in the UK was the 85 – 89 years old age range (Cancer Research UK, 2015a).

Cancer is expensive. In England, care costs attributed to the four highest incidence cancers (colorectal, breast, prostate and lung cancer) alone amounted to £1.5 billion in 2010 (3% of total hospital care spending) (Laudicella *et al.*, 2016). There is also a financial burden for the patient; across all cancer diagnoses the patient is on average £570 worse off per month (Macmillan Cancer Support, 2014). Indeed, from a purely financial perspective, estimates of cancer treatment costs to the NHS are likely underestimating the true economic burden of cancer as they do not reflect the whole economic picture. Such calculations commonly fail to include cancer-related productivity losses from sick leave, ineffective presence in the workplace, disability, premature death, or the intangible costs associated with psychological pain and stress upon cancer patients (Tangka *et al.*, 2015).

1.3 Surgery for the older adult

The prevalence of many conditions requiring major surgery increases with advancing age (Divo, Martinez and Mannino, 2014). This, in conjunction with improving perioperative care (The Royal College of Anaesthetists, 2015), advancements in surgical technique (such as minimally invasive surgery) and the ageing population (Office for National Statistics, 2017) will lead to increased numbers of older patients being offered curative surgery for

benign and malignant conditions. Despite this, the frequency with which major surgery is offered to patients declines with advancing age, highlighted in the National Cancer Intelligence Network report 'Major surgical resections England, 2004-2006' (Department of Health, 2012) and more recently in the Dunhill Medical Trust & Royal College of Surgeons joint reports 'Access all Ages' (Royal College of Surgeons, 2012) and 'Access all Ages II' (Royal College of Surgeons, 2014). These reports highlight a stark decline in access to surgical procedures after the age of 65 years.

1.3.1 Surgery as a physiological insult

One possible reason for the reduction in surgery with advancing age is the major physiological insult of an operation and the perception that older people may not recover as well, or at all, from this. Open abdominal surgery in particular (i.e., vs. laparoscopic procedures (Carli and Schricker, 2000)), such as that commonly performed for cancer resection, exerts huge physiological strain, with increased metabolic, neuroendocrine and inflammatory demands upon the body (Tew *et al.*, 2014). Major protein catabolism is triggered by cortisol release following an increased secretion of catabolic hormones around the time of surgery, leading to significant post-operative loss of skeletal muscle (Desborough, 2000). In addition, an inflammatory cascade results in the loss of lean body tissue (Carli *et al.*, 2017), both decreasing function after surgery. There can also be as much as a 40% increase in post-operative oxygen demand following major abdominal surgery (Older and Hall, 2004); this represents a significant demand for all patients, but especially so for older (potentially comorbid and/ or frail) adults with reduced physiological reserve.

1.3.2 Surgical access with advancing age

For many age-associated conditions including cancer, surgery offers the only curative treatment. There is little doubt that factors contributing to older people not being offered curative surgery are complex and varied (Royal College of Surgeons, 2012). However, a common reason to not offer surgery is the observed decrease in physical function with advancing age (Huggett, Connelly and Overend, 2005; Carlisle, 2012). Indeed, limitations in aerobic capacity have repeatedly been shown to affect outcome after major surgery, with diminished peak oxygen uptake (VO_{2PEAK}) and oxygen uptake at anaerobic threshold (VO_{2AT}), as assessed by cardiopulmonary exercise

testing (CPET), both increasing the risk of post-operative mortality and morbidity (Older, Hall and Hader, 1999; Carlisle and Swart, 2007; Smith *et al.*, 2009; Agnew, 2010; Snowden *et al.*, 2010; Hennis, Meale and Grocott, 2011; Lai *et al.*, 2013; Older, 2013; West, Parry, *et al.*, 2014; West, Lythgoe, *et al.*, 2014; Levett and Grocott, 2015). However, although chronological age is independently associated with mortality after surgery (Turrentine *et al.*, 2006), it is not a precise measure of physical performance or health (Mitnitski *et al.*, 2002; Phillips *et al.*, 2013; Sood *et al.*, 2015) and as such physical function is often erroneously evaluated by a surgical team via either a non-objective assessment of physical performance and/ or chronological age (Grocott and Pearse, 2010; Carlisle, 2012; Levett and Grocott, 2015). This in turn promotes the view that elderly individuals are unable to withstand the insult of major surgery (Carlisle *et al.*, 2012) and likely influences access to surgery in this age group. Reduced access to surgery may in part contribute to the steep decline in survival rates after the age of 70 years seen in most cancers; for example, for all bowel cancer diagnoses, the 5-year survival is 65% in 60-69 year-olds, while in the over 80 year old age group 5-year survival drops to 43% (Office for National Statistics, 2012).

1.3.2.1 Exercise training and surgical access with advancing age

Fitter people do better after surgery overall. Interventions to improve physiological function of older adults, so that they may be viewed as fit enough for surgery both subjectively and objectively could be both far-reaching and significant, with the potential to have more elderly patients offered operations and to minimise the postoperative catabolic impact to improve recovery. Therefore, this thesis will explore a novel exercise intervention strategy for improving preoperative physiological function *per se* using older comorbid individuals (Chapter 5) and within a clinical group of patients with urological cancer (Chapter 6).

1.4 Exercise Physiology

1.4.1 Physical activity vs. exercise

The terms "exercise" and "physical activity" are often used, interchangeably. However, they are different: physical activity is bodily movement produced by skeletal muscles that results in varying amounts and rates of energy expenditure, whereas exercise is a specific form of physical activity that is

structured and repetitive, with the goal of improving or maintaining physical fitness, function, or health (Stutts, 2002). It is of course possible to perform both physical activity and exercise for varying durations and in different formats at different intensities, further blurring the boundaries between these two categories. However, for the purpose of this thesis we will define exercise as a structured intervention delivered in an attempt to improve physiological function, and physical activity as the habitual movement taken outside of the prescribed exercise sessions.

1.4.2 Physiological responses to exercise

Exercise training, especially that of a dynamic nature, is widely accepted as a way of improving physical function and/ or fitness (Whyte, 2006). There are many known methods available to test these variables (Winter *et al.*, 2006). These concepts are discussed later in this chapter. The rationale behind exercise induced changes in physical function is that the physiological responses that occur in response to an acute bout of exercise do, over time, with repeated exposure to an exercise stimulus, result in physiological adaptation (Whyte, 2006).

1.4.2.1 Cardio-respiratory responses to exercise

During dynamic exercise there is increased demand for blood supply to muscle, to provide oxygen and nutrients whilst clearing waste products and carbon dioxide (McLaughlin, Stamford and White, 2007). One way of meeting this increased demand is to increase cardiac output (Q), which is the volume of blood pumped by the heart in set time period, commonly represented as litres per minute (L/min). Normal cardiac output for a 70kg reference male is ~5 L/min (McLaughlin, Stamford and White, 2007). Cardiac output is dependent upon two physiological variables; the stroke volume ((SV): volume of blood ejected from the heart every beat (ml)) and the heart rate (HR: beats per minute (BPM)) as seen in the equation below:

$$\mathbf{Q = HR \times SV}$$

Cardiac output may rise four fold during intense aerobic exercise (McLaughlin, Stamford and White, 2007). This increase is primarily met by increasing the heart rate (e.g. 70 BPM to 180 BPM), and to a lesser extent

by increasing the stroke volume (from ~70ml to ~100ml). The relationship between stroke volume and cardiac output is principally governed by the Frank-Starling Law of the heart, which states that force of contraction is proportional to the initial length of the cardiac muscle fibre (Starling and Visscher, 1926). In the context of the heart, cardiac muscle fibre length is dependent upon the preload, or filling volume of the heart (end diastolic volume), with the Frank-Starling law implying that the subsequent force of cardiac contraction increases with stretch of the ventricle to increase SV and hence avoid congestion within the heart (Figure 3).

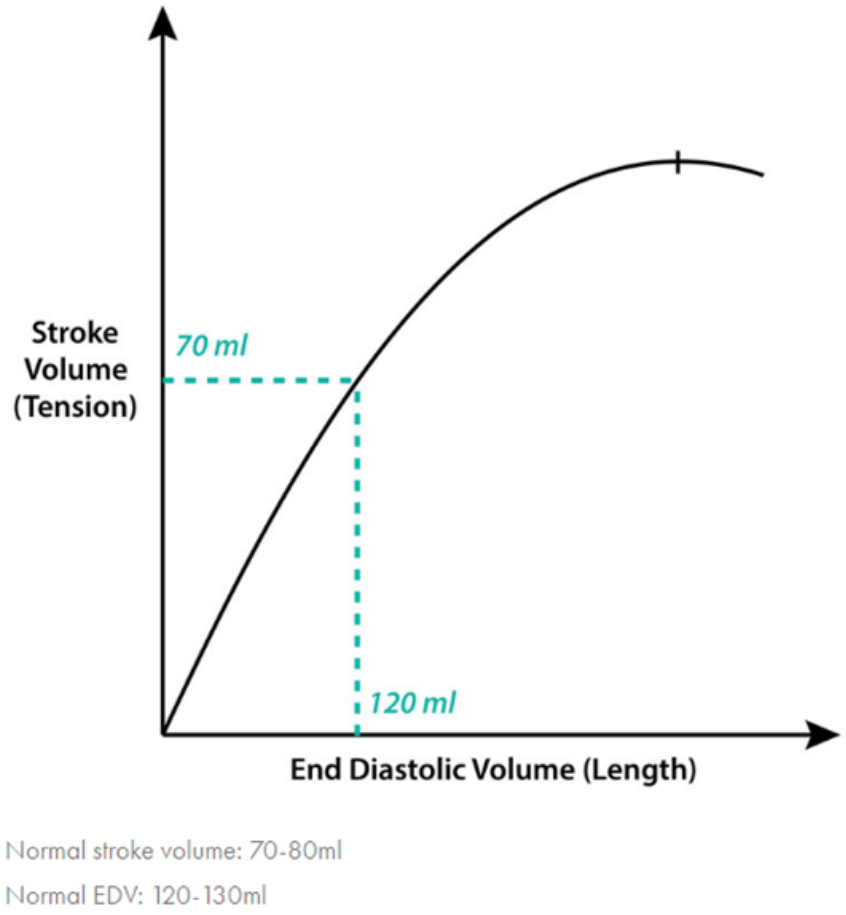


Figure 3 - Frank Starling Mechanism of the heart (Murali, 2018).

This law holds true until very high heart rates when the time for ventricular filling is so short (diastole) that only lower end diastolic volumes can be reached, leading to less stretch and in turn to less ventricular contractility, resulting in a lower stroke volume. During this type of dynamic exercise venous return to the heart is also increased to match the demand for increased cardiac output. This occurs due to muscular contraction (muscle

pumps in legs, especially calf muscles when walking/ running) and an increased respiratory rate (which reduces the intra-thoracic pressure upon the vena cava and allows increased venous return).

Alterations in blood pressure (BP) also occur with dynamic exercise modalities. BP links to cardiac output in that it is a factor of cardiac output and total peripheral vascular resistance (TPVR; the resistance to flow across all the vessels of the systemic circulation (McLaughlin, Stamford and White, 2007)) as shown below:

BP = Q x TPVR

Changes in BP occur during dynamic exercise as there is local vasodilation within muscle beds to allow increased delivery of blood to tissues, facilitating the delivery of oxygen and nutrients and the clearance of metabolic by-products. During intense dynamic exercise, skeletal muscle may consume up to 70 times more oxygen than at rest, which can equate to ~80% of total cardiac output (McLaughlin, Stamford and White, 2007).

During this time the maintenance of mean arterial pressure (MABP; the point on the blood pressure curve that, if one were to draw a horizontal line across the curve, would give two equal areas above and below that line (McLaughlin, Stamford and White, 2007) is essential for adequate cerebral perfusion. This is achieved by exercise-related vasodilation being compensated for by increasing cardiac output, thereby maintaining MABP.

It is systolic blood pressure (SBP; the maximal pressure exerted on the arterial wall during systole (contraction) (McLaughlin, Stamford and White, 2007)) that tends to rise during exercise while diastolic blood pressure (DBP; the lowest pressure exerted on the arterial wall during diastole (relaxation) (McLaughlin, Stamford and White, 2007)) falls slightly resulting in minimal changes to MABP across a wide spectrum of exercise intensities.

There is also an increase in minute ventilation (V), or total volume of air expired per minute, during dynamic exercise to meet oxygen demand (this is not to be confused with aerobic or anaerobic respiration which describe the different types of energy production as discussed later in this section). Minute ventilation is first increased via larger tidal volumes (by increased depth of breathing) and later by increased frequency of breathing (ventilation rate). To match demand, minute ventilation can rise from 6 L/min at baseline to 100 L/min during exercise, this is achieved by increasing

tidal volume and/ or ventilation rate (McLaughlin, Stamford and White, 2007).

1.4.2.2 Energy production

The muscle contraction component of exercise requires the conversion of chemical energy into mechanical work (Barrett and Ganong, 2012). If the energy source runs out then contractility decreases and ultimately ability to continue the exercise reduces and then ceases. There are a number of metabolic pathways in the human body which utilise different substrates to create energy. In health, the principle mechanisms of energy production are outlined below.

Fundamentally, there is a requirement for production of adenosine triphosphate (ATP) which is required to drive the molecular basis of muscle contraction. During normal activities of daily living at minimal exertion levels, the muscle cell metabolises free fatty acids to produce the required energy. Once exercise intensity increases, free fatty acid metabolism cannot supply energy fast enough and the cell must start to utilise carbohydrates as an alternative substrate. During exercise the majority of energy required for ATP re-synthesis comes from the conversion of glucose to CO_2 and H_2O in the presence of ample oxygen. This is called aerobic glycolysis (or oxidative metabolism of carbohydrates) (Barrett and Ganong, 2012). The breakdown of carbohydrate (glucose or glycogen) produces large amounts of ATP from ADP (Figure 4), as is shown in the equation below:

$$\textbf{Glucose } (C_6H_{12}O_6) + 2\ ADP \rightarrow 6\ CO_2 + 6\ H_2O + 40\ ATP$$

The end product of aerobic glycolysis is a molecule called pyruvate. If there is ample oxygen present then pyruvate enters the tricarboxylic acid (or Krebs) cycle as shown below (Figure 5).

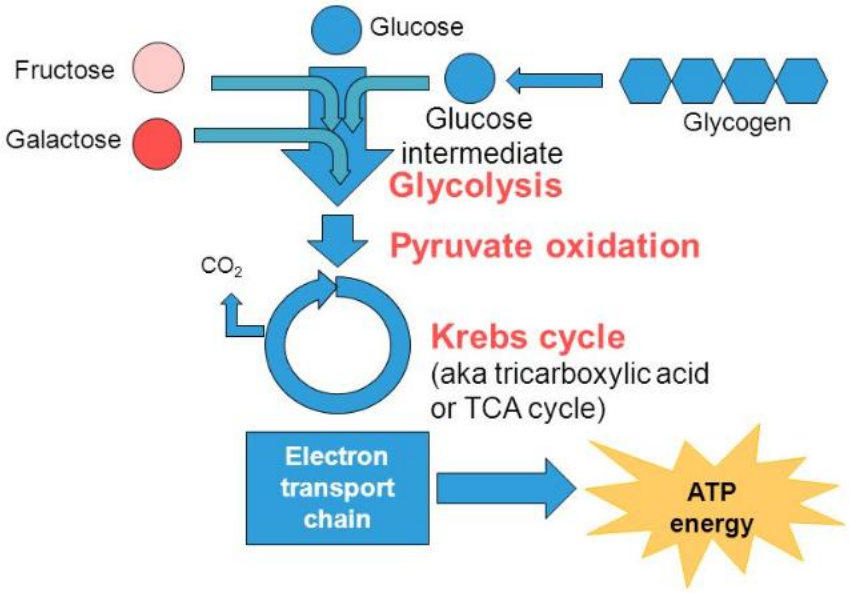


Figure 4 - Normal carbohydrate metabolism for the production of ATP (Berg et al., 2002).

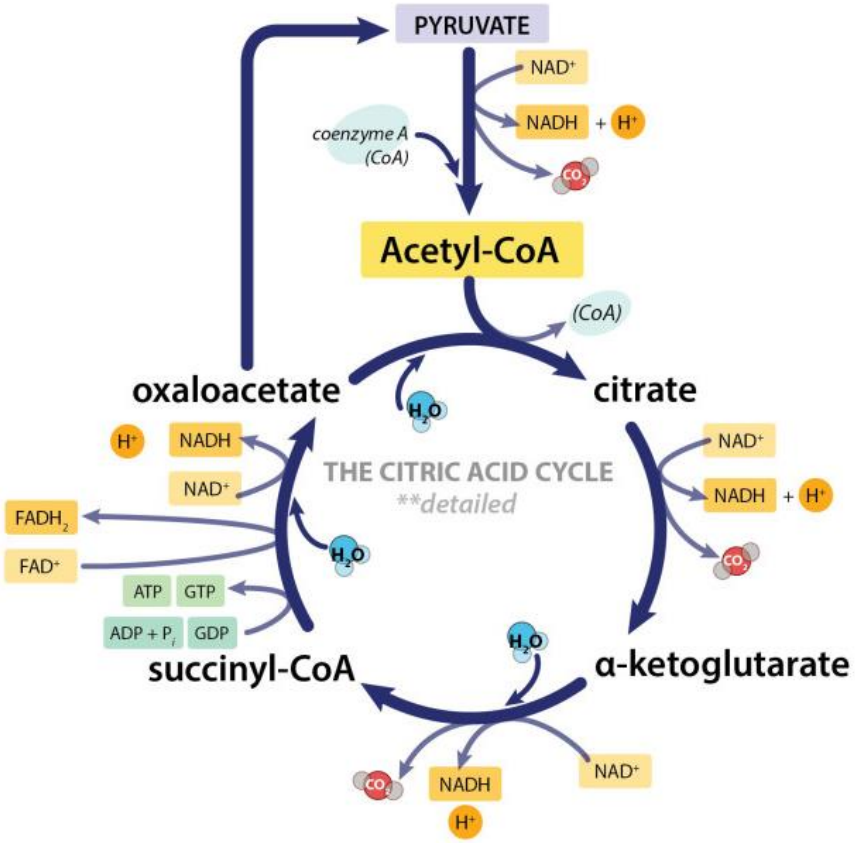


Figure 5 - Schematic of the release of hydrogen and carbon dioxide in the mitochondrion during the breakdown of one pyruvate molecule (adapted from McArdle, Katch & Katch , Fig 6.15) (McArdle, Katch and Katch, 2010).

Under anaerobic conditions (i.e. if there is insufficient oxygen) the pyruvate produced from carbohydrate metabolism does not enter the Krebs cycle but instead is reduced to lactate. This pathway yields far less ATP than aerobic glycolysis:

Glucose ($C_6H_{12}O_6$) + 2 ATP → 2 Lactic acid + 4 ATP

Anaerobic reactions of glycolysis only release about 5% of the energy within a glucose molecule, with the rest of the energy only released under aerobic conditions via the Krebs cycle (as above).

Despite the reduced ATP production, anaerobic metabolism is an important energy production adjunct when exercise demand outstrips the maximum aerobic capacity of the cell. However, because of the production of lactate it is a self-limiting process. This is because lactate dissociates to lactic acid in blood plasma (Figure 6) with an acidic end product that results in inhibition of intracellular enzymes (Barrett and Ganong, 2012) and thus reduced energy production within the mitochondria.

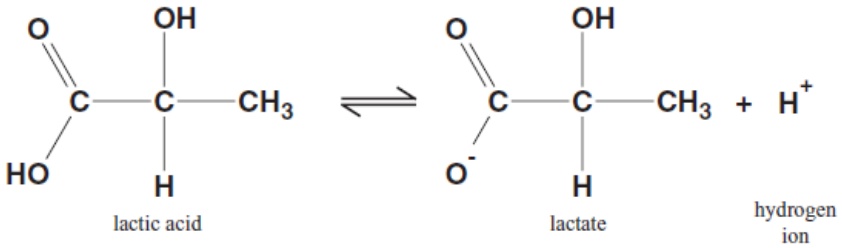


Figure 6 - The dissociation of lactic acid (Phypers and Pierce, 2006).

The point during exercise at which aerobic energy production is required to be supplemented by anaerobic mechanisms, therefore causing a sustained increase in lactate and metabolic acidosis is called the anaerobic threshold or AT (Wasserman, 1986). This term is often synonymously used with terms lactate threshold and is often deemed a measure of cardiorespiratory fitness (CRF).

1.4.3 Assessing physiological responses to exercise

1.4.3.1 Measuring the anaerobic threshold during exercise

Early work in exercise science research assessing physiological responses to exercise was based around blood lactate levels during exercise, deeming the

lactate threshold to be reached when there was a sustained increase in blood lactate above resting levels, including a non-linear increase in blood lactate of at least 1 mmol.l^{-1} (Coyle, 1995). This method of assessing exercise responses was less than ideal due to its' invasive nature requiring multiple blood draws or finger pricks to obtain blood samples. It also had limited accuracy with an accepted test-retest error of 10% (Winter *et al.*, 2006). This early work progressed to ventilatory gas exchange methods, which remain the mainstay of cardiorespiratory exercise testing (CPET) today. These methods began with the now out-dated Douglas bag ventilation collection method, which although removing the need for multiple invasive samples, had its own limitations with lengthy collection periods being required for accuracy (30-60 seconds), multiple potential sources of error during equipment set up, or environmental factors affecting derived values for VO_2 (Winter *et al.*, 2006). Within the clinical setting the Douglas bag system has almost entirely been replaced by breath-by-breath methods (such as during CPET), offering advantages in the form of determination of the VO_{2PEAK} and VO_{2AT} within a test, with minimal disruption to the participant. Additionally, this method is not only useful in healthy athletes to measure exercise performance, but also in disease groups where there is clinical need to differentiate causes of exercise performance limitation (central versus peripheral) (American Thoracic and American College of Chest, 2003; Winter *et al.*, 2006). Breath-by-breath gas exchange measurements are inherently 'noisy' due to variations in effort and depth of breathing, it is therefore important to average a number of values over a 10-15 second period (or 5 – 10 breaths) around the point of interest (Winter *et al.*, 2006).

Irrespective of the gas collection method, the physiological theory underpinning ventilatory gas exchange methods remains constant. When the AT is reached during exercise lactate accumulates in the blood. The lactate dissociation in plasma then releases hydrogen ions (H^+) which acidify the plasma creating metabolic acidosis. The Henderson-Hasselbach equation integral to human physiological systems shown below:

$$\mathbf{H^+ + HCO_3^- \leftarrow H_2CO_3 \rightarrow H_2O + CO_2}$$

In 1908 Lawrence J Henderson first wrote an equation describing the use of carbonic acid as a buffer. Later Karl Hasselbach re-expressed this formula in logarithmic terms resulting in the above Henderson-Hasselbach equation.

The simplified version of the equation above (Britannica, 2018) is helpful to understand how ventilatory gas exchange methods allow us to quantify the utilisation of oxygen and production of carbon dioxide during exercise and subsequently assess the AT. The respiratory compensation point (RCP) marks the onset of hyperventilation during an incremental exercise test (Meyer *et al.*, 2004). This is in response to not only a decreased blood pH but also muscle afferents and other sensory inputs, thus depending upon the individuals serum buffering capacity the RCP may well be at a physiologically distinct point from the AT (Meyer *et al.*, 2004).

During low intensity exercise the energy for work is delivered by complete oxidative phosphorylation, as was discussed previously. However, during higher intensity exercise where anaerobic respiration is required, the increase in hydrogen ions (secondary to anaerobic glycolysis and lactate production) pushes the Henderson-Hasselbach equation to the right thereby increasing the need for carbon dioxide to be 'blown off' (excreted from the body via the lungs) via increased ventilation. Once the respiratory centres are triggered there will be a rapid increase in the minute ventilation (or the point of hyperventilation). There can be a physical time delay between the production of lactic acid by a skeletal myocyte working anaerobically (AT) and a compensatory increased ventilatory drive with resultant increased VCO_2 (RCP) (as discussed above).

As such AT is defined, for the purpose of CPET, as the oxygen consumption above which aerobic energy production is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis (Wasserman, 1986). In addition to the development of metabolic acidosis, ventilation increases disproportionately to the metabolic requirement and a progressive tachypnea develops (Wasserman, 1986), blowing off more CO_2 to compensate, allowing the detection of a distinct point within the breath by breath data to define the point at which AT was reached. AT has recently been defined as 'the VO_2 above which arterial (lactate) first begins to increase systematically during incremental exercise, reflecting increased glycolysis' (Levett *et al.*, 2017).

1.4.3.2 Measuring maximal exercise capacity

The rate of oxygen uptake during maximal aerobic exercise is termed the VO_{2max} (McArdle, Katch and Katch, 2010). It reflects the maximum ability of

the heart, lungs and blood to transport oxygen to the muscles and also the muscles ability to utilise oxygen during exercise; this requires high levels of integration of pulmonary, cardiovascular and neuromuscular systems (McArdle, Katch and Katch, 2010). Traditionally VO_{2max} was deemed to occur when there was a plateau in oxygen consumption despite continuing increases in workload during an incremental exercise test. This is extremely physically demanding and requires self-motivation from the individual performing the test. Concerns regarding patient safety, burden of chronic disease and physical limitations contribute to the difficulty of measuring VO_{2max} in older persons with or without chronic disease (Huggett, Connelly and Overend, 2005) . As an alternative, VO_{2PEAK}; the highest rate of oxygen consumption measured during an exercise test, is often recorded as a measure of maximal exercise capacity irrespective of whether a plateau in O_2 consumption was reached. VO_{2PEAK} has been validated as an index of VO_{2max} in individuals performing a maximum-effort exercise test (Day *et al.*, 2003; Palange *et al.*, 2006).

1.4.4 Skeletal muscle

As outlined above, skeletal muscle oxygen utilisation is a component affecting maximal exercise capacity. As with the heart and lungs, skeletal muscle both responds and adapts to acute and chronic exercise.

1.4.4.1 Skeletal muscle mass

Skeletal muscle accounts for ~40% of total body weight in humans, containing 50-75% of all body proteins (Frontera and Ochala, 2015). Total body muscle mass is a value which depends upon the balance of muscle protein synthesis and degradation rates which vary in a dynamic equilibrium (Bender, 2007).

MRI is considered the 'gold standard' method to assess skeletal muscle mass, however, it is expensive, time consuming and was unavailable as a research tool for the purposes of this thesis. An accepted alternative for the assessment of skeletal muscle mass is dual-energy X-ray absorptiometry (DXA) (Heymsfield *et al.*, 2014), as DXA derived appendicular lean mass correlates highly with skeletal muscle mass quantified by MRI (R^2= 0.96) (Kim *et al.*, 2002). DXA passes two low dose x-rays of variable energy levels through the individual which allows tissue density assessment via

subtracting the received amount of x-ray from one another (Laskey, 1996). DXA allows the simultaneous assessment of lean mass, fat mass and bone mineral parameters, as well as allowing assessment of 'regions of interest' (ROI) (Boereboom *et al.*, 2016). Weight calculated by DXA and actual weight has excellent correlation and is not dependent upon other measures such as height (Laskey, 1996). As with almost all body composition measurement methods, the parameters are estimates and not measurements, however DXA has been proposed as the reference standard for measuring lean muscle mass (LMM) (Buckinx *et al.*, 2018). Any under/ over estimation of body composition components have reduced implications in longitudinal studies such as those reported in this thesis.

Computed tomography (CT) is another precise method to quantify muscle mass, however, the large radiation dose per scan (relative to DXA), largely precludes its use within research settings where there are repeated scans in often otherwise healthy volunteers. Interestingly, within clinical populations who routinely have a CT scan as part of their standard investigations, muscle mass analysis can be accurately performed to estimate whole body skeletal muscle mass (Gakhar *et al.*, 2015). The advent of next generation, low radiation dose CT scanners may change their role in measurement of muscle mass.

Ultrasound measurements correlate with muscle strength and functional capacity measures in older adults (Selva Raj, Bird and Shield, 2017). Ultrasound can be used to predict lean body mass and has good validity compared with DXA in older adults (Nijholt *et al.*, 2017). Ultrasound measures have shown high test-retest reliability (Thoirs and English, 2009) and high inter observer reliability regardless of expertise level when used for measuring quadriceps muscles (Sarwal *et al.*, 2015).

1.4.4.2 Skeletal muscle structure

As seen in (Figure 7), skeletal muscle is made up of many subunits (muscle fibres) encased within a fascial compartment. Muscle fibres are made up of many myofibrils which contain the actin-myosin muscle proteins required for the production of muscle contraction. Combining the individual actin–myosin cross-bridge forces, transmitted longitudinally and laterally within the fibre, results in generation of the force of contraction. This is dependent upon a number of other factors such as: the muscle architecture (including

pennation angle and fascicle length), muscle size, number of cross-bridges formed and the degree of neural activation (Frontera and Ochala, 2015).

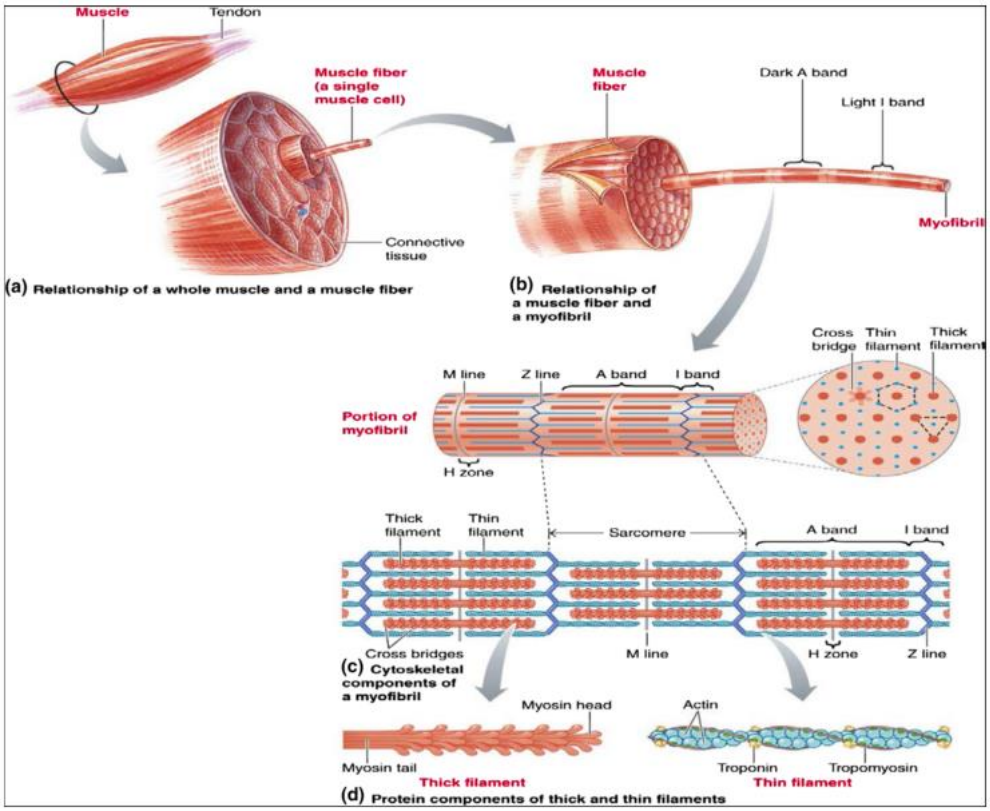


Figure 7 - Structure of Skeletal Muscle (Frontera and Ochala 2015).

1.4.4.3 Skeletal muscle function

Muscle function can be defined as the ability to 'to convert chemical energy into mechanical energy to generate force and power, maintain posture, and produce movement that influences activity, allows for participation in social and occupational settings, maintains or enhances health, and contributes to independence' (Frontera and Ochala, 2015), with skeletal muscle function having implications for activities of daily living and health ageing.

1.4.5 Skeletal muscle and cardiorespiratory interactions

During CPET the normal determinants of VO_{2PEAK}/ VO_{2max} are genetic factors (upward of 90 genes have been identified to be predictive of VO_{2max} trainability (Williams *et al.*, 2017)) and the quantity of exercising muscle (American Thoracic and American College of Chest, 2003). For example, most of the sex differences seen in VO_{2max} can be attributed to differences in fat free mass (FFM) (or lean mass), however this is difficult to assess

routinely without extra investigations (i.e. bio-impedance analysis, DXA) (American Thoracic and American College of Chest, 2003). A FFM index (FFM/height^2) can be calculated for different age and sex groups to provide additional information (Hattori, Tatsumi and Tanaka, 1997), although its relatability within clinical groups is limited due to the scarcity of its use.

In both healthy older individuals and in individuals with disease, there is a proven relationship between LMM and AT. For example, Williams *et al*., showed this relationship in both healthy older adults (Williams *et al.*, 2014) and colorectal cancer patients (Hossain *et al.*, 2012; Nyasavajjala *et al.*, 2015) (Figure 8).

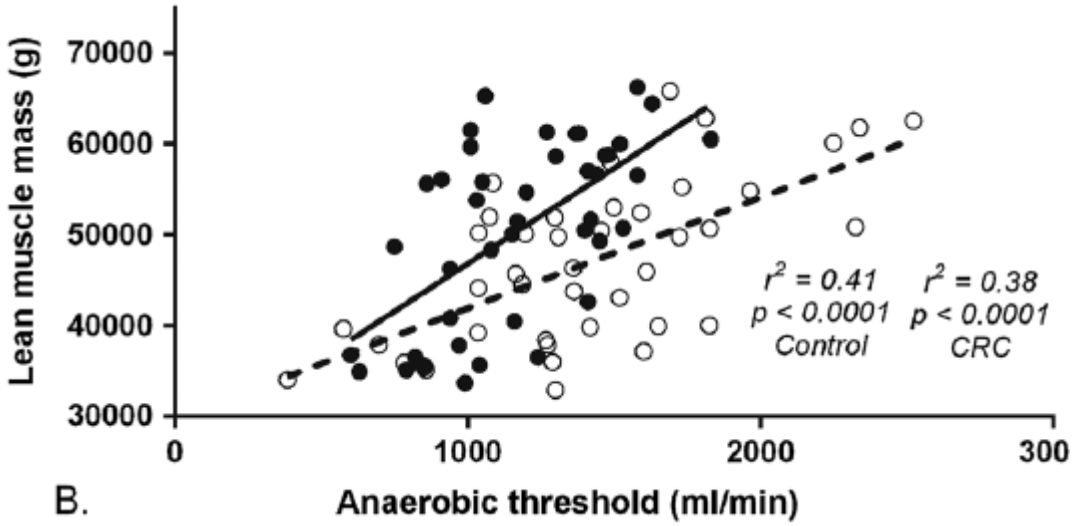


Figure 8 - Anaerobic threshold (ml/min) versus lean muscle mass (kg) Plots of anaerobic threshold (ml/min) vs. lean muscle mass (g). Open circles represent control group, while closed circles represent colorectal cancer patients (CRC) (Nyasavajjala et al., 2015).

1.5 Ageing Physiology

Most body systems (such as neuromuscular (Doherty, 2003) and cardiorespiratory fitness (Heath *et al.*, 1981)) are affected by advancing age, with many of these changes occur independently of the onset of age-associated conditions and are considered part of normal ageing physiology.

1.6 Cardiorespiratory fitness and ageing

Maximal exercise performance (VO_{2max}) declines with age (Figure 9). Males have comparatively higher values across all age groups. Sedentary individuals have lower VO_{2max} values versus active individuals within the same age range.

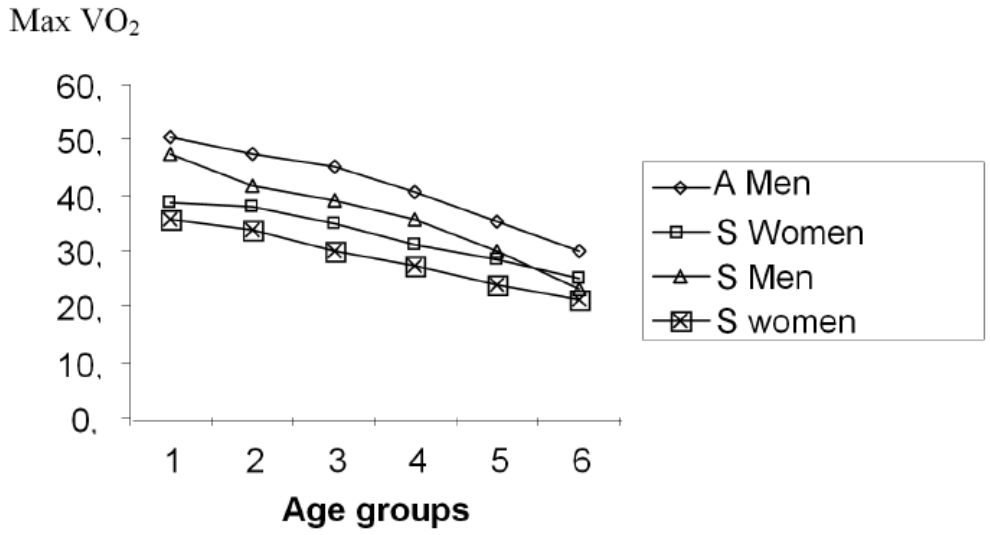


Figure 9 - VO_{2max} values (ml/kg/min) according to age. A - active patients, S - sedentary patients. Age groups (x-axis): 1 (15-24 years old), 2 (25-34 years), 3 (35-44 years), 4 (45-54 years), 5 (55-64 years) and 6 (65-74 years). Note picture taken from original publication with error as line through square should represent 'Active Women' (A Women not S Women) (Herdy and Uhlendorf 2011).

Submaximal fitness measures, such as AT, also decline with age. Figure 10 shows the declining pre-operative baseline AT with age in a large cohort of patients undergoing major abdominal surgery (Older, Hall and Hader, 1999).

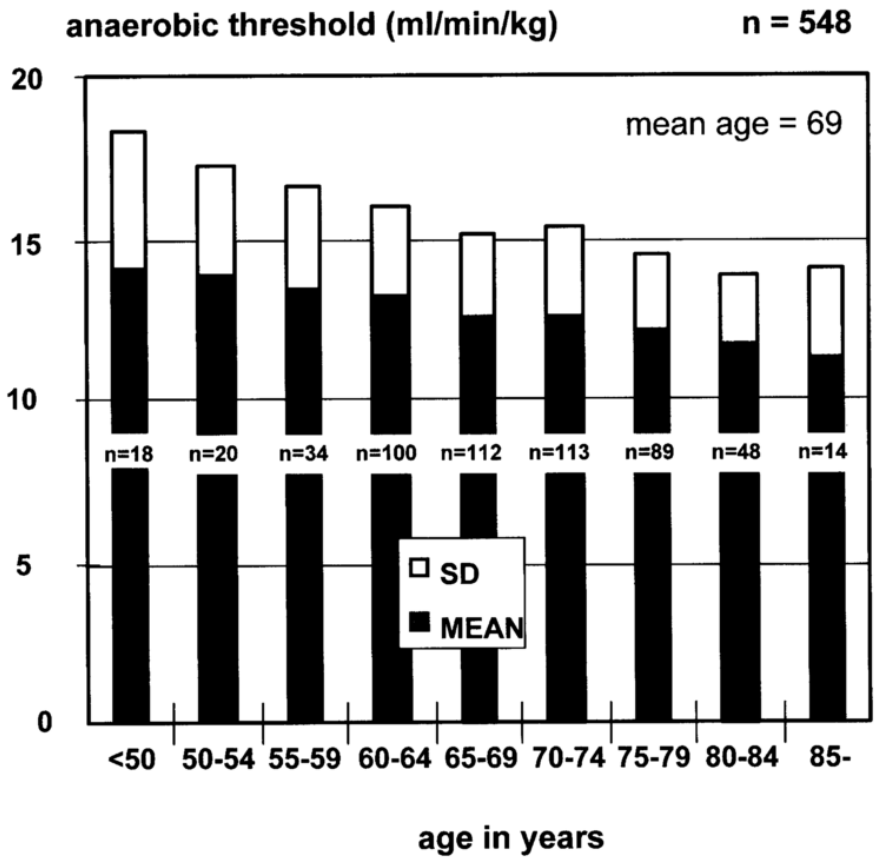


Figure 10 - Anaerobic Threshold in 548 patients presenting for abdominal surgery (Older, Hall, and Hader 1999).

1.6.1 Muscle mass and ageing

Maintenance of muscle mass and function with ageing is of paramount importance for 'healthy ageing', with significant losses of muscle mass and function described as part of geriatric syndromes (Muscaritoli *et al.*, 2010; Clark, Manini and Todd, 2012).

1.6.1.1 Dynapaenia

Dynapaenia is the age-related loss of muscle strength that is not caused by disease, which predisposes elderly adults to functional limitations and mortality (Clark, Manini and Todd, 2012). It has been proposed that muscle strength may be more important than muscle mass to estimate mortality during the ageing process (Newman *et al.*, 2006). Longitudinal studies show that muscle strength is lost more rapidly than muscle mass in later life (>75 years old) at a rate of 3-4% in men and 2.3-3% per year in women (Mitchell *et al.*, 2012). Comparatively, muscle mass is lost at a rate of 0.64%-0.7% in women and 0.8-0.98% in men (Mitchell *et al.*, 2012).

1.6.1.2 Sarcopaenia

Sarcopenia is a condition characterized by losses of muscle mass and muscle strength with age (Muscaritoli *et al.*, 2010), with the most commonly utilised definition and clinical classifications those developed by the European Working Group on Sarcopenia (EWGOS) as seen in Figure 11 and Figure 12 (Cruz-Jentoft *et al.*, 2010).

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)
1. Low muscle mass
2. Low muscle strength
3. Low physical performance

Figure 11 - EWGSOP Criteria for the diagnosis of sarcopenia (Cruz-Jentoft et al., 2010).

Stage	Muscle mass	Muscle strength		Performance
Presarcopenia	↓			
Sarcopenia	↓	↓	Or	↓
Severe sarcopenia	↓	↓		↓

Figure 12 - EWGSOP conceptual stages of sarcopenia (Cruz-Jentoft et al., 2010).

Sarcopenia can be directly responsible for functional impairment with loss of strength, reduced autonomy and increased likelihood of falls (Janssen, Heymsfield and Ross, 2002). Sarcopenia prevalence in the older population has been reported as between 4 and 27% depending upon study, gender and country (Frontera and Ochala, 2015). For patient groups, poorer clinical outcomes have been shown amongst sarcopaenic patients having surgical resection for different cancers (colorectal (Lieffers *et al.*, 2012), bladder (Psutka *et al.*, 2014), lung (Hervochon *et al.*, 2017), hepatic (Harimoto *et al.*, 2013), pancreatic (Peng *et al.*, 2012)). Sarcopenia at cancer diagnosis is also associated with worse survival in those with solid tumours (Shachar *et al.*, 2016). Sarcopenia may be modifiable within the preoperative period, which may in turn reduce length of stay and post-operative morbidity and mortality (Heard, Ramsay and Hildebrand, 2017). In longitudinal follow-up,

some elderly individuals have maintained muscle strength, despite reduced muscle mass, which is likely associated with daily activity levels and individual muscle fibres compensating for loss of size and number of muscle fibers (Frontera *et al.*, 2008). However, this is not a universal finding and has led to investigation of the architectural characteristics of muscle (Franchi *et al.*, 2014) and its intrinsic components including the reduction in satellite cells (skeletal muscle stem cells) essential for muscle growth and repair in the elderly (Verdijk *et al.*, 2006). Muscle strength declines by approximately 15% between 60 and 70 years old and then by a further 30% in the decades thereafter (Mazzeo *et al.*, 1998). There are also age related losses of mitochondria (Broskey *et al.*, 2014) and reduced excitation-contraction coupling (Weisleder *et al.*, 2006), both of which may go some way to explain reduced exercise capacity and response to training with ageing.

1.6.2 Risk stratification in surgical patients

The National Confidential Enquiry into Perioperative Deaths (1999) reported that in the UK the risk of death within 30 days of any operation is between 0.7% and 1.7% (Callum *et al.*, 1999). In larger more recent studies, such as the European Surgical Outcomes Study (EuSOS), the UK mortality rate from non-cardiac surgery is reported as 1.6%. Outside Europe 30 day mortality rates are thought to be between 1.3 and 2.0% (Pearse *et al.*, 2012). A number of methods can be used to quantify risk, either independently, or combined with each other. These are outlined below.

1.6.2.1 Subjective assessment and functional fitness scores

Subjective assessment of surgical risk is carried out by a range of medical professionals involved in surgical patients care. The ability to carry our activities of daily living is fundamental to maintaining elderly patients' independence and quality of life (Bozkurt, Yılmaz Rn and Yilmaz, 2016). This requires a certain level of 'functional fitness' which can be defined as having the physiological capacity to perform normal everyday activities, safely and independently, without undue fatigue (Santos *et al.*, 2012). Crudely surgeons often ask screening questions of a patient to assess functional fitness such as "do you do your own shopping?" or "can you walk up a flight of stairs?", with the commonly held belief amongst surgeons that if a patient can walk up 2-3 flights of stairs then he or she can survive surgery (Enright, 2003). More recent data suggests that subjective assessment has 19·2%

sensitivity (95% CI 14·2–25) and 94·7% specificity (95% CI 93·2–95·9) for identifying the inability to attain four metabolic equivalents during formal exercise testing (Wijeysundera *et al.*, 2018). This type of screening is based upon anecdotal experience of the surgeon, representing an over simplified assessment which does not provide any objective data about physiological reserve, and ideally would have no place within modern medicine other than to screen for undiagnosed functional limitation.

We also know that patients differ in their ability to reliably estimate their own functional capacity (Enright, 2003). Without the use of objective assessment, surgeons and anaesthetists alike, mistakenly use age as an objective measure for physiologic reserve (Canter *et al.*, 2015), despite age having previously been argued not to be a discriminator of mortality (Older, 2013). Conversely, when using invasive cardiac catheter investigation on 148 patients deemed fit for surgery via standard assessment, 23% of patients were shown to have advanced pathological/ functional defects negating a general anaesthetic and major surgery as a treatment option (Del Guercio and Cohn, 1980). All of the patients within this group who went on to have the planned operation died.

There are several functional fitness measures used both in pre-operative research and clinical settings. The Short Physical Performance Battery (SPPB) (Guralnik *et al.*, 1994), six minute walk tests (6-MWT) (Enright, 2003) and the 'Timed up and go test' (TUG) (Podsiadlo and Richardson, 1991) can all easily be performed in clinic to inform the pre-operative assessment process, allowing comparison of an individual's functional performance to population norms.

1.6.2.2 Risk Scores

There are a number of pre-operative scoring systems available, often available in web-based formats. This type of risk prediction in clinic allows for ample perioperative planning and potential optimisation of patients identified at this point in their surgical journey. Early risk prediction scoring also aids clinicians in obtaining fully informed consent from the patient (Smith, Jason., Tekkis, 2018).

The Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity (P-POSSUM) was originally designed for aiding surgical audit across different surgeons and sites as it reliably produces a valid assessment

of mortality and morbidity from an operation (Copeland, Jones and Walters, 1991). It encompasses age, cardiac signs, respiratory history, blood pressure, heart rate, Glasgow coma scale, pre-operative haemoglobin, white cell count, kidney function and electrocardiogram changes. P-POSSUM is often used within the emergency setting and can help compare the observed/ expected death ratio of a particular hospital. Data from this scoring system has recently been incorporated within the National Emergency Laparotomy Audit (NELA) Risk Adjustment tool to predict 30-day mortality from emergency surgery (HQIP, 2017), although there is clearly no opportunity to modify cardiorespiratory risk factors prior to unplanned emergency operation. P-POSSUM includes operative variables such as expected blood loss and intra-operative contamination level, requiring a degree of surgical expertise to use the tool effectively. In specialties other than general surgery, alternative risk scores are widely used. For example, in orthopaedics the Nottingham Hip Fracture Score (Moppett *et al.*, 2012) is commonly used. Many risk prediction tools are now available online for ease of use (e.g. www.riskprediction.org.uk, www.sortsurgery.com, www.riskcalculator.facs.org /riskcalculator) with bodies, such as The Royal College of Surgeons, recommending that they should routinely be used to aid consultation with patients regarding surgical intervention (RCS, 2008).

The risk prediction tool used for patient selection within this thesis is the American Society of Anaesthesiologists (ASA) Grade (American Society of Anaesthesiologists, 2014). ASA grade can be used to risk-stratify 'all comers' peri-operatively as seen in Table 1 (American Society of Anaesthesiologists, 2014). Higher ASA grades are associated with increases in mortality (Prause *et al.*, 1997; Turrentine *et al.*, 2006). ASA is the most routinely used risk stratification system pre-operatively, however it has come under criticism for being too crude, particularly in the very elderly (Visnjevac and Nader, 2013). Strengths of the ASA grade include: i) the strong correlation of patient outcomes with preoperative ASA grading (Davenport *et al.*, 2006), ii) its wide clinical use within the NHS, and iii) its' easy administration to all patient groups. Interestingly, the TUG (mentioned above), used in conjunction with the ASA grading, identifies twice as many onco-geriatric patients at risk of post-operative complications than ASA used in isolation (Huisman *et al.*, 2014). This shows how generic scoring systems can be combined with individualised performance data to increase the accuracy of risk scoring.

Table 1 - ASA Physical Status Classification System, last approved by the ASA House of Delegates on 15th October 2014 (American Society of Anaesthesiologists 2014). Abbreviations: BMI – body mass index, DM – diabetes mellitus, HTN – hypertension, COPD – chronic o obstructive pulmonary disease, MI – myocardial infarction, CVA – cerebrovascular accident, TIA – transient ischaemic attack, CAD – coronary artery disease, DIC – disseminated intravascular coagulation, ARD – acute renal disease, ESRD – end stage renal disease.

ASA Classification	Definition	Examples, including, but not limited to:
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Examples: current smoker, social alcohol drinker, pregnancy, obesity (30 > BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples: poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples: recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

1.6.3 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) provides 'a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, haematopoetic, neuropsychological and skeletal muscle systems' (American Thoracic and American College of Chest, 2003). Therefore, CPET provides a reproducible and objective reflection of 'global' physical fitness (Older, 2013).

This is the gold standard clinical investigation in cases of exercise limitation with diagnostic uncertainty (Ferrazza *et al.*, 2009). Clinically, occult heart failure is responsible for the majority of post-operative complications, not myocardial ischaemia as previously thought (Older, 2013), thus CPET has greater clinical relevance than an exercise electrocardiogram (ECG) (i.e., treadmill test) alone which may detect myocardial ischaemia (whereas CPET is capable of detecting both). CPET is clinically indicated in elderly patients having major abdominal surgery (Weisman and Zeballos, 1995) and can be used across a wide range of patient subgroups (American Thoracic and American College of Chest, 2003). CPET is usually performed upon a static cycle ergometer, another advantage over treadmill exercise testing as it allows safe testing over a wide range of patient groups. Although it is well known that maximal values obtained by whole body exercise testing methods (i.e. treadmill running) are higher than those obtained by cycle-ergometry (Keren, Magazanik and Epstein, 1980), the majority of research within clinical populations use cycle-ergometry CPET as it can be used by almost all patient groups. There are however, some specific clinical groups (e.g. lower limb joint limitation or very large body mass index (BMI)) for whom cycle based testing is not appropriate and perform arm-crank CPET (Mitropoulos *et al.*, 2017) as an alternative to cycling. Cycle ergometry CPET, reported as ml/kg/min, is the widest used within the literature therefore providing the best comparison of research findings. This is despite concerns that have been raised with regard to obese patients recording relatively lower VO_{2PEAK} values when they are expressed relative to weight versus absolute values (L/min) (American Thoracic and American College of Chest, 2003).

1.6.3.1 Determining anaerobic threshold via cardiopulmonary exercise testing

CPET provides continuous data which is usually displayed graphical format, commonly known as the Wasserman 9-panel plot (Figure 13), named after American Physiologist Karlman Wasserman.

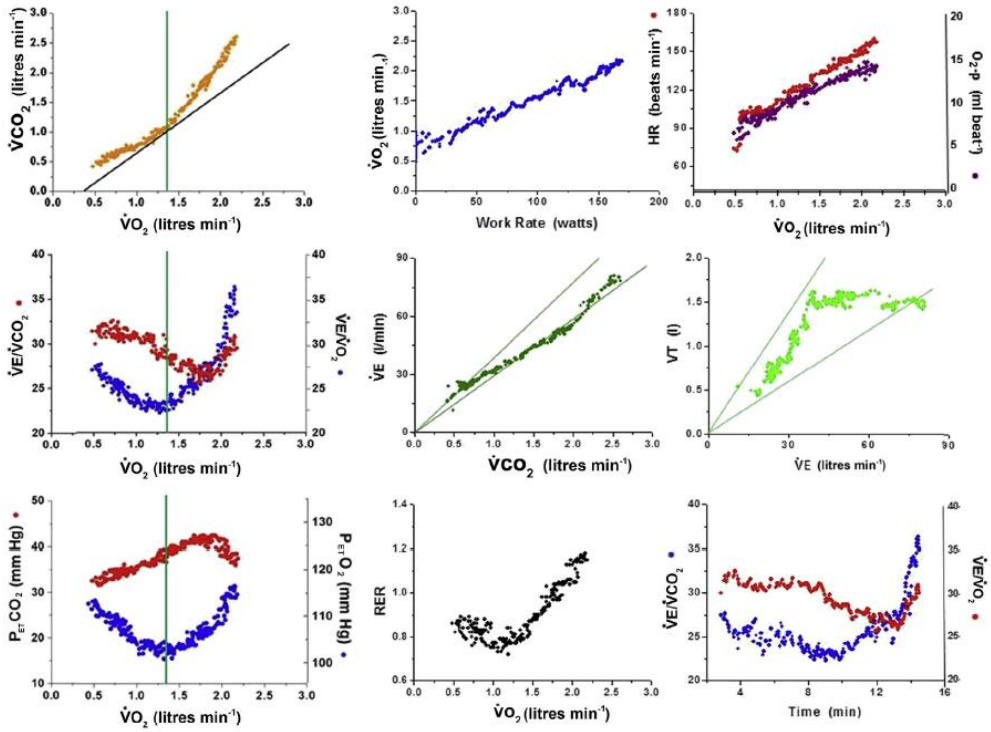


Figure 13 - Example of a Wasserman nine-panel CPET display for a normal individual (Levett et al., 2017).

Using breath by breath data it is possible to derive a value for the anaerobic threshold retrospectively after a CPET is completed. Although now slightly rudimentary, the original paper by Beaver et al (1986) clearly demonstrates how breath by breath data can be used to derive AT (Beaver, Wasserman and Whipp, 1986). As seen in Figure 14, the VO_2 rises linearly throughout a ramp test in response to linearly increased demand. As discussed above, the CO_2 production increases greatly following AT, this is seen in Figure 14 as narrowing in the gap between the VO_2 and VCO_2 curves toward the 30 minute mark. Using this graph it would be difficult to accurately say when the carbon dioxide production starts to rise out of proportion to oxygen uptake.

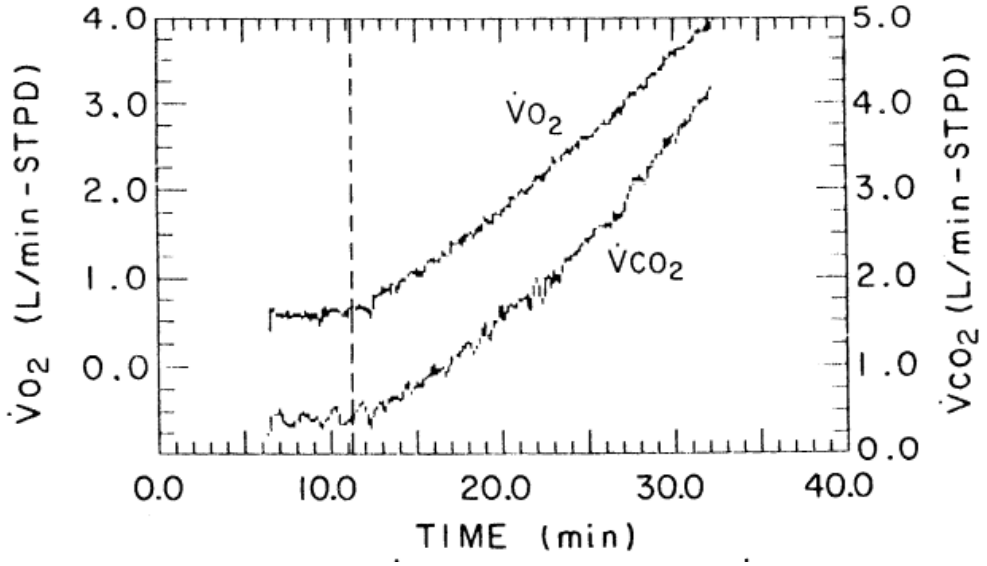


Figure 14 – Carbon dioxide production (VCO_2) and oxygen uptake (VO_2) vs. time for a 15 Watt incremental ramp exercise test (Beaver, Wasserman and Whipp, 1986).

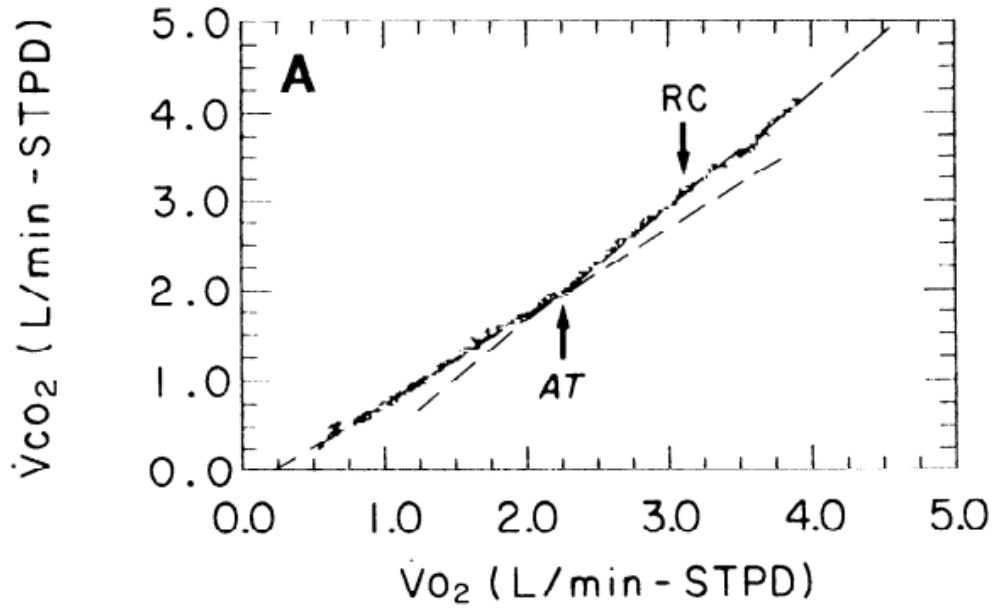


Figure 15 - CO_2 production (VCO_2) vs. O_2 uptake (VO_2) from figure above (Beaver, Wasserman and Whipp, 1986).

Using the same data but presented in the format shown in Figure 15 however, where VCO_2 is plotted against VO_2, there is an initial straight line where the increases in VO_2 utilisation are proportional to VCO_2 production. Then as anaerobic threshold is passed, the carbon dioxide production rises significantly compared to the O_2 utilisation, resulting in a second straight line relationship on the graph. A clear 'break point' or 'inflection point' on the

graph is seen where the two lines intersect, and the AT is found at this point. This is called the V-Slope Method (Beaver, Wasserman and Whipp, 1986; Wasserman, 1986; American Thoracic and American College of Chest, 2003). However, it does have inherent inaccuracies if used alone. For example it is important to ensure that any early aberrant data, during the early exercise 'kinetic phase' prior to aerobic equilibrium, is excluded from the initial line of best fit as this could lead to a false break point being identified.

Recent guidelines suggest a composite method using the V-slope principles in addition to ventilation data to more accurately define the AT (Figure 16). Ensuring that the V-Slope method 'agrees' with the ventilatory equivalents methods should ensure a more accurate derivation of AT, particularly in cases where the intersection of lines via V-Slope sits between individual data points.

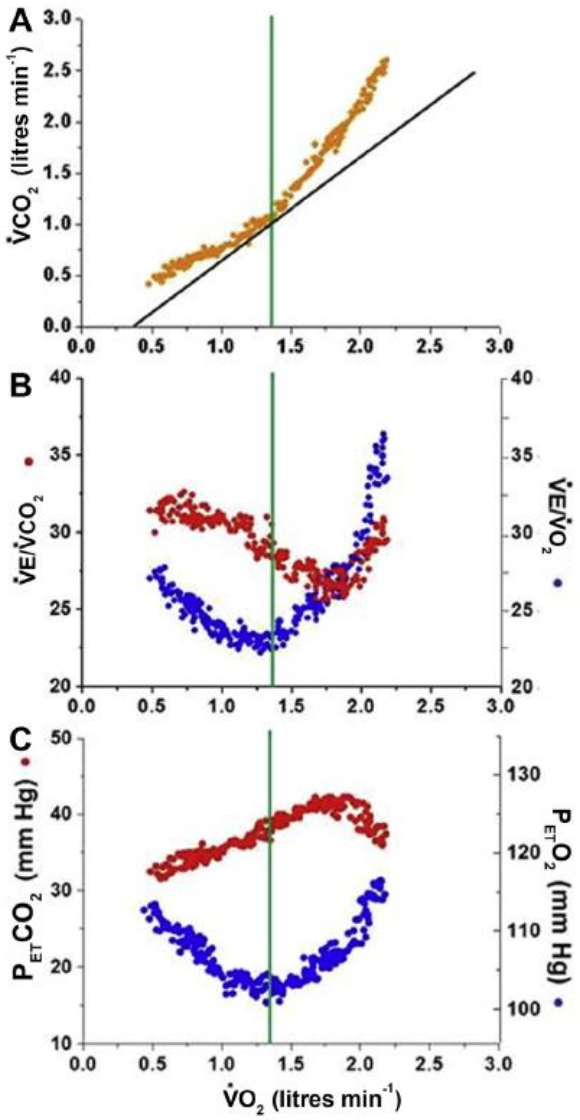


Figure 16 - Synchronous analysis of the AT using the V-slope methods with validation using both the ventilatory equivalents and end tidal values to validate AT derivation. Image taken from the POETTS 2018 guidelines on CPET interpretation (Levett et al., 2017).

1.6.3.2 Using cardiopulmonary fitness measures to predict surgical risk

In 1993 an Australian intensivist, Paul Older published a paper (187 patients, mean age 70 years old) showing that a pre-operative anaerobic threshold (derived from CPET) of <11 ml/kg/min was associated with a mortality rate of 18% in elderly individuals having major surgery (Older *et al.*, 1993), versus a mortality rate of 0.8% in those with AT >11 ml/ kg/min. This mortality figure rose sharply to 42% if there was associated myocardial ischaemia present on pre-operative CPET in those with low baseline AT. He concluded that AT is not predictable from the age of the patient, that age

should not be a barrier to CPET testing and that patients with a preoperative AT<11 ml/kg/min should be admitted to intensive care pre-operatively for optimisation *before* surgery (Older *et al.*, 1993).

In 1999 the same group analysed 548 elderly patients scheduled for major surgery. They stratified in-hospital management by pre-operative CPET parameters with AT <11ml/kg/min admitted to ITU, AT>11 ml/kg/min but with myocardial ischaemia admitted to HDU and AT >11 ml/kg/min but with no myocardial ischaemia admitted to the normal ward post-operatively. The overall mortality in this study was 3.9%, with 43% attributable to poor cardiopulmonary function detected preoperatively. Notably, no cardiopulmonary attributable deaths occurred in the cohort deemed fit for ward management (Older, Hall and Hader, 1999). It is not, however, possible to know if ITU admission improved outcomes as this was not a randomised control trial. CPET used preoperatively in this context seems to identify low risk patients suitable to be post operatively managed on a normal ward.

Since this time there have been many retrospective studies looking to use pre-operative CRF to predict peri-operative risk in major surgery. These studies have shown that CPET is able to identify high-risk patients in colorectal surgery (Chan *et al.*, 2015) and those at higher risk of post-operative complications (Lai *et al.*, 2013; West, Lythgoe, *et al.*, 2014). They have also shown that low pre-operative CRF prior to elective abdominal aorta repair reduces post-operative and mid-term survival (Carlisle and Swart, 2007; Grant *et al.*, 2015), with increased post-operative complications (Barakat *et al.*, 2015). Similarly, radical cystectomy patients with low preoperative CRF have both increased length of stay (Tolchard *et al.*, 2015) and post-operative morbidity (Prentis *et al.*, 2013). In patients having major surgery for pancreatic cancer, poor pre-operative CPET parameters predict early death and reduced long-term survival (Junejo *et al.*, 2014). In agreement with all of these studies, in 2010 Snowden *et al.* showed that CPET predicted increased post-operative complications and length of stay for all comers having major surgery (Snowden *et al.*, 2010).

Slightly less conclusive studies have reported a lack of relationship between CRF and mortality, however, even in these studies, CRF was able to predict at least one clinical outcome. For example, mortality in patients undergoing oesophagectomy was not related to pre-operative VO_{2PEAK}, despite a lower

pre-operative VO_{2PEAK} in patients with complications (Forshaw *et al.*, 2008). As is the case in many clinical cohort studies the sample size was small (n=78) so the true power to correlate VO_{2PEAK} to post-operative complications is likely low, especially given the maximally invasive nature of this operation. Similarly, hepatectomy patients identified as 'high risk' based on CRF had higher incidence of post-operative complications although no altered long-term survival (Ulyett *et al.*, 2015). Contrary to all of the evidence from the above studies, a study in patients having liver surgery showed no relationship between low preoperative VO_{2AT} and post-operative outcomes (Dunne *et al.*, 2014). Clearly there is a dearth of suitably powered, methodologically sound research to draw strong conclusions, however, the general trend is that poor preoperative cardiopulmonary fitness parameters are associated with poorer post-operative outcomes.

Large-scale studies are currently on-going, investigating CPET variables prior to surgery (Wijeysundera *et al.*, 2016) and their association with post-operative outcomes. The results of these studies will further elucidate the importance of CPET-measured parameters in risk stratification of the surgical patient.

1.6.3.3 Sub-maximal and recovery data from cardiopulmonary exercise testing

In addition to the 'maximal' values (VO_{2max} and VO_{2PEAK}) that can be obtained from CPET to assess CRF, sub-maximal measures (including AT) and recovery data may also provide further valuable information.

Vagally mediated heart rate recovery (HRR) is attenuated in athletes' but blunted in patients with chronic heart failure (Imai *et al.*, 1994). Heart rate recovery in the first minute following maximal exercise (treadmill test) of less than 12 beats per minute has been shown to be predictive of mortality in older adults (Messinger-Rapport *et al.*, 2003). Heart rate recovery can be increased with exercise training in healthy and disease groups (Álvarez *et al.*, 2017) which may confer long term mortality benefit.

Submaximal VO_2/ VCO_2 values (from CPET) can also be taken as a surrogate for exercise efficiency where pre and post training program data is available. This can also be thought of as exercise economy; the oxygen required to produce a specific power output or speed (Whyte, 2006). Improved economy may result in preservation of glycogen supplies and work at a lower

percentage of VO_{2max}, ultimately allowing superior performance and longer to be spent at any one workload (Whyte, 2006).

1.7 Exercise as medicine

1.7.1 Exercise guidelines for older adults

With an aim of maintaining and improving muscle and CRF, the UK NHS guidelines (England NHS, 2018) for older adults aged 65 and over advise, that *'those who are generally fit and have no health conditions that limit their mobility should try to be active daily and should do:*

At least 150 minutes of moderate aerobic activity and strength exercise on two or more days a week

or

75 minutes of vigorous aerobic activity and strength exercises on two or more days a week

or

A mix of moderate and vigorous aerobic activity every week. For example, two 30-minute runs plus 30 minutes of brisk walking equates to 150 minutes of moderate aerobic activity, and strength exercises on two or more days a week.'

Examples of exercise constituting moderate activity are: 'brisk walking, water aerobics, riding a bike on level ground or with few hills, doubles tennis, pushing a lawn mower, hiking, skateboarding, rollerblading, volleyball, and basketball'. The guidance suggests that 'one way to tell if you're working at a moderate level is if you can still talk, but you can't sing the words to a song' (England NHS, 2018).

Examples of exercise constituting vigorous activity are: 'jogging or running, swimming fast, riding a bike fast or on hills, singles tennis, football, rugby, skipping rope, hockey, aerobics, gymnastics, and martial arts'. They suggest that 'vigorous activity makes you breathe hard and fast, you won't be able to say more than a few words without pausing for breath' (England NHS, 2018).

These current exercise guidelines provided for older adults are generic, not tailored to the older adult (i.e., they are almost identical to those for adults aged 18-64 years (WHO, 2011)) and are not applicable to many individuals with chronic disease. This is despite our knowledge that chronic disease prevalence is much higher in older adults (Office for National Statistics, 2017), and that this is often paired with polypharmacy (Nobili, Garattini and Mannucci, 2011) and other clinical/ practicable barriers to meeting these guidelines. There is a definite need for further guidance and personalisation of exercise prescription to those who are unable to perform certain exercise due to chronic disease.

1.7.2 Adherence to current exercise guidelines in the elderly

Only 22% of adults >65 years meet the current physical activity guidelines (Allender *et al.*, 2008; Zaleski *et al.*, 2016) when assessed via self-report. Even fewer community-dwelling, older adults (70-93 years; 15% males, 10% females) meet these guidelines when activity is measured using objective accelerometery (Jefferis *et al.*, 2014). Part of the reason for this low uptake rate may be the uncertainty over the applicability these guidelines in chronic health conditions (Jefferis *et al.*, 2014). What is agreed upon is the universal benefit of exercise to whole-body health even in the presence of chronic disease. Although, when surveyed, doctors and nurses agree that exercise is important (Hébert, Caughy and Shuval, 2012), only a quarter of opportunities to instigate physical activity interventions are taken (NICE, 2014b). Only 32% of older adults who have seen their family doctor in the last 12-months report having been given exercise education at medical consultation (Zaleski *et al.*, 2016) and despite calls for a step wise change to endorse that 'exercise is medicine' (EIM), exercise prescription is still largely overlooked in medical undergraduate curriculums (Trilk and Phillips, 2014; Sallis, 2015).

1.7.3 Benefits of exercise in chronic disease groups

Physical activity reduces the risk of falls, reduces functional limitations and is an effective treatment for many chronic diseases (Nelson *et al.*, 2007). Indeed, the therapeutic role of (primarily dynamic, aerobic) exercise has been highlighted within many chronic disease groups such as coronary heart disease (Thompson *et al.*, 2003), hypertension (Fagard, 2001; Thompson *et al.*, 2003; Pescatello *et al.*, 2004), peripheral vascular disease (McDermott

et al., 2006), type 2 diabetes (Albright *et al.*, 2000; Sigal *et al.*, 2006), obesity (NICE, 2014a), high cholesterol (Leon *et al.*, 2000; Kelley and Kelley, 2006) and chronic obstructive pulmonary diseases (Pauwels *et al.*, 2001). Most disease specific guidelines acknowledge that individual disease cohorts may have poorer baseline CRF than the general population, however, they endorse appropriate exercise prescription due to its universal benefit upon global and disease specific health. Exercise has been unequivocally shown to reduce long term all-cause and cardiovascular mortality (Kokkinos, 2012).

1.7.4 Exercise prescription

As described in the American College of Sports Medicine (ACSM) 2013 guidelines, prescription of exercise should follow the FITT-VP principles, with advice on all of the components given when exercise is prescribed (Pescatello and American College of Sports Medicine., 2014). FITT-VP stands for:

Frequency (how many times per day or week),

Intensity (relative or absolute amount of effort required),

Time (duration of the session),

Type (mode of exercise i.e. walking, running, cycling),

-

Volume (a product of frequency, intensity and time, i.e. total amount of exercise performed), and

Progression (how the exercise prescription advances over time).

1.7.5 Dynamic exercise training regimes

1.7.5.1 Resistance exercise training

It is well accepted that different dynamic training modalities evoke different physiological adaptations. Resistance training (RT) or resistance exercise training (RET) provides a physical stimulus, primarily for the musculoskeletal system, which over time, initiates an adaptive response by re-ordering the control and architecture of active tissues, resulting in an advancement of maximal force expression (Whyte, 2006). RET is a key exercise method that promotes healthy ageing and is appropriately acknowledged as such in

exercise guidelines (Nelson *et al.*, 2007; Department of Health Physical Activity Health Improvement and Protection, 2011; WHO, 2011). The particular relevance of RET for older adults is based upon the observed loss of muscle mass and function, known as sarcopaenia (see 1.5.2.2). Although the exercise-interventions within this thesis largely focus upon CRF as a primary outcome measure, the importance of RET is not to be underestimated and should be prescribed in combination with aerobic (or anaerobic) exercise training modalities.

The overriding focus of this thesis was to measure effects upon CRF, a physiological exercise adaptation not commonly associated with RET (Marcinik *et al.*, 1991; Braith *et al.*, 1994). RET will therefore not be discussed further in this thesis.

1.7.5.2 Aerobic exercise training

Converse to RET, aerobic exercise training is most commonly associated with adaptations related to improved oxygen utilisation. Traditionally delivered as long-duration low-intensity exercise or moderate-intensity continuous training (MCT), adaptations to this form of exercise include increases in both the size and number of skeletal muscle mitochondrion (National Center for Chronic Disease Prevention and Health Promotion, 1999) and expansion of blood volume (thereby increasing oxygen carrying capacity) (Whyte, 2006). This form of training also increases the capacity of skeletal muscle to store glycogen and the ability to utilise fat as an energy source (Wilmore and Costill, 1994). Angiogenesis, resulting in increased capillary density, is also an adaptive response to this form of exercise, facilitating improved O_2 delivery to skeletal muscle (Whyte, 2006).

1.7.5.3 High intensity interval training (HIIT)

In addition to the above exercise training regimes, an alternative dynamic exercise training modality that has long-been used to improve athletic performance has been adopted in exercise-for-health settings. This type of exercise training is high intensity interval training (HIIT). Several research groups have shown that trained cyclists show improvements in time trial performance, peak power output, VO_{2PEAK} and AT measures following HIIT (Billat, 2001; Laursen *et al.*, 2005), while well-trained athletes demonstrate HIIT-induced increases in intense exercise performance by 2-4% (Laursen, 2010).

In the simplest terms, HIIT is defined as brief episodes of high-intensity physical exertion interspersed with low intensity recovery or rest periods. However, despite this simple explanation it must be acknowledged that HIIT is an umbrella term for numerous interval training arrangements which have a work-rest pattern, and the optimal format of HIIT sessions remains unknown (Whyte, 2006). A simple schematic comparison of the temporal and intensity aspects of MCT (A) vs. two forms of HIIT (B and C) illustrates the basic difference between these exercise modalities (Figure 17). It must also be noted that there is often no clear distinction in the literature between HIIT and sprint interval training (SIT – 'brief all out 30-s sprints with periods of active recovery' (Freese *et al.*, 2014)), or between the two acronyms of HIIT and HIT (although HIT can sometimes be used to represent a continuous period of high intensity training (i.e., no interval component)). For the purpose of this thesis and related outputs we have adopted the acronym HIIT for high-intensity interval training, with the work-recovery details of our HIIT protocol outlined later in this chapter.



Figure 17 - Schematic representation of different exercise training modalities: A) Moderate-intensity continuous training (Moholdt et al. 2009) vs. B) High-intensity interval training (HIIT) (Mobius-Winkler et al. 2016; Helgerud et al. 2007; Wisloff et al. 2007) vs. C) Sprint-interval training (SIT) (Martin J Gibala et al. 2006; Freese et al. 2014; Burgomaster et al. 2008; Burgomaster et al. 2005).

For athletic training the accepted definition of HIIT has been stated as:

'Short duration (30 seconds to 5 minutes) repetitions performed at an intensity above an athletes VO_{2max}*, with rest intervals typically lasting 15 – 120 seconds'* (Whyte, 2006).

However, a more specific definition has recently been proposed, encompassing 'all-out' and sub-maximal exertions and including very brief periods of high-intensity effort:

'Either repeated short (<45 s) to long (2 ‒4 min) bouts of rather high (not maximal) intensity exercise, or short (⩽10 s, repeated-sprint sequences) to long (20–30 s, sprint interval session) all-out sprints, interspersed with recovery periods' (Biddle and Batterham, 2015).

There are different ways to ensure and monitor 'intensity' during HIIT sessions. For example, a subjective rating of perceived level of exertion (RPE) can guide exercise prescription such as the modified Borg scale (Borg, 1982), which has been shown to be a useful tool to prescribe and self-regulate HIIT (Ciolac *et al.*, 2015). Another common way to ensure intensity is supramaximal loading, for example on a cycle ergometer during traditional Wingate HIIT (see below). Throughout this thesis, however, high-intensity was maintained and validated by ensuring that the heart rate response to exercise intervals was ⩾80% age predicted maximum for each individual (Kravitz, 2011). The strengths of this method are that it allows objective recording and monitoring of intensity throughout each single HIIT session and therefore throughout the complete training program. It would also potentially translate to a setting without the requirement for supervised training. Using a cycle ergometer, also allows maintenance of intensity after physical improvement, via increasing revolutions per minute (RPM) with or without changing the load. This allows a practicable method of self-prescription for individuals to maintain and monitor training intensity without subjective bias.

As outlined above, there are many different combinations of work to rest ratios reported within the literature. SIT in the form of 4-6 repeats of 'all out cycling' is a proven physiologically effective training method used to improve CRF (Burgomaster *et al.*, 2005; Gibala *et al.*, 2006; Rakobowchuk *et al.*, 2008; Freese *et al.*, 2014), however, it requires an extreme amount of effort and therefore may be associated with negative exercise effects in the unmotivated rendering it unsuitable for the majority of sedentary individuals

(Robertson-Wilson, Eys and Hazell, 2017). Similarly, due to poor exercise adherence rates with current guidelines (Allender *et al.*, 2008) and "lack of time" being commonly cited as reason for this (Trost *et al.*, 2002), there is research exploring the minimum volume of HIIT required to evoke improvements in CRF. The format of HIIT used for this research has been most-commonly called reduced exertion HIIT (REHIIT). Utilising only 1 or 2 'all-out' 10-20 second exertions REHIIT, as with SIT requires supra-maximal efforts to be performed (Gibala *et al.*, 2012a; Metcalfe *et al.*, 2012). The supra-maximal loading of SIT (Burgomaster *et al.*, 2005, 2008; Gibala *et al.*, 2006; Freese *et al.*, 2014) and certain REHIIT (Metcalfe *et al.*, 2012) protocols have largely been excluded from discussion within this thesis due their unsuitability within sedentary (Robertson-Wilson, Eys and Hazell, 2017), elderly/ patient populations (Gibala *et al.*, 2012b).

1.7.5.4 Proposed mechanisms of HIIT-induced adaptations

Much of the mechanistic work carried out to assess the potency of HIIT have used SIT or Wingate-style 'all out efforts' in young healthy individuals. Although these studies are discussed here to paint a picture of the body of work and the proposed mechanisms for HIIT-induced adaptations, it must be acknowledged that the these mechanisms may be different in older adults and patient cohorts due to the normal effects of ageing upon physiology and interactions that comorbidity may have upon these systems.

HIIT increases skeletal muscle oxidative capacity and induces specific metabolic adaptations during exercise that are comparable to traditional exercise training (Burgomaster *et al.*, 2008). These adaptations include increases in the protein content of mitochondrial enzymes and upregulation of oxidative capacity within the mitochondria following short term SIT training programs (2 weeks) (Gibala *et al.*, 2006, 2012b). Muscular contraction causes metabolic disturbance leading to activation of several kinases and phosphatases (such as adenosine monophosphate-activated protein kinase (AMPK), calcium–calmodulin-dependent protein kinase (CAPK), and mitogen-activated protein kinase (MAPK) cascades) involved in signal transduction which promote mitochondrial biogenesis and metabolism (Gibala *et al.*, 2006).

For example, following only 2-weeks of Wingate tests in recreationally active healthy young individuals (mean age 22 years), the maximal mitochondrial

enzyme (citrate synthase (CS)) activity increased (+38%) along with resting muscle glycogen content (+26%) (Burgomaster *et al.*, 2005). Somewhat surprisingly, endurance capacity also improved significantly (Burgomaster *et al.*, 2005). Burgomaster *et al.* consolidated these findings with a study comparing endurance exercise training to SIT. They showed that, despite a markedly lower training volume, SIT increased mitochondrial markers for skeletal muscle carbohydrate and lipid oxidation as much as endurance training (Burgomaster *et al.*, 2008). They also showed an increase in the protein content of peroxisome proliferator-activated receptor-gamma co-activator-1-alpha (PGC-1α) with SIT; a key regulator of mitochondrial biogenesis in muscle (Wu *et al.*, 1999). Increases in muscle buffering capacity following HIIT are also comparable to those following endurance training despite only ~10% training volume with HIIT over 2 weeks (Gibala *et al.*, 2006).

One suggestion as to how HIIT induces increases in PGC-1α is outlined in Figure 18. Secondary to the exercise stimulus (HIIT), intramuscular changes to ATP:ADP/AMP ratios and the generation of reactive oxygen species, probably stimulate exercise-responsive signalling kinases (Gibala *et al.*, 2012b). The phosphorylation of these protein kinases (5-AMP-activated protein kinase (AMPK) and p38 mitogen-activated protein kinase (MAPK)), directly phosphorylate and activate PGC-1α. PGC-1α ultimately leads to increased mitochondrial gene transcription resulting in translation into cytoplasmic mitochondrial proteins (Gibala *et al.*, 2012b). PGC-1α also appears to have beneficial effects upon anti-inflammatory pathways and oxidative capacity, both of which have been associated with improved oxygen utilisation (Handschin and Spiegelman, 2008; Gibala *et al.*, 2012b).

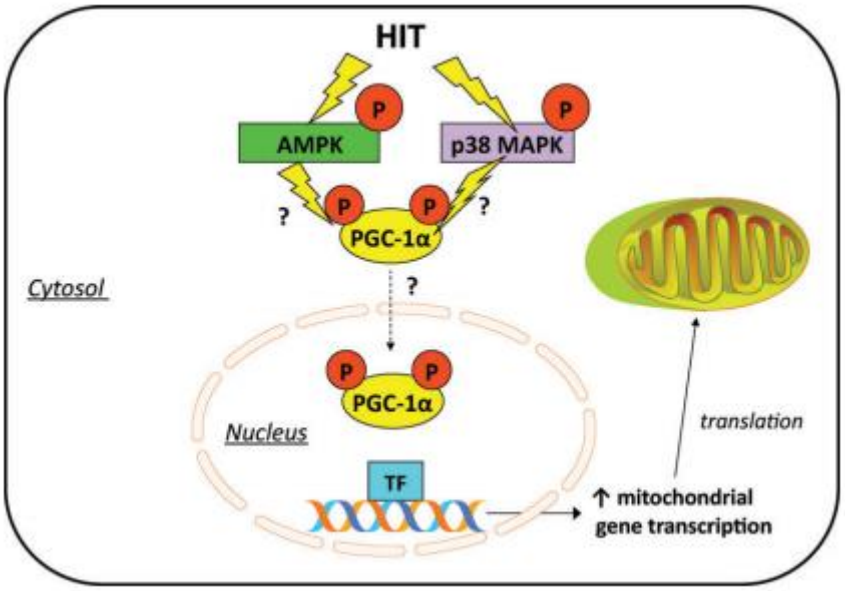


Figure 18 - Potential intracellular signalling mechanisms involved in HIIT-induced mitochondrial biogenesis (M J Gibala et al. 2012).

In addition to the proposed intracellular adaptations outlined above, HIIT also stimulates similar peripheral vascular adaptations, including improved arterial distensibility (a surrogate for reduced cardiovascular risk), to endurance exercise training. It is, however, acknowledged that longer training periods are required to evoke central cardiovascular adaptations (such as attenuation of age associated carotid artery stiffening), and as seen with endurance exercise training, studies that are longer in duration may be required to see central cardiovascular adaptations in response to HIIT (Rakobowchuk *et al.*, 2008).

1.7.5.5 HIIT in the elderly

HIIT is a safe way of rapidly improving cardiovascular fitness in older individuals (Warburton *et al.*, 2005; Tew *et al.*, 2014; Dunne *et al.*, 2016) and has been shown to be more effective than performing the same total work at lower intensities (Warburton *et al.*, 2005; Gibala *et al.*, 2006; Burgomaster *et al.*, 2008; Blackwell *et al.*, 2017). Work from our laboratory has shown that significant increases in cardiovascular fitness, measured by VO_{2PEAK} and VO_{2AT}, can be achieved using HIIT in healthy older (median age 67 years) individuals in a time period as short as 4-weeks (Boereboom *et al.*, 2016). It is, however, unclear whether these gains can be replicated in an age group over the age of 75 years suffering from co-morbid health conditions. Investigation of the efficacy of HIIT in co-morbid conditions is

required to mirror the 'at risk' older patient group commonly presenting for major intra-abdominal surgery.

1.7.5.6 HIIT in chronic disease groups

In 2016, Ross *et al.* highlighted in their systematic review that there is growing literature suggesting HIIT presents little risk for stable patients when prescribed exercise protocols are followed (Ross, Porter and Durstine, 2016). Within cardiovascular patients HIIT is superior to MCT in improving CRF with no associated increases in cardiac risk (Rognmo *et al.*, 2004; Wisloff *et al.*, 2007; Freyssin *et al.*, 2012). HIIT is at least as effective as MCT in patients with COPD (Beauchamp *et al.*, 2010; Kortianou *et al.*, 2010), with greater reduction in breathlessness symptoms following HIIT (Kortianou *et al.*, 2010). Indeed, Vogiatzis *et al*. found higher exercise tolerance, quality of life scores and less breathlessness at a given exercise level with HIIT, and HIIT induced similar magnitude improvements in cardiorespiratory parameters as MCT (Vogiatzis *et al.*, 2002). There is growing interest in HIIT for diabetic patients as studies have suggested improvements in glycaemic control, HBA1c and CRF following HIIT (Francois and Little, 2015), with particular interest in utilizing HIIT to reduce the risk of individuals with metabolic syndrome (or pre-diabetes) progressing to diabetes (Bird and Hawley, 2012). Current work suggests that HIIT may be a more advantageous exercise strategy than MCT for modulating glycaemic control if performed in a fasted state (Terada *et al.*, 2016). Supporting the suggestion that HIIT strategies may need to be tailored to individuals, one study found that REHIIT improved insulin sensitivity in males (by 28%) but not females, suggesting that the rapid utilisation of muscle glycogen during HIIT exertions may influence insulin sensitivity via release of glycogen-bound proteins (Metcalfe *et al.*, 2012), an explanation for the sexual dimorphism was not provided. Overall, poor adherence to current exercise guidelines (Allender *et al.*, 2008) and the potential to improve cardio-metabolic risk factors make HIIT's efficacy and low-time commitment a very attractive option for adults at risk of diabetes and other lifestyle-related disease.

HIIT has recently been reported as both feasible and acceptable to patients awaiting abdominal aorta repair (Tew *et al.*, 2014, 2017). Notably, however, as the authors of this work acknowledge, the intensity of exercise delivered (81.7 (SD 8.5) % maximum heart rate) was substantially lower than planned

for a large proportion of participants (with only 30% rating it as hard or very hard). In addition 20 out of 27 participants had at least one episode of intensity reduction due to a breach of safety criteria (primarily systolic BP >180mmHg) (Tew *et al.*, 2017). This raises the question of whether HIIT was actually delivered (or was it moderate-to-hard intensity interval training) or if it is indeed actually achievable within this clinical cohort given the high number of clinical safety breaches seen. For the purpose of this thesis high-intensity is defined as >80% maximum predicted heart rate (Cress, Porcari and Foster, 2015; MacInnis and Gibala, 2017).

1.7.5.7 HIIT in cancer cohorts

In studies of cancer survivors, HIIT improves symptoms of cancer-related fatigue, quality-of-life and aerobic fitness across breast (Schmitt *et al.*, 2016), testicular (Adams *et al.*, 2018), colorectal (Devin *et al.*, 2016) and mixed cancer groups (Midtgaard *et al.*, 2013; Kampshoff *et al.*, 2015). HIIT has also been shown to be safe in numerous different cancer cohorts (testicular, lung, colorectal, breast), both cancer survivors and those undergoing treatment (i.e. chemo-radiotherapy) (West, Loughney, *et al.*, 2014; Papadopoulos and Santa Mina, 2018). Of note, one individual in a 'mixed malignancies' study with a known brain tumour had a grade 3 seizure after a HIIT session which was treated conservatively, this patient was then removed from the study and the authors suggested that those with brain tumours should not partake in HIIT (Adamsen *et al.*, 2009).

It may also be that as well as improving the aspects mentioned above, the reduction in systemic inflammation, especially interleukin 6 (IL-6), seen following HIIT may reduce cancer progression (Papadopoulos and Santa Mina, 2018). HIIT increased circulating levels of natural killer cells, reduced tumour burden and enhanced metabolic health in obese patients with breast cancer (Barra *et al.*, 2017). Recently, physical activity level (versus other lifestyle modifications) has been shown to have the strongest effect on reducing the risk of breast cancer recurrence and even reduces the risk death by up to 40% in breast cancer patients who exercise following their diagnosis (Hamer and Warner, 2017). Further research is still required to investigate the potential beneficial effects of HIIT, and other exercise modalities, upon systemic and cancer-related inflammation.

Short term HIIT in patient groups with active cancer (or cancer in situ) is discussed further in the section 1.9.1 Surgical prehabilitation for cancer patients.

1.8 Development of our HIIT regime

HIIT was first described in the scientific literature in 1959 (Reindell H, 1959). Multiple international sporting individuals and teams throughout the following decades attributed their sporting success to this training method, claiming that intervals had been part of their training regime for many years (such as the Swedish cross country skiing team and Sir Roger Bannister) (Billat, 2001). During the 1960's, research from Scandinavia proposed that runners should train between 90% and 100% $VO_{2max,}$ research that began a move from high-volume low-intensity training to lower volume higher intensity training focussed upon training at race pace (Christensen EH, Hedman R, 1960). Training for shorter time-periods at higher intensities allowed athletes to spend longer overall time at VO_{2max} than continuous exercise. This shift seemingly produced beneficial gains and was endorsed by many successful Olympic athletes.

Following on from the early work of Wasserman and McIlroy in the 1960's on the assessment of AT (Wasserman and McIlroy, 1964), Bar-Or published the Wingate anaerobic test (Bar-Or, 1987) which subsequently became a very popular method of HIIT in young healthy athletic individuals (Billat, 2001). Characterised by up to ten very short intervals (30 seconds) of supramaximal exertion performed on a cycle ergometer (Bar-Or, 1987), Wingate HIIT was not suitable for all comers with concerns raised over both safety and practicality (Little *et al.*, 2010). Ready *et al*. published an alternative low-volume or 'reduced exertion' HIIT protocol in 1981 which consisted of ten 1-minute intervals at 110% of baseline VO_{2max} with 1-minute rest periods. Performed for 6 weeks by young healthy females (mean age 23.9 years) this protocol elicited significant gains in VO_{2max} (+7.7%), maximum oxygen debt (19.8%) and time to bicycle ride exhaustion (+47.5%) versus a control group (Ready, Eynon and Cunningham, 1981).

In the 2000's Gibala began an extensive research programme into the health-benefits of HIIT utilising many different formats. He showed that rapid gains in CRF and athletic performance could be achieved using minimal

volume HIIT (4-6 'all-out' efforts with 4-minutes recovery), postulating that HIIT is a time-efficient strategy to induce rapid adaptations in skeletal muscle and exercise performance that are comparable to endurance training in young active men (Gibala *et al.*, 2006). Notably this protocol was performed for just two-weeks with a total work-load of just 10% in comparison to traditional endurance training. Gibala and colleagues then showed that, over just two weeks, a low-volume, lower-intensity HIIT protocol (8-12 x 1 minute intervals at 100% peak power output with 75 seconds recovery), similar to Ready et al. (1981) was a potent stimulus for increasing skeletal muscle mitochondrial capacity and improving exercise performance, whilst also acknowledging that this was a more practical protocol than Wingate HIIT (Gibala and McGee, 2008).

Following on from the work of Ready and Gibala, a large recently published study (n=136) using an adaptation of the Ready et al. protocol showed that a HIIT protocol with as few as five one-minute exertions (5-by-1 min, with 1 minute rest intervals) was able to significantly improve VO_{2max} in adults with risk factors for cardio-metabolic disease (Phillips *et al.*, 2017). Interestingly they also noticed (from interim analysis) that a 7-by-1 min HIIT protocol at a fixed intensity was no more efficacious at improving CRF parameters than a 5-by-1 min HIIT protocol where the intensity of exercise was based on individuals starting ability, therefore they focussed solely upon 5-by-1 min HIIT (Phillips *et al.*, 2017). The optimal dose-response or work-rest ratio for HIIT is not yet clearly defined and this will likely vary between populations (gender, clinical conditions etc.). There is, however, data to suggest that HIIT protocols which provide an intensity around that of VO_{2PEAK} are sufficient to elicit CRF benefit, whereas no further benefit is gained by increasing intensity to 150% VO_{2PEAK}, which may be unachievable for many populations (Raleigh *et al.*, 2016). Therefore, as described in more detail later in this section, our HIIT protocol utilised a 5-by-1 min format, with 90 seconds recovery between each effort and an individual assessment of ability prior to HIIT to determine intensity (Phillips *et al.*, 2017).

1.8.1.1 Using FITT-VP principles to develop our HIIT programme

As discussed above, the American College of Sports Medicine suggests usage of their FITT-VP acronym to develop exercise programs (Pescatello and American College of Sports Medicine., 2014). As such, within this framework,

the rationale behind HIIT interventions used within patient groups are described below.

Frequency: There is no specific guidance stating what the optimal frequency of exercise should be, especially for older comorbid adults or specific patient groups, such as cancer patients. Exercise guideline commentary usually state '30 minutes on 5 days a week' but this is non-specific. We know that the majority of older adults fail to meet this total weekly exercise requirement (Zaleski *et al.*, 2016). In addition, when starting HIIT from a sedentary level rest days are advisable (Kravitz, 2011) and this actually fits quite well with a future roll-out of HIIT for clinical populations, as until the advent of a 'true' 7-day a week NHS service, supervised interventions are liable to a 2 day weekend break where no delivery could occur. Given that the majority of elderly are retired from work, it may be perceived that the most commonly reported barrier to physical activity participation; "lack of time" (Trost *et al.*, 2002) is not as significant of a barrier as in working age individuals. This reason is still cited by older individuals, however, perceived poor health status and a belief that activities of daily living (ADLS) suffice to maintain fitness are other barriers to exercise guideline adherence in the elderly (Wocken, 2013).

Intensity: The rationale for intensity of exercise that we have chosen (high intensity) is discussed in depth in Chapter 2: A systematic review and meta-analysis of short term (<8 weeks) high-intensity interval training in diseased cohorts. The general premise of this thesis, however, is that to make significant gains in a short period of time will likely require higher intensity exercise than proposed in current exercise guidelines to provoke an adaptive response.

Time: For future clinical translation, time is an important consideration, with a number of different facets to consider. For HIIT in patient groups requiring supervision, training regimes which can represent maximum gains within short session duration have positive resource and cost implications for service delivery. For example, potentially two patients could perform 5-by-1 min HIIT within a 1-hour period, whilst only one could undergo 4x4-min HIIT or MCT (Figure 19 A). Although supremely time-efficient, it is unlikely that patient groups would be able generate sufficient disturbance of intracellular homeostasis (via inability to generate sufficient power output

for 10-20 second exertions), the proposed mechanism underpinning improvement (Metcalfe *et al.*, 2012), to benefit from REHIIT.

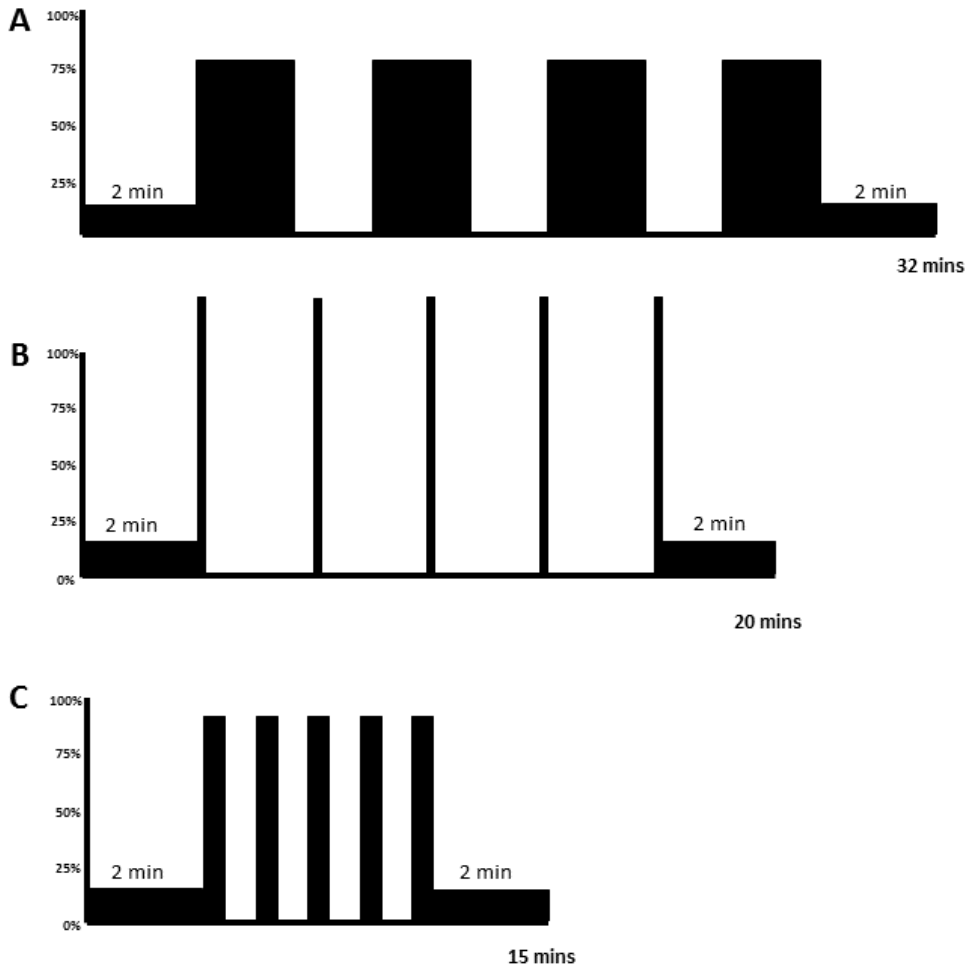


Figure 19 - Schematic representations of A: Norwegian HIIT model (4x4 minute exertions with 3 min rest period) (Wisloff et al., 2007; Moholdt et al., 2009), B: Wingate style HIIT (30 sec 'all out' efforts with 5 mins rest) (Burgomaster et al., 2005; Rakobowchuk et al., 2008), C: Our HIIT protocol, modified from Meta Predict protocol (Phillips *et al.*, 2017) *(5 x 1 min exertions with 90 sec rest periods)*(Boereboom *et al.*, 2016; Blackwell *et al.*, 2017).

Within an individual session, time can also be thought of as 'exertion time' and 'rest time' making up the total time of the session (Figure 20). Considering this, the nature of Wingate HIIT with short 'all out' efforts (if even attainable) may have a low exertion time but, require long 'rest time' in between exertions, leading to a long total time per session versus slightly lower intensity intervals (Figure 19 B). Our group have consistently (Boereboom *et al.*, 2016; Blackwell *et al.*, 2017) been able to administer our 5-by-1 min HIIT protocol, with a 15-min session length (Figure 19 C), using a 30-min 'door to door' policy. This 30-min includes meet and greet, changing into exercise clothing, application of non-invasive monitoring, a full HIIT session (warm-up, HIIT protocol, and recovery), further bookings, review and departure. This may be appealing within the clinical setting where scheduling has cost implications.

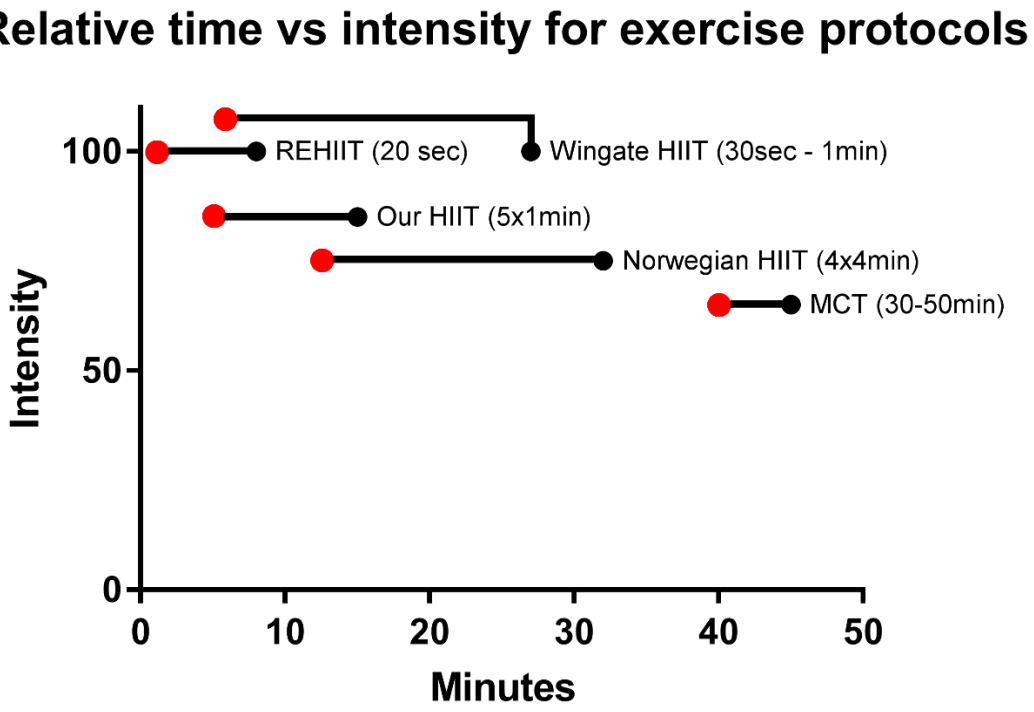


Figure 20 - Comparison of aerobic exercise protocols. Time vs. intensity. Session time shown as black dots with respective exertion time within each session shown as red dots. Session time included a 2-minute warm up and 2-minute final recovery period for each protocol.

A final time-factor to consider is the clinical timeframe available as discussed in the previous section (Department of Health, 2012) in that the intervention employed must be likely to show benefit within the available timeframe, as

we have shown previously in aged matched healthy controls to those presenting with colorectal cancer (Boereboom *et al.*, 2016).

Type: When considering unimodal exercise interventions to improve CRF, HIIT has been shown to have similar if not greater efficacy over MCT (Milanović, Sporiš and Weston, 2015), within certain disease groups (Wisloff *et al.*, 2007; Moholdt *et al.*, 2009; Munk *et al.*, 2009) over long periods of time (>12 - weeks). The relative efficacy of HIIT vs MCT across all disease groups within clinically relevant periods of time (i.e. <62 days from GP referral or <31 days from 'decision to treat' (Department of Health, 2012)) is at present unclear and is discussed further in Chapter 2. Whilst different formations of work and rest are available to make up different types of HIIT (i.e. Wingate, REHIIT, SIT), there are also ways of delivering these protocols with different types of exercise. For example, running, swimming or arm-crank cycling (as alternatives to cycle ergometry). Elderly individuals may have pathological joint limitations (i.e. osteoarthritis (Hunter and Eckstein, 2009)) as well as increased risk of falls (Skelton and Beyer, 2003) when performing certain types of exercise.

Volume: Combining the frequency, intensity and time (as outlined above) gives the total volume of exercise performed (Weston *et al.*, 2016). In certain circumstances reducing the volume of intense exercise does not seem to reduce its effectiveness (Zelt *et al.*, 2014; Phillips *et al.*, 2017), leading to interest in defining the minimal training volume required to make significant gains. Reduction in total training volume reduces training associated negative effects (i.e. muscle soreness) (Ross, Porter and Durstine, 2016) and improves enjoyment (Martinez *et al.*, 2015).

Progression: With the hypothesis that our 5-by-1 min HIIT will invoke rapid improvements in CRF it is important to maintain intensity throughout the training period. Objectively, using heart rate monitoring, intensity can be maintained with verbal encouragement (i.e. titrating HR to >85% by increasing RPM), whilst load delivered during the exertions can be increased with improvements in exercise performance. This is another benefit of HIIT delivered by an electronically loaded cycle ergometer as the protocol can easily be tailored between sessions. The participants subjective response (RPE <8 on the modified Borg scale at the end of the last exertion of a session) can also be used to dictate an increase in load (by 10% of original

peak power output) used previously (Boereboom *et al.*, 2016; Blackwell *et al.*, 2017; Phillips *et al.*, 2017).

1.9 Surgical prehabilitation

In broad terms, surgical prehabilitation is described as *'a strategy to address modifiable risk factors that impact treatment outcomes'* (Carli *et al.*, 2017), and in terms of exercise prehabilitation specifically may be defined as *'exercise interventions used in an attempt to reduce mortality and morbidity'* (Dickinson and Blackmon, 2015). In a variety of situations, exercise is actually just one facet of multi-modal prehabilitation with other common components being nutritional and psychological support (Carli and Scheede-Bergdahl, 2015). Exercise programmes directed at improving physical fitness and modulating surgical risk factors in the pre-operative period are an attractive option (Carli and Zavorsky, 2005; Kothmann *et al.*, 2009; Carli *et al.*, 2017) yet an optimal form of exercise training programme is yet to be clarified (Jack, West and Grocott, 2011) and there are currently no pre-operative exercise guidelines (Carli *et al.*, 2017).

Carli *et al*. has proposed a theoretical model of surgical prehabilitation (Carli and Zavorsky, 2005; Carli *et al.*, 2017) as shown in Figure 21. In this model, a patient is exposed to the same physiological insult (i.e. intra-abdominal surgery) suffers less of a deficit after prehabilitation because their functional capacity is higher prior to the insult and they then recover to baseline faster than those with lower pre-operative functional capacity.

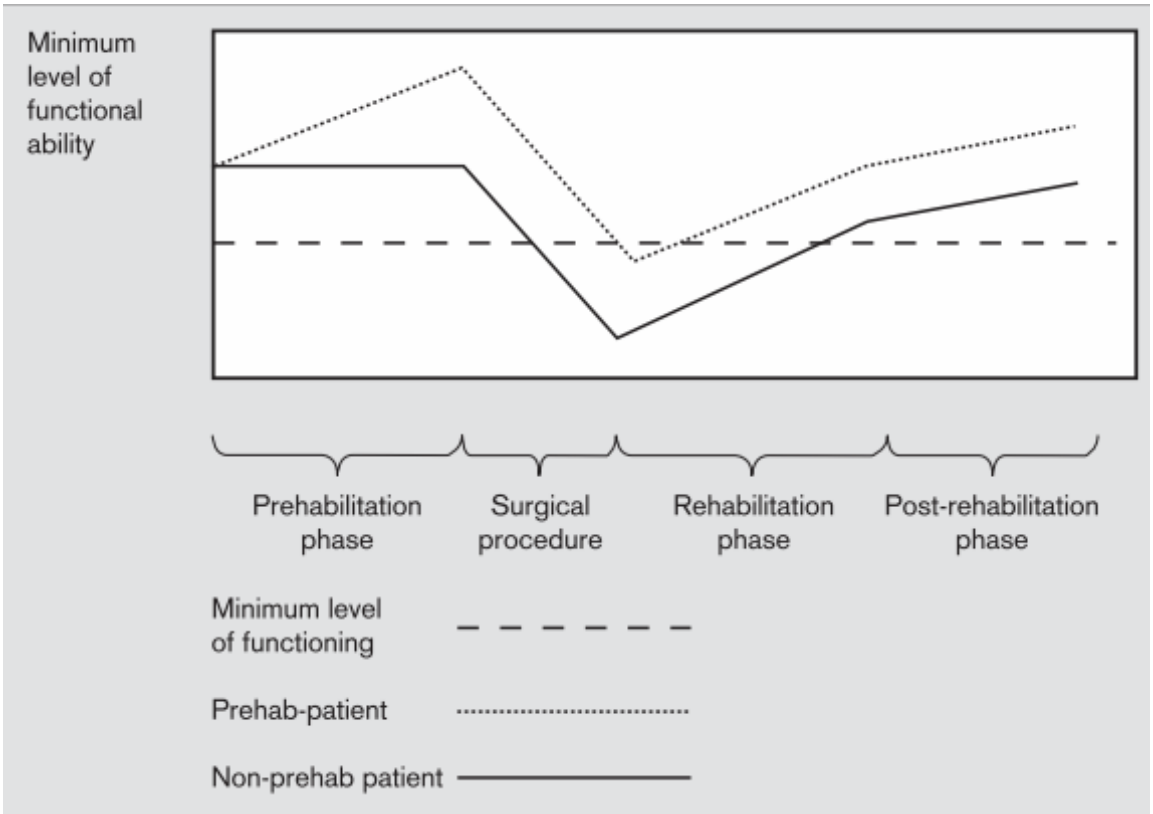


Figure 21 - Theoretical model of surgical prehabilitation based on the concept of increasing functional capacity before surgery (Carli F et al. 2005).

Research suggests that patients who undertake exercise training pre-operatively regain baseline fitness post-operatively more rapidly than the untrained (Carli and Zavorsky, 2005). Although recent studies have shown an overall positive effect of prehabilitation on post-operative outcomes (D Santa Mina *et al.*, 2014), robust data with regard to clinical outcomes is still lacking (National Institute for Academic Anaesthesia, 2015).

A panel of subject experts in Canada recently published recommendations for future research within the field of prehabilitation in patients with cancer (Carli *et al.*, 2017). They highlighted a lack of robust data and recommended that there is a need to know whether elderly comorbid patients would benefit from multi-modal prehabilitation (including exercise).

Perioperative management of surgical patients has evolved in recent years with enhanced recovery programmes now common place. The Enhanced Recovery After Surgery (ERAS) society recommends that increasing exercise pre-operatively may be of benefit but highlights that the research base is inconsistent and further work is needed to elucidate its usefulness in relation to post-operative patient outcomes (Gustafsson *et al.*, 2012).

1.9.1 Surgical prehabilitation for cancer patients

Cancer patients are a specific at risk group for poor baseline physiological reserve. This is due to the incidence of cancer rising with age, malnutrition, the effects of adjuvant therapy and the negative physiological effects of the cancer itself. As already outlined, older patients have a higher incidence of co-morbidity (Office for National Statistics, 2014). Cancer patients often present as malnourished due to loss of appetite and pre-existing malnutrition, however, poor nutritional intake alone cannot explain the degree of malnutrition seen in certain cancer patients (Argilés, 2005). Inflammatory cytokines and hormones produced either by the tumour itself or the hosts response to the tumour have been implicated in the complex picture that is cancer related malnutrition (Argilés, 2005). Malnutrition leads to muscle wasting and physiological deterioration (Nicolini *et al.*, 2013). In addition, neo-adjuvant chemo-radiotherapy (NACRT) delivered prior to surgical resection has been shown to reduce CRF preoperatively (West, Loughney, *et al.*, 2014). Taken together, the resultant group of patients with active cancer undergoing adjuvant therapy are extremely high risk for significant malnutrition, muscle wasting and detrimental reductions in CRF whilst awaiting surgical resection.

There have been many small cohort studies looking at exercise-based prehabilitation in varying intra-abdominal cancer types. The majority of these interventions are designed to comply with cancer waiting times (Department of Health, 2012) and thus are short in duration, utilizing the window between diagnosis and treatment. Most studies have reported *some* benefit of a pre-operative exercise intervention. For example, Dronkers *et al*. reported increased respiratory muscle endurance after 2-4 weeks of RET and MCT in colorectal cancer patients scheduled for surgery compared to control (Dronkers *et al.*, 2010). Kim *et al.* failed to show improvements in maximal exercise parameters, other than peak power output, following 4 weeks MCT (40-60% HRR) in colorectal cancer patients awaiting theatre (Kim *et al.*, 2009). CRF was shown to improve in response to aerobic exercise (30 mins/ twice weekly; 60-85% max HRR) combined with resistance exercise within 39 mixed cancer patients (pancreatic, liver, colon, rectal, sarcoma, oesophageal), albeit over a 5-week period (Timmerman *et al.*, 2011) taking this intervention outside the National Cancer Action Team

(NCAT) decision to treat window (Department of Health, 2012). The NCAT decision to treat window is based on the Department of Health 2011 Policy: Improving Outcomes - A strategy for cancer (Department of Health, 2011). This policy mandates that operations for cancer should be completed within 31-days of decision to treat and within 62 days of first referral. This stipulation provides a narrow window to optimise patients' CRF prior to their operation date.

Given this narrow time-window, demonstration of an ability to improve aerobic performance in a truncated time-frame in such a population could, coupled with advancements in peri-operative care and surgical techniques, allow for access to surgery for older patients becoming more available. HIIT training provides a significant opportunity to increase fitness for surgery' in comparison to current best advice or more traditional methods of exercise.

1.9.1.1 Effect of prehabilitation exercise upon patient outcome

A review of patients undergoing joint, cardiac or intra-abdominal cavity surgery suggests pre-operative exercise can reduce length of stay and post-operative complications (Valkenet *et al.*, 2011). O'Doherty et al. (2013) included ten papers (524 patients) having intra-cavity (cardiac, thoracic and intra-abdominal) surgery, concluding that pre-operative aerobic exercise is beneficial in patients awaiting cardiac surgery, but the effect in patients before major intra-thoracic and intra-abdominal operations is uncertain (O'Doherty *et al.*, 2013). In contrast to this, Moran et al (2016) stated that pre-operative exercise training (aerobic, inspiratory muscle training and resistance exercise training) can reduce all types of post-operative complications in patients having intra-abdominal operations. They could not comment upon length of stay however, and attribute this to small study numbers and very low methodological quality of the included studies. Patient outcomes are rarely reported, and when they are the quality and reliability of the conclusions are questionable. This is mainly due to the small sample sizes within studies included resulting in insufficient power to detect real changes in complications, selection bias of participants for exercise studies and multifactorial nature of post-operative complications. Exercise prehabilitation in colorectal cancer patients can increase cardiorespiratory fitness levels and improve functional fitness scores, however it is unclear whether this translates into meaningful clinical improvements (C. L. Boereboom *et al.*, 2016). The first suitably powered prospective randomised

control trial, powered for change in post-operative morbidity (as measured by the Clavein Dindo classification (Dindo, Demartines and Clavien, 2004)), investigating the effects of prehabilitation exercise in colorectal cancer patients awaiting curative resection is underway (Swart, 2016). Favourable patient outcomes from suitably powered studies could give provide more robust evidence to validate smaller observational studies previously published claiming up to 50% reduction in post-operative complication rates following prehabilitation (Barberan-Garcia *et al.*, 2018).

1.10 Thesis aims

This thesis aims to explore whether HIIT could be a useful preoperative exercise intervention in at risk patients presenting for major surgery. It is unknown whether HIIT represents an efficacious means of training above and over current exercise guidelines (MCT), within elderly cohorts suffering different diseases, over very truncated time periods compliant with cancer waiting times. What is also unknown is whether elderly individuals would be able to make similar clinically important improvements in CRF over these time frames comparable to younger healthy counterparts. In relation to patients with cancer, a catabolic influence upon the body, it is unknown whether there may be a negative effect upon trainability or whether significant gains in CRF could realistically be made prior to operation.

The aims of this thesis are therefore:

To perform a systematic review of the literature looking at evidence supporting the use of HIIT in individuals with chronic disease.

To investigate whether HIIT can be delivered safely and effectively at home compared to a supervised HIIT program.

To investigate the benefit of a 4 week HIIT program in elderly individuals suffering comorbid conditions.

To investigate the feasibility and effectiveness of a 4 week HIIT program in individuals scheduled for surgery for urological malignancy.

2 A systematic review and meta-analysis of short term (<8 weeks) high-intensity interval training in diseased cohorts

2.1 Chapter focus

This chapter systematically reviews the effectiveness of short term (<8 weeks) aerobic exercise interventions, within different disease groups, to improve cardiorespiratory fitness. It compares traditional moderate continuous training (MCT, sometimes referred to as moderate intensity continuous training (MICT)), reflective of current exercise guidelines (WHO, 2011; NICE, 2014b), to newer HIIT protocols which have shown potential to improve cardiorespiratory parameters to a similar or greater extent than MCT in aged disease groups (Blackwell *et al.*, 2018).

Given the time efficiency and potential ability to improve cardiorespiratory fitness despite low overall training volume, as outlined within the introduction, HIIT may represent a viable preoperative training intervention within comorbid patient groups representative of those commonly presenting for major intra-abdominal surgery. However, aside from reviews within individual disease groups (i.e. cardiovascular patients), there is not any published data regarding HIIT's ability to improve 'all comers' (i.e., reviews and meta-analyses to date are either in healthy younger individuals, or have inclusion/ exclusion criteria which would exclude studies incorporating patients that may be offered surgery despite multiple comorbidities). Additionally, the vast majority of HIIT studies are of 12 weeks or greater duration (as is traditional in exercise physiology research), while this chapter will explore the relative efficacy of HIIT and MCT over a shorter time period (<8 weeks) which is more in keeping with clinical time-frames available prior to operation.

The following abbreviations are used for additional members of the research team who aided with data collection and statistical analysis within this review:

Samuel Ricketts (SR)

Dr Brett Doleman (BD)

Mr Phillip Herrod (PH)

2.2 Introduction

2.2.1 Background

Objective measures of cardiorespiratory fitness (CRF) (e.g. VO_{2PEAK} and anaerobic threshold (AT)) predict whole-body health, morbidity and mortality (Kodama *et al.*, 2009; Kokkinos, 2012; Older, 2013; Snowden *et al.*, 2013). These measures of CRF can be altered via participation exercise training regimens, which in turn may improve general health. Traditionally endurance based aerobic activity or 'moderate continuous training' (MCT) has been employed to improve CRF (Chodzko-Zajko *et al.*, 2009) and exercise tolerance (Whyte, 2006).

Despite MCT (150 minutes of moderate aerobic activity every week) forming the primary basis of almost all public health exercise-based recommendations (Haskell *et al.*, 2007; WHO, 2011), greater attention has recently been paid to the utility of higher intensity exercise (75 minutes of vigorous activity every week) as an alternative to MCT (WHO, 2011) in the context of 'exercise-for-health' (Department of Health Physical Activity Health Improvement and Protection, 2011) as the latter is more time efficient, which may improve compliance (Trost *et al.*, 2002).

Patients can have modification of disease risk factors through exercise interventions (e.g. reduction of blood pressure in those at risk of stroke) (Law, Morris and Wald, 2009) and exercise can also be used to help optimise patients prior to a planned intervention (e.g. patients with suspected cancer or those awaiting urgent elective surgery for malignancy) (Dunne *et al.*, 2016). For those having major surgical procedures perioperative outcome is in large part dependent upon preoperative CRF (Older, 2013). An ability to rapidly improve CRF would therefore be attractive if deliverable in the short time available between the suspicion of cancer and initiation of primary treatment (Department of Health, 2012).

2.2.2 Clinical timeframes

There is not an extended period available from clinical suspicion of cancer before first definitive treatment to complete exercise programmes: for example, in the United Kingdom the National Cancer Action Team imposes two cancer waiting time service standards (Department of Health, 2012).

The first is a 62 day target from initial GP referral for suspected cancer or urgent referral from NHS screening program, whilst the second is a 31-day window from the decision to treat to primary treatment (surgery, drug treatment or radiotherapy) of the cancer (Department of Health, 2012). These standards have led to increasing interest in novel exercise interventions to improve CRF within truncated timeframes. It has been suggested that exercise regimens such as high intensity interval training (HIIT) may deliver clinically important improvements in CRF within a clinically relevant time frame with minimal time commitment from the patient.

2.2.3 High intensity interval training as an alternative

HIIT can bring more pronounced improvements in objective measures of CRF than MCT in healthy individuals over an equivalent number of weeks (Milanović, Sporiš and Weston, 2015). It is unknown whether individuals with disease will benefit from HIIT in the same way. In any exercise intervention it is essential that there are high levels of adherence and compliance to maximise benefit, especially given that co-morbid patients have been shown to be poor compliers with exercise interventions (Van Der Wal, Jaarsma and Van Veldhuisen, 2005). HIIT has previously been reported to be more enjoyable than MCT (Kilpatrick, Jung and Little, 2014). Time pressure has been identified as one of the most commonly cited barriers to exercise adherence (Trost *et al.*, 2002). HIIT's reduced time commitment and training volume makes it an attractive option for rapidly achieving maximal gains in CRF.

2.2.4 Previous work

Previous reviews in distinct disease groups exploring the efficacy of HIIT over longer time durations (median 12 weeks) have reported benefits of HIIT over MCT in cardio-metabolic disease (Weston, Wisloff and Coombes, 2014) and possible improved efficacy in patients with chronic obstructive pulmonary disease (COPD) (Beauchamp *et al.*, 2010). Whereas, equal effects on CRF have been seen in HIIT and MCT in patients with coronary artery disease during cardiac rehabilitation (Tschentscher *et al.*, 2016). In general within disease groups, 8 – 16 week exercise programmes involving HIIT have been shown to be as effective as MCT (Ross, Porter and Durstine, 2016), while uncontrolled studies have shown large increases in CRF

following HIIT across co-morbidities as varied as cardiac disease (Wisloff *et al.*, 2007), diabetes (Little *et al.*, 2011), obesity (Alahmadi, 2014) and asthma (Emtner, Herala and Stålenheim, 1996). HIIT retains the advantage of requiring significantly less time commitment than MCT.

2.2.5 Aim

The aim of this review was to compare the effect of HIIT to no exercise control (CON) or MCT on cardiorespiratory fitness (VO_{2PEAK}/ AT) in differing disease states over short timeframes (≤8 weeks). We also aimed to identify conditions where HIIT might be particularly effective compared to CON or MCT.

2.3 Methods

2.3.1 Study design

This systematic review was prospectively registered with PROSPERO (registration number CRD42016042299) and performed according to the PRISMA statement (Moher *et al.*, 2009). Only randomised control trials (RCT's) evaluating HIIT vs. CON or HIIT vs. MCT were included. Other inclusion criteria were participants aged >17 years old with disease, an intervention duration of 8 weeks or less and trials where outcome data was reported pre and post intervention. Trials involving a drug treatment or dietary supplementation were excluded. We classified trials as delivering high-intensity interval training if they satisfied the following criteria: i) high intensity efforts interspersed with reduced or no effort recovery periods, and ii) high intensity bouts >85% predicted heart rate or heart rate reserve, or iii) high intensity bouts >85% of peak power output or peak power achieved at baseline exercise test. Studies using 'supra-maximal' loading of >100% Wattage max at CPET or similar loading criteria were not included.

2.3.2 Literature search

Literature searches were carried out by a research team members (JB and BD) using the following databases: MEDLINE, EMBASE, CINAHL, AMED, and PubMed, all searched from their inception to 4th July 2016, with no language restriction. A detailed search for unpublished studies was carried out on Clinicaltrials.gov. The Cochrane library of systematic reviews was searched for relevant previous reviews, whilst previous systematic reviews of related topics were also searched for relevant primary studies. References of all identified potentially relevant primary studies were hand-searched for further relevant studies. Finally, we searched for studies citing the identified potentially relevant primary studies on Google Scholar to identify any further work potentially meeting the inclusion criteria.

Medical subject headings (MeSH) included the terms 'HIIT', 'HIT' and 'EXERCISE'. Free-text words included 'exercise', 'high AND intensity' and 'interval'. Abstracts of identified studies were screened by two authors independently (JB and BD). Full text versions of potentially relevant primary studies were then independently screened against the inclusion and

exclusion criteria by two authors (JB and SR) and agreement to inclusion reached by consensus.

2.3.3 Data extraction

Study characteristics (authors and year of publication, mean age (years), % female individuals, training intervention duration (weeks), number of planned exercise sessions in total, disease state, individual exercise protocols and country of origin) were extracted by one author (JB) with outcome data (VO_{2PEAK}, AT, SBP, DBP, 6-MWT, QoL questionnaires, adherence data) independently extracted and verified by two authors (JB and SR). Risk of bias for included studies was assessed using the Cochrane Collaboration tool for assessing risk of bias. This was performed independently by two authors (JB and BD), with any disagreement resolved by consensus with a third party author (PH). When outcome data was only reported in graphical form, data were extracted using WebPlotDigitizer (Version 3.12, Austin, Texas, USA).

2.3.4 Statistical analysis

To facilitate meta-analysis of change variables when standard deviations (SD) of change were not reported, SDs were imputed using recommended methods described in the Cochrane Handbook (Collaboration, 2006). First, studies that reported data as SD of the difference between pre versus post values were used to calculate correlation coefficients, these were then averaged for each outcome and used these to calculate change SDs from reported baseline and final SDs. Outcomes were aggregated using a random-effects model. Changes in VO_{2PEAK} and AT are presented as mean difference (MD) with 95% confidence intervals (CI), in the unit $ml \cdot kg^{-1} \cdot min^{-1}$. All other continuous outcomes are also reported as MD. Minimal clinically significant improvements were defined as follows: change in VO_{2PEAK} and AT >1.5 $ml \cdot kg^{-1} \cdot min^{-1}$ (Dunne *et al.*, 2016), six minute walk test (6-MWT) >17-23 meters (Gremeaux *et al.*, 2011; Kwok *et al.*, 2013), <systolic/ diastolic blood pressure (BP) of 10mmHg/ 5mmHg (Law, Morris and Wald, 2009).

The I^2 statistic was used to quantify statistical heterogeneity, with values above 50% taken as evidence of statistical heterogeneity. Publication bias was assessed qualitatively using funnel plots and quantitatively using Egger's linear regression test ($p<0.05$ as evidence of imprecise study

effects). We investigated heterogeneity using a random effects, restricted maximum likelihood meta-regression. Covariates included mean age of participants, duration of intervention (weeks) and co-morbidity. For co-morbidity, we created dummy variables and used the least effective subgroup as the reference category. We report the between-study heterogeneity explained by the model (R^2 analogue) with a corresponding p-value. The Knapp-Hartung modification was used as the variance estimator. To assess the quality of evidence, the GRADE approach (Collaboration, 2006) was used with evidence downgraded to moderate, low or very low quality owing to concerns over unexplained heterogeneity, indirectness of evidence, possible publication bias, imprecision in effect estimates and concerns over risk of bias. All calculations were carried out using STATA 15 (StataCorp, Texas USA).

2.4 Results

2.4.1 Search results

A total of 2612 abstracts were screened for inclusion; 2570 from the initial literature search and 42 from the reference lists of other identified studies, Google Scholar citations and other systematic reviews. Of the 2612 abstracts screened, 2559 were excluded as not being relevant or duplicates, leaving 53 studies for full-text review. Of the 53 studies undergoing full text review, 14 were excluded, leaving 39 studies for inclusion in the qualitative analysis and 34 studies for quantitative analysis (Figure 22).

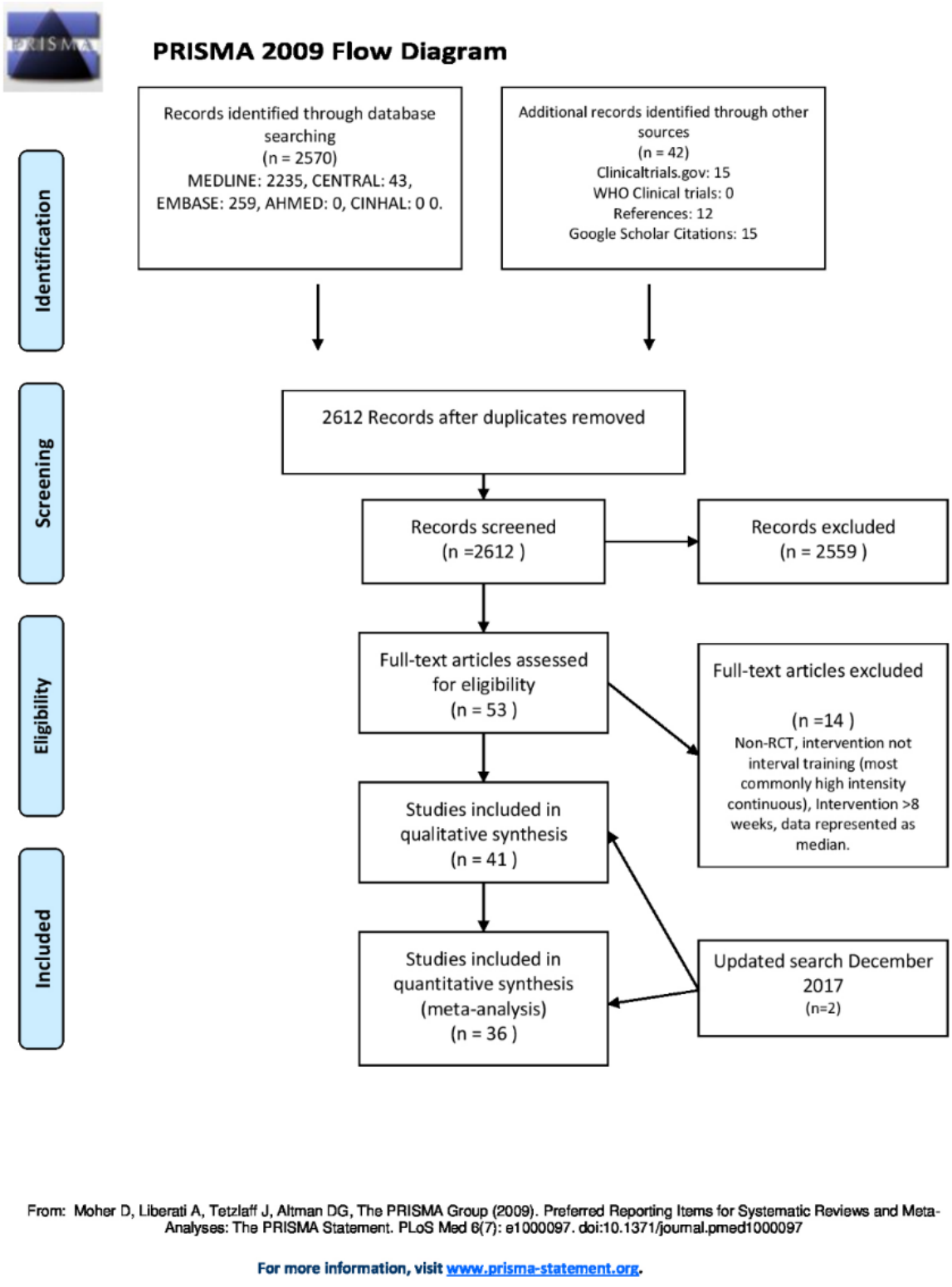


Figure 22 - PRISMA Flow Chart (Moher et al., 2009).

2.4.2 Study characteristics

The characteristics of the included studies can be found in Table 2 (HIIT vs. CON) and Table 3 (HIIT vs. MCT). The specific HIIT regimes can be found in the Appendices (8.2 Chapter 2 Appendices). The earliest study meeting the inclusion criteria was published in 1999 and the latest in 2016. All studies were published as journal articles. The interventions studied were HIIT vs. CON or HIIT vs. MCT. Three studies were included in both analyses which compared HIIT vs. CON vs MCT (Wallman *et al.*, 2009; Dolan *et al.*, 2016; Mobius-Winkler *et al.*, 2016).

Table 2 - Paper Characteristics (HIIT vs CON)

Author	Year	Mean age (years)	%female	Duration (weeks)	Exercise sessions	Comorbidity	Country
Andersen et al.	2017	50	33%	8	24	Neurological/muscular	Denmark
Dolan et al.	2015	57	100%	6	18	Cancer	Canada
Dunne et al.	2016	62	29%	4	12	Cancer	UK
Flemmen et al.	2014	32	19%	8	24	Psychiatry	Norway
Freese et al.	2014	52	100%	6	18	Obesity / Metabolic / Endocrine	USA
Heggelund et al.	2011	33.6	32%	8	24	Psychiatry	Norway
Hermann et al.	2011	50	19%	8	24	Cardiovascular	Denmark
Hwang et al.	2012	60	50%	8	24	Respiratory	Taiwan
Licker et al.	2017	64	40%	4	~12	Cancer	Switzerland
Mobius-Winkler et al.	2016	64	25%	4	20	Cardiovascular	Germany
Monk-Hansen et al.	2014	50	22%	8	24	Cardiovascular	Denmark
Smith-Ryan et al.	2016	34	100%	3	9	Obesity / Metabolic / Endocrine	USA
Trilk et al.	2010	31	100%	4	12	Obesity / Metabolic / Endocrine	USA
Wallman et al.	2009	42	75%	8	32	Obesity / Metabolic / Endocrine	Australia

Table 3 - Paper Characteristics (HIIT vs MCT)

Author	Year	Mean age (years)	%female	Duration (weeks)	Exercise sessions	Comorbidity	Country
Angadi et al.	2015	70	20	4	12	Cardiovascular	USA/Canada
Baekkerud et al.-4x4	2015	41.4	63.3	6	18	Obesity / Metabolic / Endocrine	Norway
Baekkerud et al.10x1	2015	41.4	63.3	6	18	Obesity / Metabolic / Endocrine	Norway
Boyne et al.	2016	58	31.2	4	12	Cardiovascular	USA
Coppoolse et al.	1999	65	0	8	40	Respiratory	Holland
Devin et al.	2016	61.5	21	4	12	Cancer	Australia
Dolan et al.	2015	57	100	6	18	Cancer	Canada
Fisher et al.	2015	20	0	6	18	Obesity / Metabolic / Endocrine	USA
Freyssin et al.	2012	54	50	8	40	Cardiovascular	France
Gloeckl et al.	2012	53	53.3	3	18	Respiratory	Germany
Higgins et al.	2016	20.4	100	6	18	Obesity / Metabolic / Endocrine	USA
Jaureguizar et al.	2016	58	15.3	8	24	Cardiovascular	Spain
Jung et al.	2015	51	84.4	6	22	Obesity / Metabolic / Endocrine	Canada

Kim et al.	2015	59	21	6	18	Cardiovascular	South Korea
Kong et al.	2016	21	100	5	20	Obesity / Metabolic / Endocrine	China
Lanzi et al.	2015	36.5	0	2	8	Obesity / Metabolic / Endocrine	Italy
Mador et al.	2009	72	Missing info 'majority male'	8	24	Respiratory	USA
Matsuo et al.	2015	47	0	8	24	Obesity / Metabolic / Endocrine	Japan
Moholdt et al.	2009	61.1	22	4	20	Cardiovascular	Norway
Puhan et al.	2006	69	33.7	3	15	Respiratory	Switzerland
Robinson et al.	2015	52	82.2	2	10	Obesity / Metabolic / Endocrine	Canada
Sawyer et al.	2016	35	50	8	24	Obesity / Metabolic / Endocrine	USA
Schmitt et al.	2016	54	100	3	8	Cancer	Germany
Skleryk et al.	2013	37.8	0	2	(HIIT 6, MCT 10)	Obesity / Metabolic / Endocrine	New Zealand
Slordhal et al.	2005	66.2	Missing info	8	24	Cardiovascular	Norway
Uhleman et al.	2016	64	25	4	20	Cardiovascular	Germany
Wallman et al.	2009	42	75	8	32	Obesity / Metabolic / Endocrine	Australia

2.4.3 Risk of bias

All included studies were at high risk of bias in at least one domain (Figure 23). The majority of studies were at high risk of bias due to the innate difficulties in blinding participants to a physical activity intervention. A large number of studies did not describe their random sequence allocation or allocation concealment in sufficient detail to be judged as low risk of bias, and many did not describe blinding of their outcome assessment. Many studies were at risk of reporting bias and some may have suffered from attrition bias.

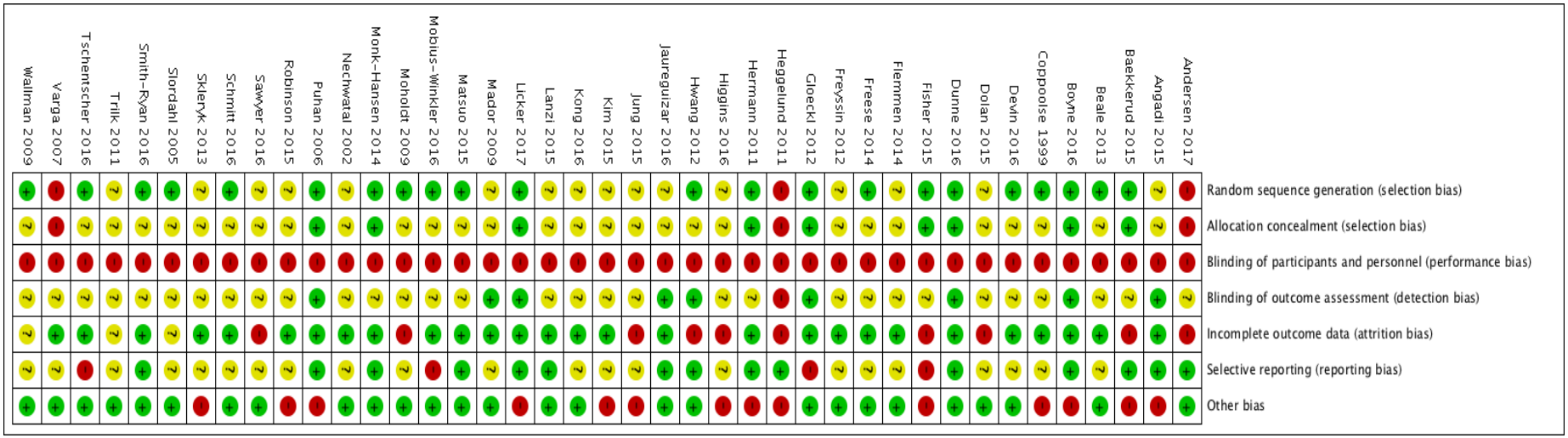


Figure 23 - Risk of Bias Tool.

2.4.4 Data synthesis

There were sufficient studies to perform independent meta-analysis for VO_{2PEAK}, AT, 6-MWT, SBP and DBP for both HIIT vs. CON and HIIT vs. MCT interventions.

2.4.5 VO_{2PEAK}

Of 11 study groups from 11 trials analysed for the comparison of HIIT vs. CON, comprising 153 individuals in the HIIT groups and 124 CON participants, HIIT produced a clinically significant increase in VO_{2PEAK} compared with CON (MD 3.38 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI 2.70 to 4.05; I^2=47.8%) (Figure 24). Of 25 study groups from 24 trials comparing HIIT to MCT, comprising 359 individuals in the HIIT groups and 341 MCT participants, HIIT provided additional mean increase in VO_{2PEAK} compared with MCT (MD 0.79 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI 0.20 to 1.39; I^2=50.5%) (Figure 25). However, this improvement did not meet our a priori target of clinical significance (>1.5 $ml \cdot kg^{-1} \cdot min^{-1}$). Cardiovascular patients showed the greatest improvement, with clinically significant mean increases in VO_{2PEAK} following HIIT (MD 1.68 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI 0.67 to 2.70, I^2=37.0%) when compared to MCT (Figure 25).

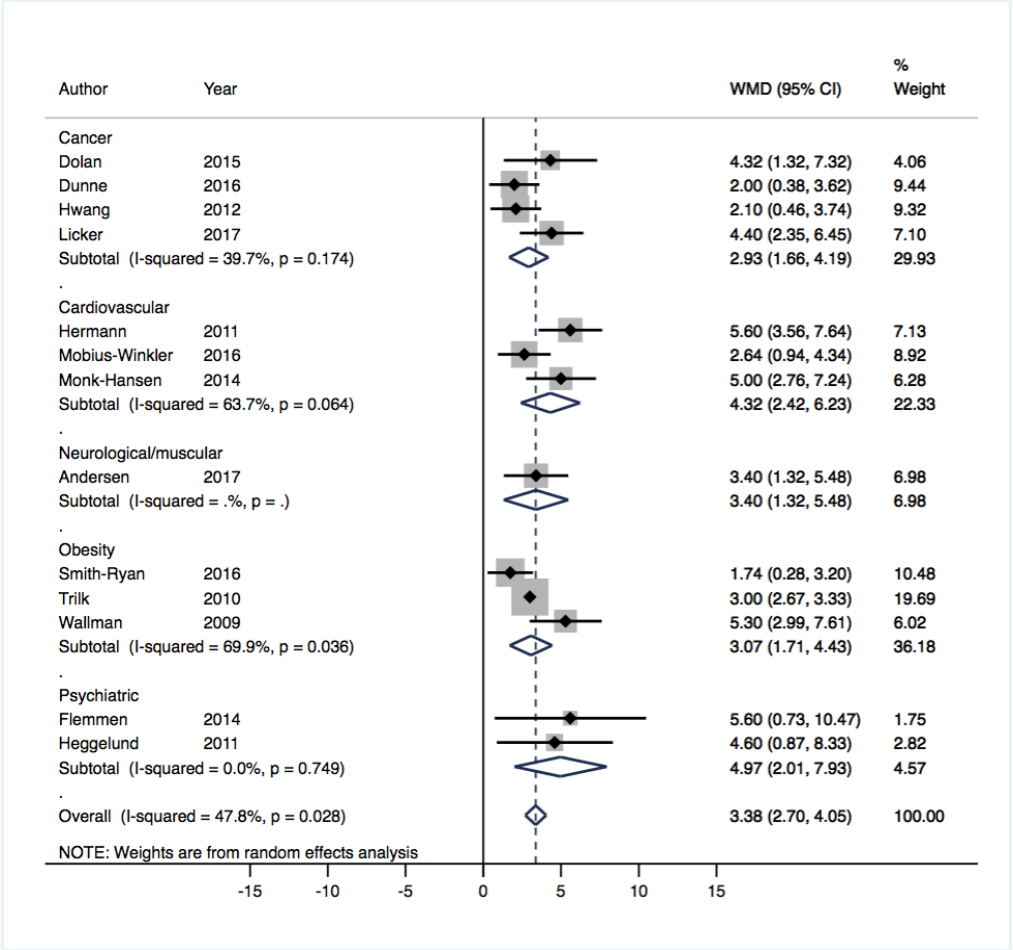


Figure 24 - Forest plot showing meta-analysis of VO_{2PEAK} data for HIIT vs CON (WMD ml·kg-1·min-1). Diamonds to the right of the plot show benefit with HIIT.

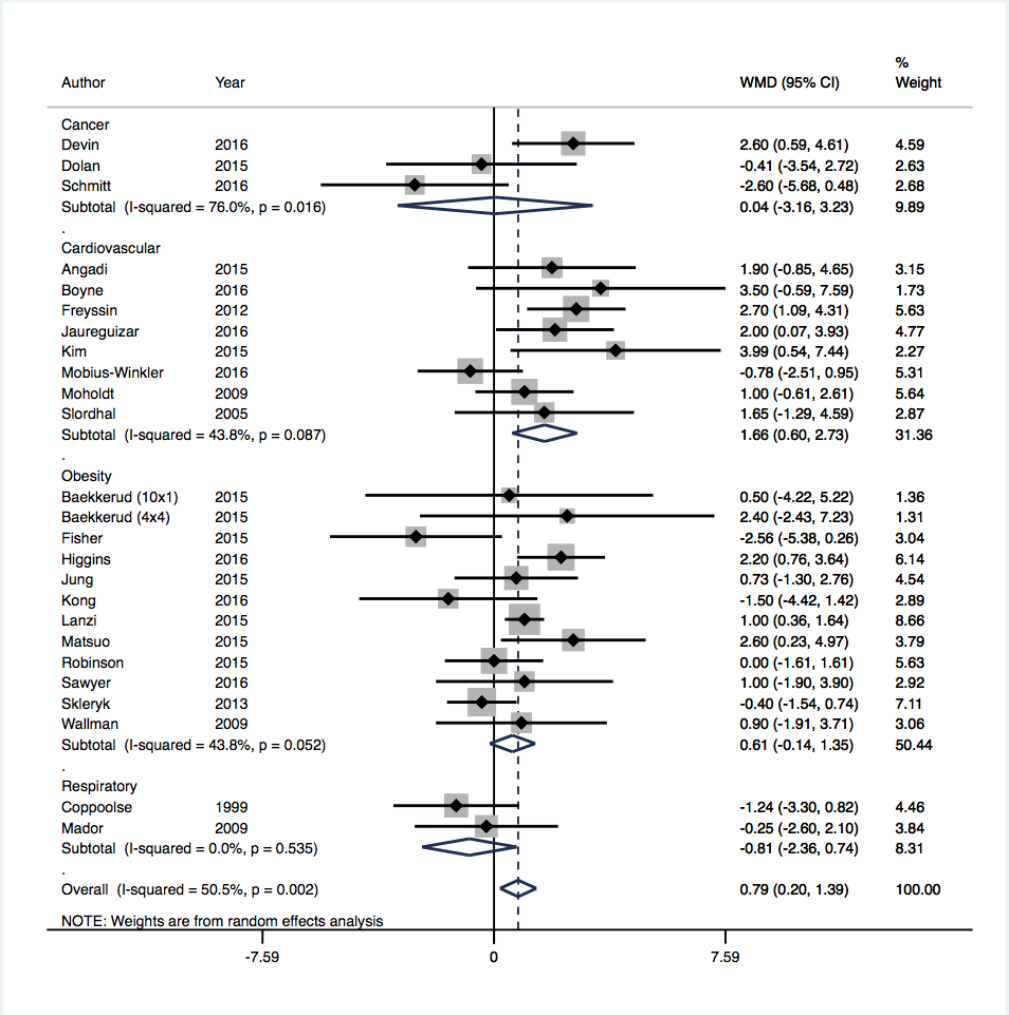


Figure 25 - Forest plot showing meta-analysis of VO_{2PEAK} data for HIIT vs MCT (WMD ml·kg-1·min-1). Diamonds to the right of the plot show benefit with HIIT.

On meta-regression analysis, duration of intervention showed significance for HIIT vs. CON (R^2=60.96%, p=0.027) but non-significant for HIIT vs. MCT (R^2=5.54%, p=0.245). For HIIT vs. CON, longer duration of interventions led to larger increases in VO_{2PEAK}. Neither HIIT vs. CON nor HIIT vs MCT showed significant interaction for age (R^2=0%, p=0.637 and R^2=0%, p=0.529 respectively). On meta-regression analysis of HIIT vs. MCT, HIIT was more effective in cardiovascular patients (R^2=4.46%, p=0.057) than respiratory patients.

There was no evidence of publication bias in either analysis (p=0.27 and p=0.91). The quality of evidence of VO_{2PEAK} data was regarded as moderate for HIIT vs. CON (downgraded owing to concerns over risk of bias) and low for HIIT vs. MCT (downgraded owing to concerns over risk of bias and

unexplained heterogeneity) using GRADE criteria (Abbasi and Paterson-brown, 1998).

2.4.6 AT

A single study reported AT following HIIT vs. CON, showing a mean improvement in AT following HIIT vs. CON (MD 1.5 ml·kg^{-1}·min^{-1}; 95% CI 0.18 to 2.82). There was no further data available for meta-analysis to be performed in relation to anaerobic threshold for HIIT vs CON.

HIIT provided additional increase in AT compared with MCT of borderline statistical but not clinical significance (MD 1.26 ml·kg^{-1}·min^{-1}; 95% CI -0.02 to 2.54, I^2=38.3%) in 6 study groups from 5 trials, comprising 84 individuals receiving HIIT and 79 MCT. Cardiovascular patients showed the greatest mean improvement in AT following HIIT in comparison with MCT (MD 1.61 ml·kg^{-1}·min^{-1}; 95% CI 0.33 to 2.90, I^2=39.8%) (Figure 26). The quality of evidence of AT data for HIIT vs. MCT was regarded as low using GRADE criteria (downgraded owing to concerns over risk of bias and imprecision) (Abbasi and Paterson-brown, 1998).

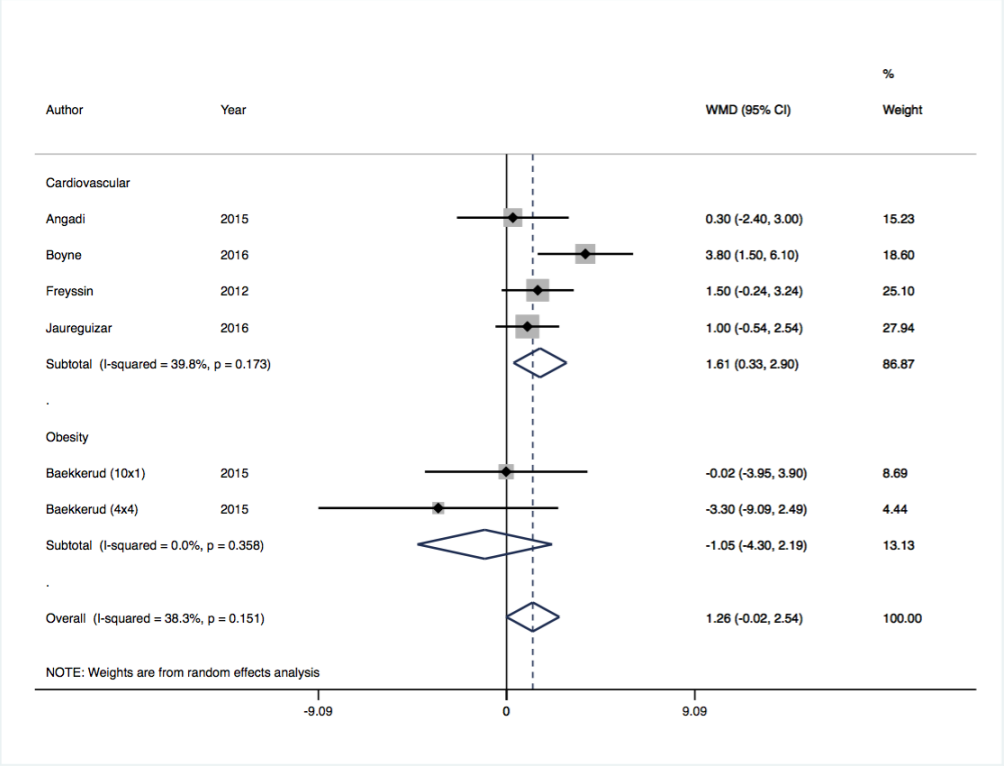


Figure 26 - Forest plot showing meta-analysis of AT data for HIIT vs MCT (WMD ml·kg-1·min-1). Diamonds to the right of the plot show benefit with HIIT.

2.4.7 Other outcome measures

2.4.7.1 Six minute walk test

No studies reported 6-MWT outcomes for HIIT vs. CON. For the comparison of HIIT vs. MCT, six study groups from 6 trials were analysed, comprising 151 individuals in the HIIT groups and 149 participants in the MCT group. HIIT delivered an increase in 6-MWT distance compared with MCT (MD 11.67 meters; 95% CI 1.28 to 22.06; I^2=38.9%). Cardiovascular patients showed a greater, yet clinically insignificant improvement (MD 16.64 meters; 95% CI 5.22 to 28.07; I^2=31.9%) compared to respiratory patients (MD 2.05 meters; 95% CI -12.57 to 16.66; I^2=0%).The quality of evidence 6-MWT was regarded as low using GRADE criteria (downgraded owing to concerns over risk of bias and imprecision)(Abbasi and Paterson-brown, 1998).

2.4.7.2 Blood Pressure

When analysing blood pressure changes in HIIT vs CON 6 study groups from 6 trials reported systolic blood pressure (SBP) results, whereas only 5 trials presented data for analysis of diastolic blood pressure (DBP) changes due to unreliable data in one study (Hwang *et al.*, 2012). These studies comprised 79 individuals for SBP in the HIIT groups (DBP 66 individuals) and 67 individuals for SBP in the CON groups (DBP 57 individuals). Compared to CON, HIIT provided a non-significant reduction in SBP (MD -4.48 mmHg; 95% CI -11.13 to 2.18; I^2=58.8%) and a statistically significant reduction in DBP (MD -3.05 mmHg; 95% CI -5.41 to -0.69; I^2=0%), which however did not meet our a priori target of clinical significance (DBP -5mmHg).

When analysing BP changes in HIIT vs. MCT, for SBP and DBP 8 study groups from 8 trials were included. These studies comprised 116 individuals for both SBP and DBP in the HIIT groups and 113 individuals for SBP and DBP in the CON groups. HIIT provided no additional benefit in either SBP (MD 0.48 mmHg; 95% CI -2.01 to 2.97; I^2=0.0%) or DBP (MD -0.51 mmHg; 95% CI -2.53 to 1.50; p=0.136; I^2=36.8%) compared to MCT. The quality of evidence for blood pressure was regarded as moderate to low using GRADE criteria (downgraded owing to concerns over risk of bias and imprecision for some analyses)(Abbasi and Paterson-brown, 1998).

2.4.7.3 Quality of life

There was marked variation in both instrument selection and reporting of quality of life (QoL) qualitative measures and questionnaire outcomes were equivocal between both HIIT vs CON and HIIT vs MCT (Table 4 (HIIT vs. CON) and Table 5 (HIIT vs. MCT). The most commonly reported QoL questionnaire was SF-36 (Ware, J. E., 1999). Studies including SF-36 data did so either with a total score (overall scores) or by domains (summary scores) of the full questionnaire (i.e: Physical Health, Perceived Health, Mental Health). Dunne et al. (2016) reported that HIIT prehabilitation was associated with improvements in overall SF-36 QoL and SF-36 mental health scores (change of +11 $p=0.028$ and +11 $p=0.037$ respectively) (Dunne et al., 2016). Gloeckl et al. (2012) reported increased overall SF-36 scores following both HIIT and MCT, however only the physical health summary score in the MCT group (MD 4.3 $p<0.05$) and the mental health summary score in the HIIT group (MD 9.7 $p<0.05$) improved significantly (Gloeckl, Halle and Kenn, 2012). Freese et al. (2014) reported clinically meaningful improvements in role-physical scores, bodily pain, vitality, social functioning, mental health and total SF-36 score following 6 weeks HIIT (Freese et al., 2014). Jaureguizar et al. (2016) reported significant increases in the role emotional, mental health, self-reported health status and the mental health index following HIIT only (Jaureguizar *et al.*, 2016). Other quality of life questionnaires used in more than one study are summarized in Table 4 and Table 5.

Table 4 - Quality of life and mood questionnaires (HIIT vs CON), Negative values represent decreases in scores. SF-36 = 36 item Short Form Survey, HADS = Hospital anxiety and depression score, EORTC QLQ-C30 = Colorectal specific quality of life questionnaire.

Author	Year	Questionnaire	HIIT	CON	p value	Comments
Dunne et al.	2016	SF-36	12	1	HIIT vs CON 0.028	
Freese et al.	2014	SF-36	6.6	3.4	not reported	
Freese et al.	2014	POMS-B	-9.9	-5.3	not reported	
Heggelund et al.	2011	SF-36 (physical + mental health)	no total scores	no total scores	not reported	no p value - states no significant difference from pre - post test or within groups.
Heggelund et al.	2011	Positive and negative syndrome scale	-1.4	-2	not reported	no p value - states no significant difference from pre - post test or within groups.
Heggelund et al.	2011	Calgary Depression Scale for Schizophrenia	-0.1	-0.5	not reported	no p value - states no significant difference from pre - post test or within groups.

Hwang et al.	2012	EORTC QLQ-C30 and LC13	3.1	5.1	HIIT p=0.17 / MCT p=0.34	Between group effect 0.45.
Flemmen et al.	2014	HADS - anxiety	-0.8	-2.8	p < 0.05 - favours CON	
Flemmen et al.	2014	HADS - depression	-3.2	-1.4	p < 0.05 - favours HIIT	
Flemmen et al.	2014	HADS - insomnia	-1.7	-1.8	no significant difference	

Table 5 - Quality of Life and Mood Questionnaires (HIIT vs MCT), Negative values represent decreases in scores. SF-36 = 36 item Short Form Survey, HADS = Hospital anxiety and depression score, EORTC QLQ-C30 = Colorectal specific quality of life questionnaire.

Author	Year	Questionnaire	HIIT	MCT	p value	Comments
Freyssin et al.	2012	HADS Depression	-3.2	-4.2	Both p = <0.5	
Freyssin et al.	2012	HADS Anxiety	-2.7	-2.3	Both p = <0.5	
Puhan et al.	2006	HADS Depression	2.05	2.93		Mean changes from baseline.
Puhan et al.	2006	HADS Anxiety	1.95	2.25		Mean changes from baseline.
Puhan et al.	2006	Chronic Respiratory Questionnaire Total score	1	1.02		Mean changes from baseline.
Mador et al.	2009	Chronic Respiratory Questionnaire Total score	9.7	12.2	Both p<0.05	
Moholdt et al.	2009	Macnew Questionnaire for post CABG - emotional	0.5	0.5	Both p<0.001	
Moholdt et al.	2009	Macnew Questionnaire for post CABG - physical	0.5	0.6	Both p<0.001	
Moholdt et al.	2009	Macnew Questionnaire for post CABG - social	0.9	0.9	Both p<0.001	

Jaureguizar et al.	2016	SF36 split into individual domains. X11				
Jaureguizar et al.	2016	Macnew Questionnaire for post CABG - emotional	0.5	0.3	HIIT p<0.01	
Jaureguizar et al.	2016	Macnew Questionnaire for post CABG - physical	0.3	0.4	HIIT p<0.01, MCT p<0.05	
Jaureguizar et al.	2016	Macnew Questionnaire for post CABG - social	0.4	0.4	HIIT p<0.01, MCT p<0.05	
Jaureguizar et al.	2016	Macnew Questionnaire for post CABG - global	0.5	0.3	HIIT p<0.01, MCT p<0.05	
Gloeckl et al.	2012	Short form SF36 Physical helth	2.3	4.3	MCT p<0.05	
Gloeckl et al.	2012	Short form SF36 Mental health	9.7	2.9	HIIT p<0.05	
Schmitt et al.	2016	EORTC QLQ-C 30 (QoL)	9.5	17.4	Both p<0.005	
Schmitt et al.	2016	EORTC QLQ-C 30 (emotion)	11	31.5	Both p<0.05	

2.4.7.4 Anxiety / Mood

Questionnaires used for anxiety and mood can be seen Tables 4 (HIIT vs. CON) and Table 5 (HIIT vs. MCT). The most commonly reported questionnaire to determine anxiety and mood was the Hospital Anxiety and Depression Scale (HADS). Again due to paucity of studies reporting values no meta-analysis was performed across HIIT vs. CON or HIIT vs. MCT. Flemmen *et al.* (2014) showed a significant reduction in anxiety favouring CON ($p<0.05$) and a significant reduction in depression following HIIT ($p<0.05$), with no significant difference in reported insomnia (Flemmen *et al.*, 2014). For HIIT vs. MCT both studies showed improvements in the HADS anxiety and depression domains however with no significant benefit between intervention arms (Puhan, 2006; Freyssin *et al.*, 2012).

2.4.7.5 Adherence

Due to widespread lack of reporting and insufficient information included within published papers, we deemed it inappropriate to analyse adherence from the number of drop-outs to each intervention, as very few studies reported the direct reason for participants dropping out in HIIT or MCT groups. Disparity in duration of exercise (weeks) led to varying numbers of scheduled sessions per study. Overall, adherence to scheduled sessions was high in both groups (Table 6).

Table 6 - Adherence to scheduled exercise sessions.

Author:	Year:	HIIT	MCT
Uhleman et al.	2016	-	-
Dolan et al.	2015	98.70%	98.70%
Wallman et al.	2009	-	-
Angadi et al.	2015	99%	99%
Boyne et al.	2016	100%	100%
Fisher et al.	2015	-	-
Freyssin et al.	2012	100%	100%
Jung et al.	2015	100%	100%
Kim et al.	2015	100%	100%
Lanzi et al.	2015	98.60%	100%
Matsuo et al.	2015	97.10%	97.40%
Puhan et al.	2006	86.70%	86.70%
Schmitt et al.	2016	93%	93%
Slordhal et al.	2005	96%	98%
Coppoolse et al.	1999	-	-
Devin et al.	2016	96.7	94.1
Gloeckl et al.	2012	-	-
Higgins et al.	2016	83.30%	87.80%
Kong et al.	2016	-	-
Mador et al.	2009	100%	100%
Moholdt et al.	2009	82%	83.50%
Robinson et al.	2015	100%	100%
Sawyer et al.	2016	100%	100%
Skleryk et al.	2013	100%	100%
Jaureguizar et al.	2016	92%	88%
Baekkerud et al. - 4x4	2015	100%	100%
Baekkerud et al. - 10x1	2015	100%	100%

2.5 Discussion

In this review of the current literature exploring the effectiveness of short duration HIIT in disease cohorts, we found that HIIT elicits clinically important improvements (>1.5 $ml \cdot kg^{-1} \cdot min^{-1}$) in VO_{2PEAK} within 8 weeks or less when compared to non-intervention control subjects.

This is in keeping with previous data in both healthy young and older individuals (>60 years), where HIIT has been shown to improve aspects of fitness. In healthy young individuals completing sprint interval training (4-6 intervals, 30 second all-out sprints), similar adaptations in human skeletal muscle oxidative capacity and exercise performance to those undertaking MCT (90-120 minutes continuous cycling at 65% VO_{2PEAK}) were seen in as little as 2-weeks, despite a vastly reduced time commitment and training volume (approximately 90% lower vs. MCT) (Gibala *et al.*, 2006). Similarly, in healthy older individuals HIIT has been shown to increase VO_{2PEAK} (+8%) and reduce systolic blood pressure (-9%) in just 6-weeks (Adamson *et al.*, 2014). Moreover, in a separate study of healthy older individuals, HIIT has also recently been shown to elicit clinically significant improvements in CRF within just 31-days (Boereboom *et al.*, 2016), a time-frame which is compliant with the aforementioned UK National Cancer Action Team policy on time from decision-to-treat to surgery. In addition to the reduced time-frame and training volume required by HIIT to elicit improvements in CRF, HIIT may also have the added advantage of rapid adaptation at the level of skeletal muscle, resulting in fewer negative training symptoms (e.g. delayed onset muscle soreness (Ross, Porter and Durstine, 2016), which is postulated to lead to increased adherence.

HIIT is at least as effective as MCT over short time periods across all groups. Subgroup analysis showed additional benefit in cardiovascular patients versus other patient groups following HIIT. To exemplify, cardiovascular patients showed additional increases in VO_{2PEAK} and AT following HIIT when compared with MCT. It is likely that the rapid benefit shown in this review is a result of peripheral adaptations such as mitochondrial oxidative enzyme upregulation and increased buffering capacity (Gibala *et al.*, 2006) as it is only in longer-term training programs (≥12 weeks) that improvements in cardiac structure and systolic function have been shown (Cassidy *et al.*, 2016). In response to HIIT the contribution of cardiac change may be

underestimated due to the research focus primarily being upon mitochondrial upregulation, with potential cardiac changes being understudied.

A small number patients with cancer were included in this review, with varying outcomes. Lung, colon and breast cancer groups all showed improvement in CRF with HIIT when compared to no exercise. There was no added benefit of HIIT over MCT. Blunted adaptation in these cancer groups (shown as a lack of CRF improvement in response to HIIT compared to the overall effect of HIIT vs. CON) may be explained by blunted mitochondrial enzyme activity whilst cancers remain in situ (Phillips, B E. *et al.*, 2013). In addition, colorectal cancer patients presenting for resection have lower CRF than age-matched controls whilst the cancer is still in situ. However, removal the cancer facilitates a return toward normal CRF (Williams *et al.*, 2014). Taken together, these studies may lead to a suggestion that tumour presence hinders adaptive capacity to exercise training, at least in this cancer type. Adjuvant chemotherapy has negative effects upon cardiorespiratory fitness preoperatively in colorectal cancer patients (Jack *et al.*, 2014) and have resulted in higher rates of heart failure and cardiomyopathy following breast cancer chemotherapy (Bowles *et al.*, 2012), as such these confounding drug regimens must be considered when interpreting trainability within these groups.

The beneficial psychological effects of exercise *per se* are well known but it is unclear whether HIIT is superior to MCT in improving QoL from this review. This lack of clarity is due to the heterogeneity of tools used, small numbers of studies reporting QoL outcomes and lack of suitable comparisons for many of the questionnaires.

Beyond mechanistic propositions based on small-scale non-RCTs in distinct disease groups, reasons why certain pathological subgroups might not show CRF improvements with HIIT is far from clear. One possible explanation for certain subgroups is that exercise intervention studies mainly report mean improvements in CRF parameters as $ml \cdot kg^{-1} \cdot min^{-1}$, rendering obese patients at a relative disadvantage for demonstrating improvement over short periods; as in the authors' experience individuals normally remain weight-stable during short-term HIIT protocols (often due to increased lean muscle mass and fat mass reductions). A recent meta-analysis in obesity concluded that HIIT was superior to traditional exercise to improve CRF and reduce

body fat percentage. Notably the median duration of training protocol for this meta-analysis was 12 weeks, with a wide range of 2-52 weeks (Türk *et al.*, 2017), which is does not comply with clinical time-frames for cancer surgery. In contrast, but in agreement with this review, another recently published meta-analysis found no clinical benefit of HIIT versus MCT in reduction of total body fat or fat mass over shorter training duration (<12 weeks) (Keating *et al.*, 2017).

To achieve benefit from HIIT it is thought that a minimal dose of exercise expenditure, or training load is required to significantly disturb intracellular homeostasis and stimulate mitochondrial biogenesis (Gibala *et al.*, 2012b). This may explain why the respiratory patients seem to gain less benefit versus other pathological groups as respiratory limitation may result in low maximal exercise scores and therefore lower training loads, given that most protocols prescribe the training load as a percentage of VO_{2PEAK} or maximal wattage achieved at CPET.

HIIT can represent a time efficient training method by which to improve CRF, potentially removing the commonly cited "lack of time" as a barrier to exercise (Trost *et al.*, 2002). Time efficiency can be due to two facets, reduced work duration within a session and/ or individual session time. For example, one of the most commonly employed HIIT protocols within studies in this review employed 10 intervals of 1-minute with 1-minute rest periods in between (Jung *et al.*, 2015; Lanzi *et al.*, 2015; Robinson *et al.*, 2015; Baekkerud *et al.*, 2016; Sawyer *et al.*, 2016; Smith-Ryan *et al.*, 2016) totalling a session duration of ~20 minutes. However, another frequently used HIIT protocol employed 4 intervals of 4-minutes high intensity work with 3 minute rest periods in between each bout, which led to sessions typically lasting >30-minutes (Moholdt *et al.*, 2009; Heggelund *et al.*, 2011; Flemmen *et al.*, 2014; Angadi *et al.*, 2015; Kim, C. Choi, HE. Lim, 2015; Baekkerud *et al.*, 2016; Devin *et al.*, 2016; Dunne *et al.*, 2016) including a work duration of 16-minutes (vs. 10-minutes in the aforementioned example). Herein we show that, excluding warm-up and end of session recovery periods, median work duration during a HIIT session was half of that for MCT protocols (16-minutes vs. 30-minutes). In addition, a number of studies in this review (Mador *et al.*, 2009; Trilk *et al.*, 2011; Freyssin *et al.*, 2012; Skleryk *et al.*, 2013; Freese *et al.*, 2014; Jung *et al.*, 2015; Matsuo *et al.*, 2015; Robinson *et al.*, 2015; Boyne *et al.*, 2016; Sawyer *et al.*, 2016;

Schmitt *et al.*, 2016; Smith-Ryan *et al.*, 2016; Higgins *et al.*, 2016; Jaureguizar *et al.*, 2016; Kong *et al.*, 2016) used low volume HIIT protocols, involving 10 minutes (or less) total work duration (Gibala, Gillen and Percival, 2014). Indeed, CRF improvements have been shown in as little as ten percent of the training volume with HIIT when compared to MCT (Burgomaster *et al.*, 2008). Taken in combination, reductions in regime duration, total volume of training and weekly time commitment represent important drivers for enhancing adherence and reducing costs associated with patient training. However, further work is required to elucidate the optimal work-to-rest ratios within HIIT protocols, which may further reduce the total time commitment for the individual. It is also worth noting whilst the majority (>90%) of studies within this review utilised a static cycle-ergometer for HIIT other training modalities (e.g. running) maybe viable. However further work is needed to assess the efficacy and tolerability when compared to cycle ergometry within certain patient groups.

Quality of life and mood outcomes analysed in this review were pre-to-post training program questionnaires; mostly global QoL scores or disease specific questionnaires. These outcomes are not specific enough to draw conclusions as to whether individuals preferred HIIT or MCT. However as there were no significant differences in the number of non-compliers, adherence to scheduled sessions (Table 6) or reported serious adverse events leads us to believe that neither HIIT nor MCT are inferior for enjoyment, acceptability or safety when compared.

2.5.1 Limitations

The studies in this review have a high risk of bias, some of which is unavoidable because of the nature of exercise intervention studies and the inability to blind participants as seen in the risk of bias summary chart (Figure 23). There is also a risk of contamination between HIIT and non-intervention controls. In addition, heterogeneity amongst HIIT protocols, training duration, chronological age and pathology leads to uncertainty about the true effectiveness of interventions (Hijazi, Gondal and Aziz, 2017) (Table 2, Table 3, Table 8 and Table 9).

In the period between the initial search (July 2016) and date of submission (December 2016), two further qualifying studies were published both of which were in keeping with the main findings of this review. The Licker et

al., (2016) study of preoperative HIIT in patients with operable lung cancer (n=74, median 26 days) versus usual care (n=77) resulted in significant improvements in VO_{2PEAK} (median +2.9 $ml \cdot kg^{-1} \cdot min^{-1}$; CI 95% 1.1 to 4.2, p=0.004) and 6-MWT (median +66 meters; 95% CI 8 to 125, p=0.001) in the HIIT group only (Licker *et al.*, 2017). The more recently published study by Andersen et al., (2017) compared HIIT to usual care in patients with facioscapulohumeral muscular dystrophy type 1. During the supervised exercise phase (8-weeks) of the study a significant treatment effect for fitness (VO_{2max} 3.3 $ml \cdot kg^{-1} \cdot min^{-1}$; CI 1.2–5.5, P<0.01) was observed (Andersen *et al.*, 2017).

2.5.2 Chapter Conclusions

HIIT produced statistically significant larger improvements in CRF when compared to MCT. This finding was true when all subjects were grouped together, and also true for cardiovascular disease patients in isolation. Due to HIIT's time-efficiency and improved efficacy versus MCT (including in certain clinical groups), HIIT can be promoted as a viable and valuable clinical exercise intervention to rapidly improve CRF.

As discussed in the introduction, the frail elderly surgical patient is at particular risk of perioperative morbidity and mortality, especially in the presence of pre-existing or occult cardiac disease. This makes the findings of this review even more interesting. For example, when considering the suitability of HIIT for 'all comers' to general surgery for surgically curative disease, pre-operative HIIT may be the most efficacious exercise method for those at highest risk (i.e. cardiovascular disease patients).

One caveat to the clinical relevance of the work outlined in this review is that the vast majority of the studies included were conducted in a supervised laboratory setting; a costly and resource dependent endeavour. It is unclear whether individuals would be able to make similar rapid gains in CRF by employing HIIT away from the laboratory (e.g., at home or in a community-gym type setting). If this was possible, this could represent a more feasible way to improve large numbers of patients' CRF prior to surgery, therefore this aspect is investigated further in Chapter 4.

3 Experimental Methods

3.1 Chapter focus

This chapter provides an overview of the common experimental methods used within studies in this thesis. Specific details regarding the individual study design, specific inclusion and exclusion criteria (in addition to the ATS/ ACCP CPET guidelines as stated below (American Thoracic and American College of Chest, 2003)) and any additional methods used in each study are given in Chapters 4, 5 and 6 respectively.

3.2 Screening

In order to determine potential participants' eligibility for the studies, after thorough explanation of the study by a member of the research team and provision of written informed consent by the participant, all participants underwent a screening session by a medically qualified doctor. This session lasted ~1 hour and included taking a full medical history, auscultation of the heart sounds and lung fields, recording a 12-lead ECG, non-invasive blood pressure (NIBP), height (cm) and weight (kg) (for calculation of BMI). Lastly venepuncture for baseline full blood count, renal and liver function. A coagulation tube was sent at this point for any individual consenting to undergo muscle biopsies.

3.2.1 Inclusion/ Exclusion criteria

Absolute exclusion criteria for all studies within this thesis were taken from the ATS/ ACCP guidelines for CPET (Figure 27) (American Thoracic and American College of Chest, 2003).

TABLE 8. ABSOLUTE AND RELATIVE CONTRAINDICATIONS FOR CARDIOPULMONARY EXERCISE TESTING

Absolute	Relative
Acute myocardial infarction (3–5 days)	Left main coronary stenosis or its equivalent
Unstable angina	Moderate stenotic valvular heart disease
Uncontrolled arrhythmias causing symptoms or hemodynamic compromise	Severe untreated arterial hypertension at rest (> 200 mm Hg systolic, > 120 mm Hg diastolic)
Syncope	Tachyarrhythmias or bradyarrhythmias
Active endocarditis	High-degree atrioventricular block
Acute myocarditis or pericarditis	Hypertrophic cardiomyopathy
Symptomatic severe aortic stenosis	Significant pulmonary hypertension
Uncontrolled heart failure	Advanced or complicated pregnancy
Acute pulmonary embolus or pulmonary infarction	Electrolyte abnormalities
Thrombosis of lower extremities	Orthopedic impairment that compromises exercise performance
Suspected dissecting aneurysm	
Uncontrolled asthma	
Pulmonary edema	
Room air desaturation at rest ≤ 85%*	
Respiratory failure	
Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise (i.e. infection, renal failure, thyrotoxicosis)	
Mental impairment leading to inability to cooperate	

Figure 27 - ATS / ACCP guidelines on exercise testing - Absolute and Relative contra-indications for CPET (American Thoracic and American College of Chest 2003).

3.3 Assessment Sessions (pre- and post-intervention)

The main experimental assessment sessions are similar throughout the studies within this thesis. Individual differences are discussed within the

methods of each Chapter. All participants were asked to refrain from consuming caffeine on the day of their initial or reassessment sessions. They were instructed to take regular prescribed medicines as per usual. They also underwent re-assessment at approximately the same time of day (am/ pm) as the initial assessment to account for any effect that diurnal cycle may have on physiological parameters (Fernandes *et al.*, 2014).

3.3.1 Anthropometric measurements

Weight (kg) was recorded at the baseline and reassessment sessions with height (meters (m) and centimetres (cm)) measured at initial screening.

3.3.2 Blood pressure and resting heart rate

At both the baseline and reassessment visits, NIBP was recorded on the right arm using oscillometry after being seated for 5 minutes (British and Irish Hypertension Society, 2017). Three consecutive recordings were taken and the mean value recorded. Resting heart rate was recorded at these time-points.

3.3.3 Hand-grip strength

Maximum voluntary handgrip contraction was assessed using an electronic hand-grip dynamometer (Grip-D, Takei, Japan) whilst seated with elbow flexion of 90 degrees (Liu *et al.*, 2017). The highest score from three attempts was recorded with 1 min rest between efforts. This assessment protocol was repeated for both hands and side of hand dominance was recorded. When stratified for sex and BMI, weak grip strength is phenotypic indicator of frailty (Clegg *et al.*, 2013). Reduced hand grip strength in midlife is highly predictive of functional decline and disability in later life (Rantanen *et al.*, 1999). Poor handgrip strength predicts accelerated cognitive decline and loss of independence in the oldest old (Taekema *et al.*, 2010).

3.3.4 Short Physical Performance Battery (SPPB)

The Short Performance Battery (SPPB) is a group of measures of lower extremity function combining gait speed, chair stand and balance tests to create an overall score for physical performance (Guralnik *et al.*, 1994). It can be used to predict possible disability and mortality (J. M. Guralnik *et al.*, 1994; Pavasini *et al.*, 2016) and monitor physical function in older adults

(Pavasini *et al.*, 2016). It is recognised that the SPPB may be less effective for measuring function in high-functioning younger adults (Treacy and Hassett, 2018).

3.3.5 Systemic clinical chemistry

Peripheral venepuncture provided samples which were analysed in the Royal Derby Hospital haematology and clinical chemistry laboratory. A full blood count (Ethylenediaminetetraacetic acid (EDTA)) tube facilitated assessment of haemoglobin (Hb; g/L), absolute neutrophil count (10^9/L), absolute lymphocyte count (10^9/L) and HBA1c (mmol/mol). A clinical chemistry tube (Serum separating tube (SST)) facilitated liver function tests (LFT's (IU/L)), urea and electrolytes (Na^+, K^+, urea, creatinine (mmol/L)), an estimated glomerular filtration rate (eGFR; ml/min/1.73m^2), a random lipid profile (total cholesterol, HDL cholesterol, non-HDL cholesterol, Chol/HDL ratio, triglyceride (mmol/L)) and C-reactive protein (mg/L). A coagulation screen was also checked for any participant planned to undergo muscle biopsies.

3.4 Cardiopulmonary exercise testing (CPET)

3.4.1 CPET calibration

Cardiopulmonary exercise testing was carried out in the Clinical Physiology Exercise Suite at the University of Nottingham Medical School at the Royal Derby Hospital Centre. The metabolic cart (ZAN 680, nSpire Health, Colorado, USA) is subject to annual service visits with the analyser validated regularly as per manufacturer's guidelines. Sensor flow rate and gas composition are calibrated prior to each test. Flow rate through the mouth piece is calibrated against a known volume (3 litre diamond cut syringe attached to the cart). The inline gas analyser is calibrated against both room air (Oxygen 21%, Carbon dioxide 0.04%, Nitrogen 78%, other gases) and another validated set gas (composition: Oxygen: 15%, Carbon dioxide 5%, Nitrogen 80%; BOC, Guilford, UK). Ambient room conditions at time of testing are recorded via an environmental module including room temperature (degrees Celsius), humidity (%) and atmospheric pressure (mbar) to ensure that conditions for pre- and post-intervention testing were not different. The CPET system also underwent biological calibration with a healthy experienced member of the research staff exercising at steady state

versus varying workloads (W: Watts) (50W, 100W, 150W) as recommended (American Thoracic and American College of Chest, 2003).

3.4.2 CPET set-up

A thorough explanation of the CPET protocol, including safety and termination criteria was explained to participants prior to setting up the machine and attaching any monitoring equipment.

Before the test began, a 12-lead ECG (CardioCollect12S, DelMar Reynolds, USA) was attached to the participant to record continuously throughout the test. NIBP was collected every 2 minutes from the left arm (SunTech Medical, Morrisville, USA). Preparing the skin, by shaving contact areas and cleansing with an alcohol wipe and using exercise specific electrodes ensured a reliable trace for the ECG throughout the CPET. Pulse oximetry provided blood oxygenation levels throughout the CPET via a pulse oximeter (iMEC8 Mindray, Shenzen, China) attached to the left index finger throughout the test. After the ECG, NIBP monitor and pulse oximeter were attached, participants were fitted with a silicone face mask (small, medium or large) using elasticated head gear (V2 mask, Hans Rudolph, Shawnee, USA). The flow sensor was then attached to the front of the mask for the quantification of volume and sampling of inspired and expired gases during rest and exercise. In order to ensure accurate gas analysis, the fitting of the mask was checked for air leaks prior to initiating any testing (by ensuring no obvious air leaks around the nose and mouth and ensuring no downward drift in tidal volume on screen).

Participants were then seated onto a cycle-ergometer (Lode Corival, Lode, Groningen, Netherlands) with the seat height adjusted for comfort and recorded for consistency and reproducibility across assessment sessions. The CPET equipment and participant set up can be seen in Figure 28.



Figure 28 - A 76-year-old male participant undergoing a CPET. Reproduced with participants' written consent.

3.4.3 CPET Procedure

At the start of each CPET, participants underwent a two-minute warm-up period of unloaded cycling, to allow physiological equilibrium prior to starting the test. The cycling workload was then increased in a ramp-wise manner as per the Bruce Ramp protocol (Bruce, 1971) with a range 5-30 Watts per minute aiming to achieve VO_{2PEAK} in 8-12 minutes. Participants were encouraged to i) maintain a cadence of 50-60 revolutions per minute (RPM), ii) exercise to 85% or more of age-predicted maximal heart rate (Max HR=208–(0.7*Age)) (Tanaka, Monahan and Seals, 2001), and iii) exercise to a respiratory exchange ratio (RER; VCO_2/VO_2) above 1.1. Tests were terminated when participants indicated that they had reached 'volitional exhaustion' or they were unable to maintain a cadence above 50 RPM. The

ramp protocol was selected upon the basis of clinical opinion of an experienced CPET operator (American Thoracic and American College of Chest, 2003) in addition to estimated VO_{2PEAK} information gained from a subjective physical activity questionnaire (Dukes Activity Questionnaire (DASI)). Immediately after test cessation subjective effort level was measured using a modified (10-point) Borg scale rating of perceived exertion (RPE) (Borg, 1982) and the participant was asked what caused them to stop maintaining the required cadence (i.e. were your legs tired? was it because of shortness of breath?). There was then a 5-minute recovery period of low-load cycling (load 10W) where the participant was instructed to cycle at 30 RPM.

CPET testing criteria were as per The American Thoracic Society Statement of Cardiopulmonary Exercise Testing (American Thoracic and American College of Chest, 2003), including CPET termination criteria as outlined below:

"Exercise will be stopped immediately if a volunteer complains of any adverse reaction to the exercise including: chest pain or tightness, faintness, sudden pallor, loss of co-ordination, confusion, dizziness, signs of respiratory failure, palpitations, ischaemic changes (>2mm ST depression with symptoms or >3mm without symptoms) on ECG, arrhythmias on ECG (prolonged runs of multiple ectopic heart beats or heart block), blood pressure drops by greater than 20mmHg from previous reading or >250mmHg systolic or >120mmHg diastolic, sudden onset bradycardia with a drop in heart rate of >20bpm from previous reading or desaturation with a SpO2 <80% (American Thoracic and American College of Chest, 2003)."

3.5 CPET Analysis

3.5.1 Validation

Prior to analysing the CPET data a review of the overall test was performed to ensure the data reliability. This review included ruling out:

- abnormal resting values in comparison to normal limits (VO_2 250-350 ml/min, VCO_2 200 ml/min, $P_{ET}CO_2$ 35-40 mmHg, $P_{ET}O_2$ 100 – 110 mmHg, O2 pulse 8 – 18 ml O_2/heartbeat, RER <1.0 (may start higher

(anticipatory acute hyperventilation) then fall during steady state with loss of conscious control of breathing), VE/VCO_2 25-30 mmHg, VE/VO_2 25-30) (Jack, S; West M, Loughney L, 2015).

- an air leak via monitoring of tidal volumes throughout the test and ensuring resting values for VO_2 and VCO_2 are >200 ml/min (Jack, S; West M, Loughney L, 2015).
- a pseudo-threshold (Ozcelik, Ward and Whipp, 1999; Levett *et al.*, 2017)
- acute hyperventilation (low PETCO2 <32 mmHg and high RER >1.0) (Ozcelik, Ward and Whipp, 1999; Levett *et al.*, 2017)

Individual breath by breath data was interpreted as 5-breath rolling averages with absolute values from each CPET are divided by body weight (kg) on then day of testing to derive AT and VO_{2PEAK} in relative units (ml/kg/min).

3.5.2 Defining anaerobic threshold

Two experienced CPET assessors, blinded to subject identification and test time-point, determined the AT (L/min) using a dual-methods approach which considered both V-slope and Ventilatory Equivalents methods (Wasserman *et al.*, 1994; Palange *et al.*, 2006), with disagreement resolved by third party. Detailed explanation of the V-slope and Ventilatory Equivalents methods are given in Chapter 1.

3.5.3 Defining VO_{2PEAK}

Absolute VO_{2PEAK} (L/min) achieved at CPET was determined as a 15 data point rolling average including the highest value (at the midpoint) attained during the last 20 seconds of the test (Phillips *et al.*, 2017).

3.5.4 Defining VO_{2max}

Absolute VO_{2max} (L/min) achieved at CPET was determined as a 15 data point average including the highest value (at the midpoint) attained during the last 20 seconds of the test (Phillips *et al.*, 2017). Tests were considered to have achieved VO_{2max} if 3 or more of the following criteria were achieved (Blackwell *et al.*, 2017):

(1) a plateau in the oxygen uptake curve (sustained flattening of VO_2 curve despite rising VCO_2);

(2) a respiratory exchange ratio (RER) of >1.15;

(3) HR over 85% age-predicted maximum, and

(4) a rating of perceived exertion (RPE); modified Borg scale (Borg, 1982) ≥9 immediately following the test.

3.5.5 Submaximal exercise measures

Resting heart rate, maximal wattage and maximum heart rate achieved during the test were recorded from the equidistant data with submaximal measures (HR, VO_2 (L/min), VCO_2 (L/min), RER, O_2 pulse) recorded at three points in the test (in addition to baseline and maximal) corresponding to 25%, 50% and 75% of Wattage achieved at baseline CPET.

3.5.6 Heart rate recovery

Following cessation of the CPET and reduction of the load to 10W/min participants were encouraged to continue cycling slowly (30 RPM) for a period of 5-minutes warm-down. During this period heart rate recovery (HRR) was recorded based on heart rate (HR) measurements at two time-points; 1 minute (HRR1) and 2 minutes (HRR2) into the recovery period. HRR is calculated by subtracting the HRR1 and HRR2 from the maximum HR achieved during the test. Vagally mediated HRR is blunted in heart failure patients, whilst enhanced in athletes (Imai *et al.*, 1994). Heart rate recovery is an independent predictor of all-cause mortality, and has been proposed to have a substantially stronger link to death than traditional exercise test measures such as ST-segment changes and exercise induced angina pectoris (Messinger-Rapport *et al.*, 2003). During treadmill exercise, a fall of less than 12 beats per minute within the first minute following exercise cessation was considered abnormal (Messinger-Rapport *et al.*, 2003).

3.6 Muscle architecture

Muscle architectural measures such as muscle thickness, pennation angle and fascicle length can be non-invasively measured to provide functional information upon an individual's lean muscle bulk. Vastus lateralis and

gastrocnemius medialis muscle thickness, have been shown to be associated with functional performance (TUG, 6MWT, vertical jump performance and stair climbs) in older adults (Selva Raj, Bird and Shield, 2017).

Muscle architecture was assessed using ultrasonography of the right leg. Images were acquired using B-mode ultra-sonography (Mylab 70, Esaote Biomedica, Italy) with a 100mm, 10-15MHz, linear array probe with the participant lay supine on an examination bed as previously described (Franchi *et al.*, 2014). In brief, the ultrasound operator first defined and measured the distance between a number of anatomical landmarks (Longitudinal: greater trochanter of the femur to mid patella, Saggital: midpoint of distance from medial to lateral borders of VL assessed using ultrasound) to ensure images captured the mid belly of the *vastus lateralis* (VL) muscle in both the longitudinal and sagittal planes. This measurement method, based upon bony anatomical landmarks, allowed the operator to be confident that they were imaging the same portion of muscle at reassessment as before the intervention. The transducer was also aligned to the fascicle plane allowing optimal imaging of the whole fascicle (Reeves, Maganaris and Narici, 2004) (Figure 29). Pre and post intervention images were collected by the same experienced operator to remove any inter-operator error.

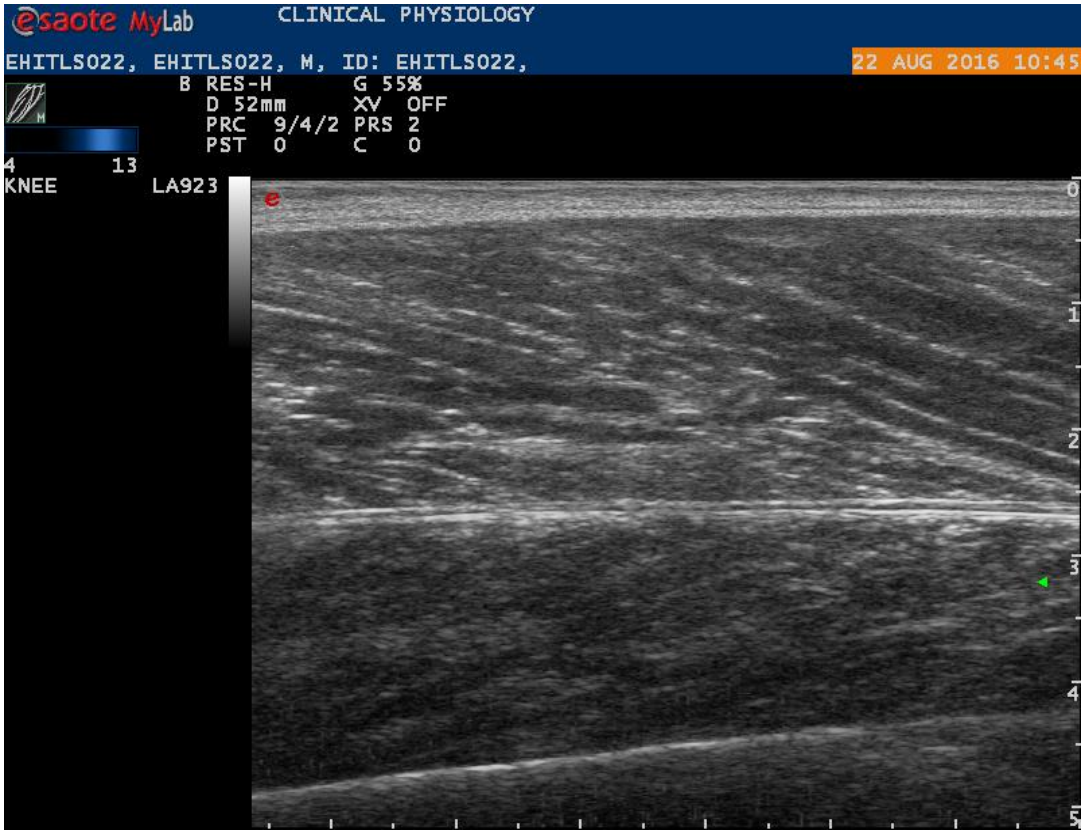


Figure 29 - Ultrasound image of the vastus lateralis muscle in a 78 year-old participant.

3.6.1 Analysis of ultra sound images

Digital analysis of the images was performed using imageJ software (Public domain image processing program, developed by National institutes for Health, Maryland, USA) with muscle architecture measurements as shown in *Figure 30*. Wherever possible, muscle fascicle length was measured directly with linear extrapolation only applied in cases where the whole fascicle was not visible in the field of view (Franchi *et al.*, 2014). Pennation angle was measured as the intersection between fascicles and the deep tendon aponeurosis and muscle thickness was measured as the perpendicular distance between the superficial and the deep tendon aponeurosis (Franchi *et al.*, 2015).



Figure 30 - Ultrasound Image of the vastus lateralis muscle in a 78 year-old participant with annotation to show parameters relating to the assessment of muscle architecture. The two facial planes (superficial and deep) are shown as the red lines with muscle thickness the length between A and B (green line). The yellow line from B to C represents muscle fascicle length using linear extrapolation, with the pennation angle also shown in yellow and marked by the letter P.

3.7 Body Composition

Body composition, including total mass, fat mass and lean tissue mass was assessed via dual-energy x-ray absorptiometry (DXA) scans on a GE Lunar Prodigy II scanner (GE Medical Systems, Buckinghamshire, UK) before and after the intervention. DXA uses two low dose x-ray beams (at different energies) to quantify tissue density making use of the differential attenuation of the x-ray beams to calculate tissue compositions (Laskey, 1996), as such DXA does carry a small radiation burden (equivalent of ~two days background radiation). Other recognised methods of quantifying body composition without radiation burden include hydrostatic weighing and whole-body air displacement plethysmography which are unavailable at our unit and do not allow regional assessment. Additionally, DXA is less affected by hydration status and diet than bioelectric impedance testing.

3.7.1 DXA Analysis

Whole body mass, lean muscle mass and fat mass were assessed as part of the standard DXA report. DXA scans were performed by a research staff member having completed the ionising radiation exposure regulator (IRMER) training. For most individuals the DXA scan takes 6 minutes, with individuals undergoing a 'thick' scan (increased x-ray dose) due to high body mass taking 11 minutes. Individuals are lay supine throughout the duration of the scan. Customised region of interest (ROI) analysis was also performed for these parameters with the leg divided into 2 separate ROI's; whole leg ROI; from the greater trochanter to soles of feet, upper leg ROI; from the greater trochanter to the midpoint of the patella (Figure 31).

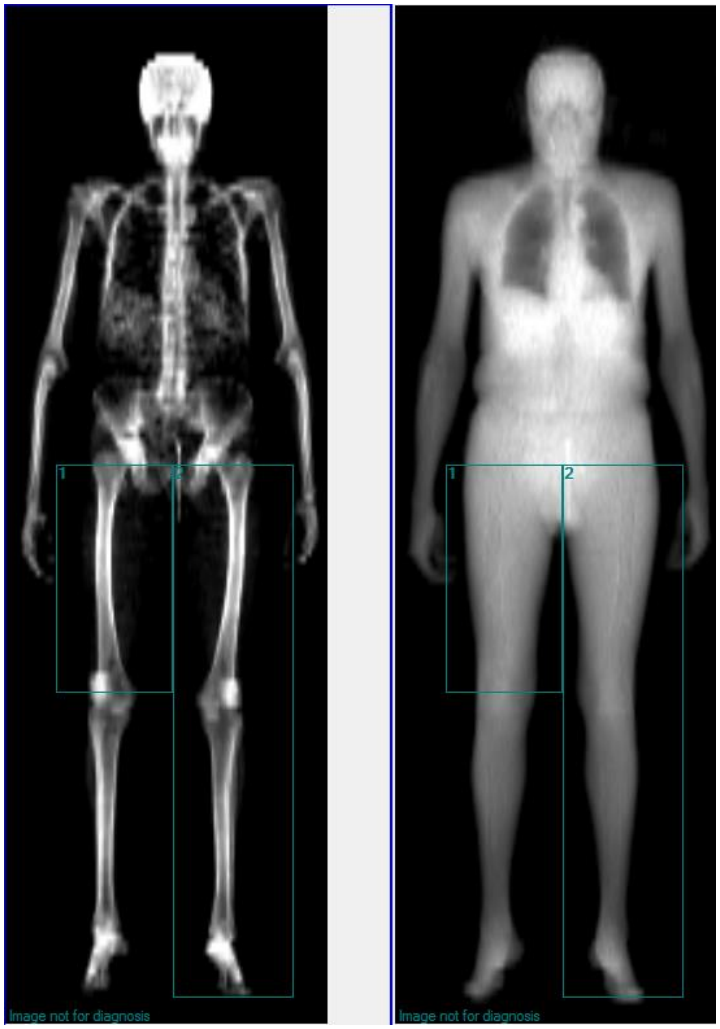


Figure 31 - DXA region of interest (ROI). Box 1 measures upper leg, Box 2 measures whole leg.

3.8 Questionnaires

In order quantify expected baseline fitness and the effects of HIIT on subjectively reported daily activity levels, quality of life and subjective health status a series of questionnaires were completed by all participants.

3.8.1 Dukes Activity Status Index (DASI)

DASI is a self-administered questionnaire which accurately measures functional capacity and assesses aspects of quality of life. This 12-item scale has been shown to correlate significantly with peak oxygen uptake, allowing prediction of exercise capacity (Hlatky *et al.*, 1989a). Each item (e.g., 'Can you climb a flight of stairs or walk up a hill?') on the DASI scale is weighted per its metabolic cost, with a summated range from 0 to 58.2. The total value across the 12 items is then used in the following equation to estimate peak oxygen uptake at exercise:

VO_{2PEAK} (ml/kg/min) = 0.43 x (Duke Activity status index) + 9.6

The estimated VO_{2PEAK} can aid the CPET operator when deciding which specific loading ramp protocol (5 W/min – 30 W/min) to use during a CPET for any single individual, although this was used in conjunction with clinical experience of the CEPT operator to decide upon a suitable Ramp protocol.

The full DASI questionnaire is available in the Appendices.

3.8.2 EuroQuol 5-dimension questionnaire (English)

The EQ-5D-5L is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Janssen and Van Reenen, 2015). The EQ-5D-5L provides 5 possible levels of answer to questions (versus the 3L version) and consists of a descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises of 5 dimensions (mobility, self-care, usual activities, pain/ discomfort, anxiety/ depression). With each dimension having 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS section consists of a 0 to 100 graduated scale wherein the individual is asked mark the scale where they would rate their health in response to 'We would like to know how good or bad your health is TODAY'.

The full EQ-5D- 5L questionnaire is available in the Appendices.

3.8.3 Warwick-Edinburgh Mental Well-being Scale (WEMWBS)

The WEMWBS is a self-report tool that was developed to help evaluate mental health promotion initiatives aimed at improving mental well-being on a population basis, (Tennant *et al.*, 2007) and has been used within a variety of settings (Maheswaran *et al.*, 2012). Mental well-being describes positive states of being, thinking, behaving and feeling and is distinct from 'mental health' (Putz. R., O'Hara, K., Taggart, 2012).

The full WEMWBS is available in the Appendices.

3.8.4 HIIT acceptability questionnaire

This 5-point Likert scale questionnaire, developed within our research group, has previously been used to assess individuals' opinions regarding our HIIT protocol to assess general acceptability; with questions relating to enjoyment, time burden and physical exertion (Boereboom *et al.*, 2016). It also includes two free text answers to questions ('What has been the most challenging part of HIIT training?' and 'What has been the best part of HIIT training?') to try and inform on any future HIIT-based interventions and/ or applications.

The full HIIT acceptability questionnaire is available in Appendix 1.

3.9 Activity monitoring

3.9.1 Objective physical activity monitoring

Habitual physical activity level was measured using a dual heart rate and activity monitor (Actiheart, Cam'N'tech Ltd, Cambridge, UK), worn for a minimum of 5 days during 2 periods, both before and during the intervention. Combining HR data and activity counts (set on 30 second collection windows), Actihearts provide validated (Brook *et al.*, 2016) physical activity data in the form of MET's. Previously used to assess the contribution of a HIIT programme to changes in physical fitness in individuals at risk of metabolic disease (Phillips *et al.*, 2017); a similar analysis was performed in our studies. Data for a participant was deemed valid if greater than 80% of minute-by-

minute data was recorded over a 24-hour period, and two or more 24-hour periods were available for a measurement period.

3.9.2 Subjective physical activity monitoring

To complement the object physical activity monitoring, and to assess the relationship between real and perceived levels of physical activity the International Physical Activity Questionnaire (long last 7 days self-administered format) (IPAQ) was used to record subjective recall of participation in physical activity in the preceding week (Booth, 2000; Craig *et al.*, 2003).

3.10 High intensity interval training (HIIT) Protocol

3.10.1 HIIT Protocol Schematic

Below is a description and schematic of the specific HIIT protocol (Figure 32) used in this thesis (using the FITT-VP framework as outlined in the introduction).

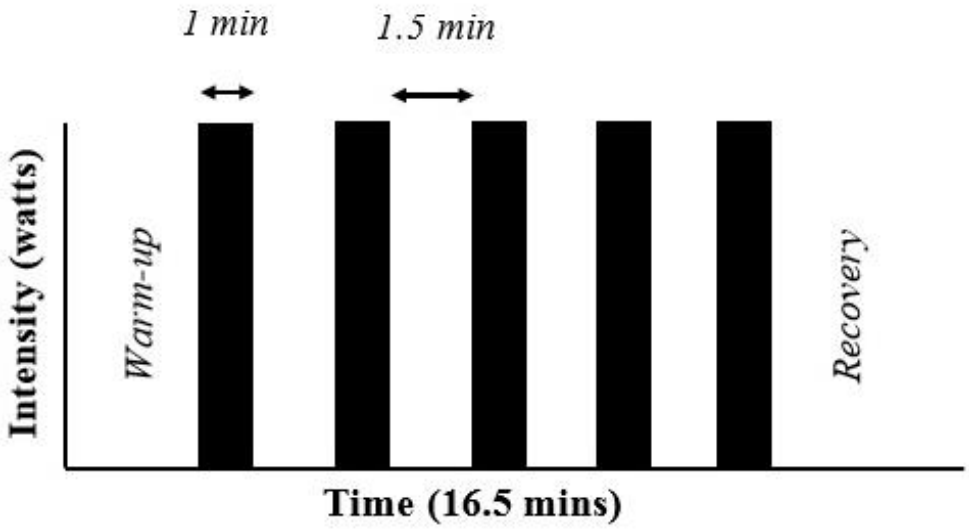


Figure 32 - High intensity interval training protocol (HIIT) schematic. Warm-up and recovery entailed 2 minutes unloaded cycling. Intensity (Watts) determined by maximum wattage achieved at initial CPET.

Frequency: a frequency of 3-5 sessions per week (during Monday to Friday) was therefore deemed reasonable, considering the imposed 2-day weekend break and the recommendation of rest days when initially starting HIIT.

Intensity: the absolute workload during the HIIT protocol is tailored to the individual based upon their baseline CPET result. The maximum wattage (W) achieved at initial CPET is used to determine a stepwise HIIT assessment session ranging from 90% - 110% of max wattage. The initial HIIT assessment session exertions ensures that each individual is pushed to a heart rate response >85% age predicted maximum (i.e. high intensity) for their specific baseline fitness level. The maximum wattage maintained for one minute is taken forward to the second HIIT session and then titrated upward after 6 sessions as described below (see Progression). Determining the initial training load from the baseline CPET is favourable versus simply tailoring the HIIT protocol based upon non-specific demographic factors like height/ weight, gender or age. In our experience most individuals achieve between 100-110% wattage and this elicits a satisfactory heart rate response (>80% maximum) if sustained for one minute at 70-100 revolutions per minute.

Time: total session duration 16.5 minutes with a work:rest ratio of 1:1.5 (60 seconds work : 90 seconds rest).

Type: we consider exercise performed on a cycle-ergometer the most suitable modality to deliver specific HIIT protocols across 'all comers' within clinical cohorts.

Volume: the maximum volume of our HIIT protocol would be 12 sessions within 31 days.

Progression: participants are given verbal encouragement within each exertion to maintain a heart rate >85%. Following the 6th HIIT session, and immediately following the last HIIT exertion, participants subjectively rate the exertion of the session using the modified Borg scale (Borg, 1982). If they rate ≤8 then the training load is increased by 10% to maintain training intensity and promote progression.

3.10.2 Example heart rate response to HIIT

In Figure 33 below you can see that there is a rapid increase in hear rate in response to the first exertion. Between exertions the HR lowers with passive unloaded cycling at low RPM (<30). Each exertion begins with a higher starting HR as there is not sufficient time for HR to return to baseline during the recovery period. Participants tend to achieve the highest peak HR's in exertions 3-5. HR gradually returns closer to baseline during the recovery phase.

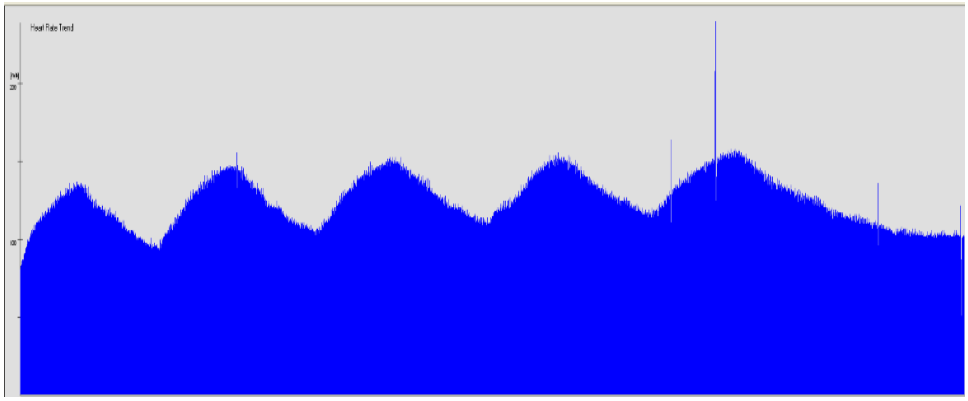


Figure 33 - This graph (taken directly from the Zan 600 analysis metabolic cart analysis software) shows a typical heart rate response to our HIIT protocol (x-axis time, y-axis heart rate) NB: aberrant spikes in heart rate are excluded from analysis automatically.

3.10.3 Example HIIT assessment and training log

Study ID: eHIIT12345

HIT Assessment Session: 1 Watt Max from CPET: 150

% Watt max	Watt	Interval achieved fully?	Notes
90%	135	Yes	Well tolerated
95%	143	Yes	Well tolerated
100%	150	Yes	Well tolerated
105%	158	Yes	Well tolerated
110%	165	No	Could not maintain cadence >50, stating leg fatigue.

	Pre:	Max:	Post:
HR:	60	130	75
BP:	120/80	180/95	130/82

Training Wattage: 158

Session Number + Watts achieved	Pre: HR + BP	Max: HR + BP	Post: HR + BP	Notes
2 3 x 158 2 x 150	68 120/80	130 180/95	75 130/80	Session completed without incident
3 3 x 158 2 x 150	68 120/80	132 185/95	75 130/80	VE's during recovery periods
4 4 x 158 1 x 150	68 120/80	135 190/95	75 130/80	Asymptomatic
5 4 x 158 1 x 150	68 120/80	135 190/95	75 130/80	Tired during 4th and 5th exertions
6 5 x 158	68 120/80	135 190/95	75 130/80	Completed all 5 exertions with RPM >90

Figure 34 - HIIT assessment session and training log with typical written responses and progression with HIIT training.

As seen above in Figure 34, this 70 year old male achieved a maximum wattage of 150 Watts during the baseline CPET. He then underwent his pre-training assessment session which entails 5 graded exertions ranging from 90% - 110% of the maximum wattage achieved at initial CPET, for 1 minute

with 90 second rest periods in between (as discussed above 3.10.1). If the individual completed the full 1 minute exertion they would progress to the next interval at a higher wattage. Clinical information and failure criteria are recorded for each individual exertion. Baseline, maximum and recovery heart rate and blood pressures are recorded at all sessions for safety monitoring and titration of leg RPM to ensure HIIT is performed (>85% heart rate maximum response). Progression can be seen in the column titled 'Session number and Watts achieved', in most cases the individuals/ patients would achieve 5 exertions of at least 100% initial CPET Watt maximum by HIIT session 6.

4 The efficacy of unsupervised home-based exercise regimens in comparison to supervised lab-based exercise training upon cardio-respiratory health facets

4.1 Chapter focus

Systematic review of the literature suggests that HIIT is more effective more quickly than MCT for different comorbid groups (Chapter 2). Efficacy and ease of translation into use in patients is of paramount importance for planning preoperative exercise interventions. We now aimed to investigate whether our laboratory based HIIT protocol could be adapted to be delivered at home with the same total time and work:rest basis as we have performed in the laboratory. This could demonstrate that wide scale roll out of this intervention at very little cost compared to supervised laboratory based HIIT might be possible. We also investigate another exercise training modality, which can be performed away from the laboratory, which has shown promise in reducing cardiovascular risk factors over short periods.

4.2 Introduction

The risk of developing cardiovascular (D'Agostino Sr. et al. 2008) and metabolic (Veronica and Esther, 2014) disease(s) increases with advancing age. However, ageing is not the only risk factor for cardiovascular disease (CVD); sedentary middle-aged adults have been identified as a specific high-risk group, with inactive lifestyles associated with all-cause mortality (Biddle, S et al. 2010). It therefore follows that exercise is the most well-established non-pharmacological countermeasure to CVD risk (Myers, 2003). Current guidelines state that adults should complete at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or do at least 75 minutes of vigorous-intensity aerobic physical per week (WHO, 2011). However, less than 40% of men and 30% of women meet these guidelines (UK Department of Health 2011). Poor uptake and adherence to exercise is driven by a multitude of factors, such as "lack of time", aversion to exertion, and access to specialist equipment (Trost *et al.*, 2002; Gillen and Gibala, 2013). Moreover, these current physical activity guidelines do not consider the potential benefits of novel exercise modes i.e. short intense bouts of exercise, or static isometric training.

High intensity interval training (HIIT) (Trost et al. 2002; Gillen & Gibala 2013) is one such novel exercise mode (Kravitz, 2011). Indeed, laboratory-based (supervised) HIIT (L-HIIT) has been shown to elicit improvements in cardiorespiratory fitness (CRF), over very short time-periods (2-6 weeks) in athletes (Iaia et al. 2009), moderately trained (Helgerud *et al.*, 2007; Little *et al.*, 2010), sedentary (Trilk et al. 2011; Klonizakis et al. 2014) and patient groups (Gibala *et al.*, 2012b; Weston, Wisloff and Coombes, 2014; Lanzi *et al.*, 2015). These improvements were seen despite low exercise volume and minimal time commitments (Gillen *et al.*, 2014).

Nonetheless, despite these findings supporting the benefits of L-HIIT, the efficacy of home-based *unsupervised* HIIT-based strategies (H-HIIT), which overcome the need for specialist equipment and personnel, is unknown. Previously most HIIT protocols have been studied in the laboratory setting, however newer protocols requiring no specialist equipment have been investigated showing positive effects on CRF. Whole body aerobic resistance training (McRae *et al.*, 2012) and more recently low volume intense stair climbing (Allison *et al.*, 2017) has improved CRF in untrained females over

a four week period whilst supervised but with no specialist equipment. Similarly, while home-isometric handgrip training (H-IHGT) is a promising, simple and rapid task that has been shown to lower resting blood pressure (RBP) within ~10 weeks (Millar *et al.*, 2008; Garg *et al.*, 2014), how it compares to HIIT-based strategies in relation to modulating RBP is unknown. Herein, we aim to resolve this by comparing the effects of H-HIIT to an already established efficacious supervised L-HIIT protocol, on VO_2 max and anaerobic threshold (AT). We also aim to compare the effects of H-IHGT on RBP versus L-HIIT and H-HIIT.

4.3 Methods

4.3.1 Subjects

In total 26 middle-aged (52±5 y; 17:9 female:male) individuals not engaged in any formal exercise regime (<2 times per week) were recruited to the study and provided written informed consent. Exclusion criteria were as per ATS/ACCP Guideline for CPET (American Thoracic and American College of Chest, 2003). Inclusion criteria included no musculoskeletal limitations and availability for the whole study duration. Six subjects were randomly assigned to each intervention group (L-HIIT, H-HIIT, H-IHGT and H-MCT) prior to baseline testing. Number and reasons for drop outs can be seen in the Prisma flow diagram (Figure 35). The study was approved by the University of Nottingham Medical School ethics committee and complied with the Declaration of Helsinki.

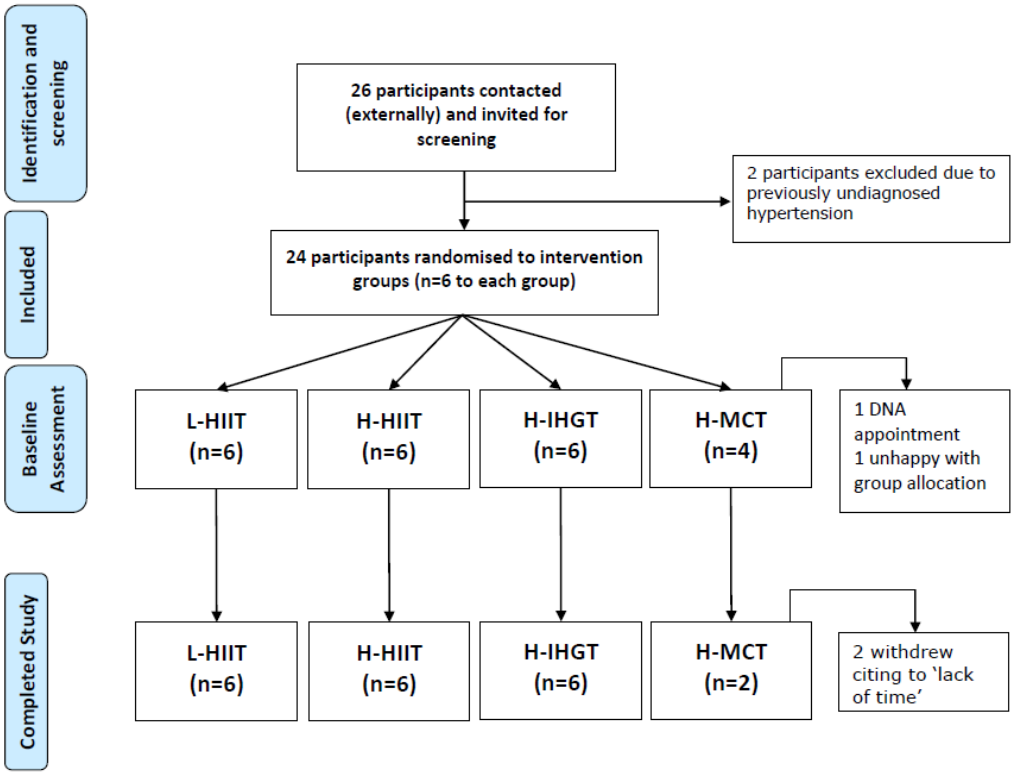


Figure 35 - Adapted Prisma flow diagram (25), DNA = did not attend scheduled session.

This study was completed in conjunction with the BBC (British Broadcasting Company) to produce a health promotion episode of the television programme 'Trust Me I am a Doctor'. The research study was advertised via

the BBC website with recruits knowing that HIIT would be the focus of the television program in advance of attending screening.

4.3.2 Baseline and post-training measures

All measurement equipment was calibrated and fully maintained throughout the study period. Subjects' height and weight was measured on arrival. Resting heart rate and non-invasive blood pressure was taken following 5 minutes seated rest with an automatic blood pressure monitor (A&D Medical, Saitama, Japan) prior to any exercise testing. All subjects then underwent cardiopulmonary exercise testing (CPET; Lode Corival, Lode, Groningen), with inline breath by breath data collected via a metabolic cart (nSpire Zan 600, Germany), using a modified Bruce ramp protocol as previously described (Boereboom *et al.*, 2016). Tests were considered maximal if 3 or more of the following criteria were met: 1) plateau in the oxygen uptake curve (sustained flattening of VO_2 curve despite rising VCO_2); 2) a respiratory exchange ratio (RER) of >1.1; 3) HR over 85% age-predicted maximum, and 4) a rating of perceived exertion (RPE); modified Borg scale (Borg, 1982) ≥9 immediately following the test. CPET interpretation was performed by two independent experienced assessors blinded to time-point (i.e. pre or post-training) and group information. VO_2 max values were taken as the highest reading in the last 30 seconds of the test. AT was determined using a modified V-slope and ventilatory equivalents method (Boereboom *et al.*, 2016). All baseline measures were repeated >3 but <7 d after the last training session.

4.3.3 Training regimes

Volunteers performed their respective regime 3 times each week for 4 weeks. Compliance was monitored via a self-report training diary (H-HIIT, H-IHGT, H-MCT) or attendance (L-HIIT), and was 100% for each intervention.

L-HIIT comprised a 2 min unloaded warm-up, followed by 5x1 min exertions at 95-110% of the maximal load (watts (W)) achieved during subjects' baseline CPET (determined by an initial assessment session (Boereboom *et al.*, 2016), interspersed with 90 seconds unloaded cycling. A 2 min unloaded recovery completed each session. All participants underwent a 10% intensity increase at the mid-way point of training (after session 6). Participants were given verbal encouragement throughout each session to ensure a rate of

cadence sufficient to evoke a HR response greater than 85% predicted maximum (i.e. 220 – age (years)).

H-HIIT comprised a 2 min jogging warm-up, followed by 5x1 min exertions of three different equipment-free exercises (star-jumps, squat thrusts and static sprints). To try and ensure that exercise intensity remained constant throughout each session, subjects were instructed to complete the maximum number of repetitions possible with good form during each exertion, and to match the number of repetitions achieved during exertions 1 (star-jumps) and 2 (squat thrusts) during exertions 4 and 5 when these exercises were repeated. Each exertion was interspersed with 90 seconds walking, with 2 min light static jogging completing each session.

H-IHGT comprised 4x2 min isometric hand-grip holds with their dominant hand at 30% of maximal voluntary contraction (MVC), interspersed with 2 min rest periods (Camry EH101 Electronic Hand dynamometer, USA). MVC was recorded as best of three maximal contractions on the dominant arm whilst stood in the anatomical position (Takei 5401 Grip strength dynamometer, Japan).

H-MCT comprised 50 min light exercise (e.g. jogging, swimming, cycling) to meet the UK guidelines of 150 minutes moderate-intensity aerobic physical activity throughout the week.

4.3.4 Statistical Analysis

Descriptive data are presented as means ± standard deviation. ANCOVA was used to compare post-intervention efficacy between groups with pre-intervention scores as a covariate. Results are presented with Bonferroni adjusted p values. We also tested for the assumption of homogeneity of regression slopes by testing the interaction of the independent variable with the covariate. Paired t-tests were used for within group analyses. Pearson's correlation was used to test the association between change in blood pressure and baseline values. Statistical significance was set at $P<0.05$. All analyses were conducted on STATA Version 14.2, SPSS Version 22 and Graphpad Prism Version 6.

Figure 35 above shows the high drop-out rate in the H-MCT group. It was decided that due to the very small completers sample size this group would be removed from statistical analysis.

4.4 Results

4.4.1 Subject baseline characteristics

Subject baseline characteristics can be seen in Table 7. There were no adverse events during the study and all subjects within the L-HIIT, H-HIIT and H-IHGT groups completed all testing and training sessions (L-HIIT monitored by research staff, H-HIIT and H-IHGT recorded by individual participants). Adherence to the study protocol was poor in the H-MCT group (Figure 35) and as such has been removed from the analysis due to small sample size. All subjects fulfilled our $VO_{2\ max}$ criteria as outlined above. There were no significant differences in body weight (kg) in any group after the training period.

*Table 7 - Subject baseline characteristics (analysis via paired Students t-test. *=P<0.05).*

Characteristic	L-HIIT (n=6)	H-HIIT (n=6)	H-IHGT (n=6)
Age (years)	51.5 (2.7)	52.2 (2.0)	51.5 (2.3)
BMI (kg/m²)	27.5 (1.1)	26.3 (2.0)	28.3 (1.8)
VO_{2max} (ml/kg/min)	26.5 (2.6)	27.8 (1.9)	23.7 (2.4)
VO_{2AT} (ml/kg/min)	15.2 (1.1)	13.93 (0.7)	13.6 (1.5)
SBP (mmHg)	127 (6.5)	129 (5.4)	138 (4.2)
DBP (mmHg)	84 (0.9)	81 (5.1)	93 (2.7)

4.4.2 Cardiorespiratory fitness results

There was a significant mean improvement in CRF in both L-HIIT (AT: 15.28±2.73 to 18.23±2.54 ml/kg/min, P<0.01; VO_{2max}: 26.50±6.31 to 31.00±6.69 ml/kg/min, P<0.001) and H-HIIT (AT: 13.93±1.82 to 15.35±2.27 ml/kg/min, P<0.05; VO_2 max: 27.77±4.75 vs. 29.98±6.094 ml/kg/min, P=<0.05), with no significant effect of H-IHGT (AT: 13.55±3.61 to 13.63±3.25 ml/kg/min, P=0.88; VO_2 max: 23.65±5.98 to 24.60±4.80 ml/kg/min, P=0.39 (Figure 36 and Figure 37).

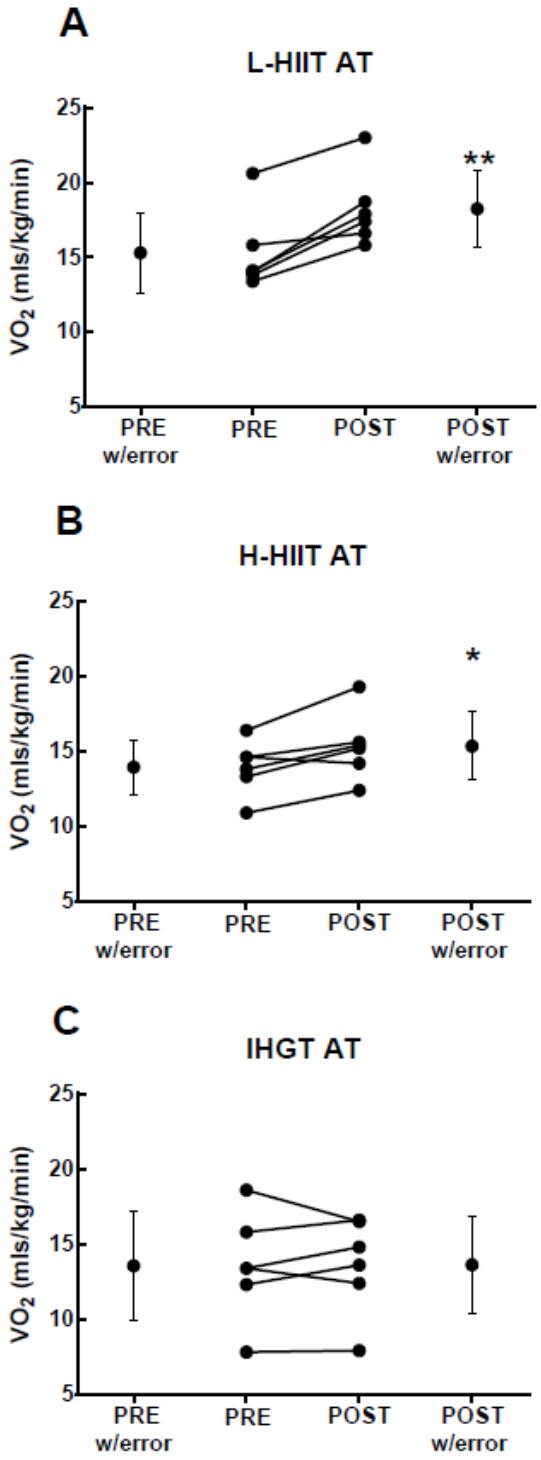


*Figure 36 - Anaerobic threshold (AT) before (PRE) and after (POST) 4 weeks laboratory-based high intensity interval training (L-HIIT; A), home-based HIIT (H-HIIT; B) or isometric hand-grip training (H-IHGT; C). Graphs depict mean±SD and individual changes. Analysis via paired Students t-test. *=P<0.05, **=P<0.01 vs. PRE training.*

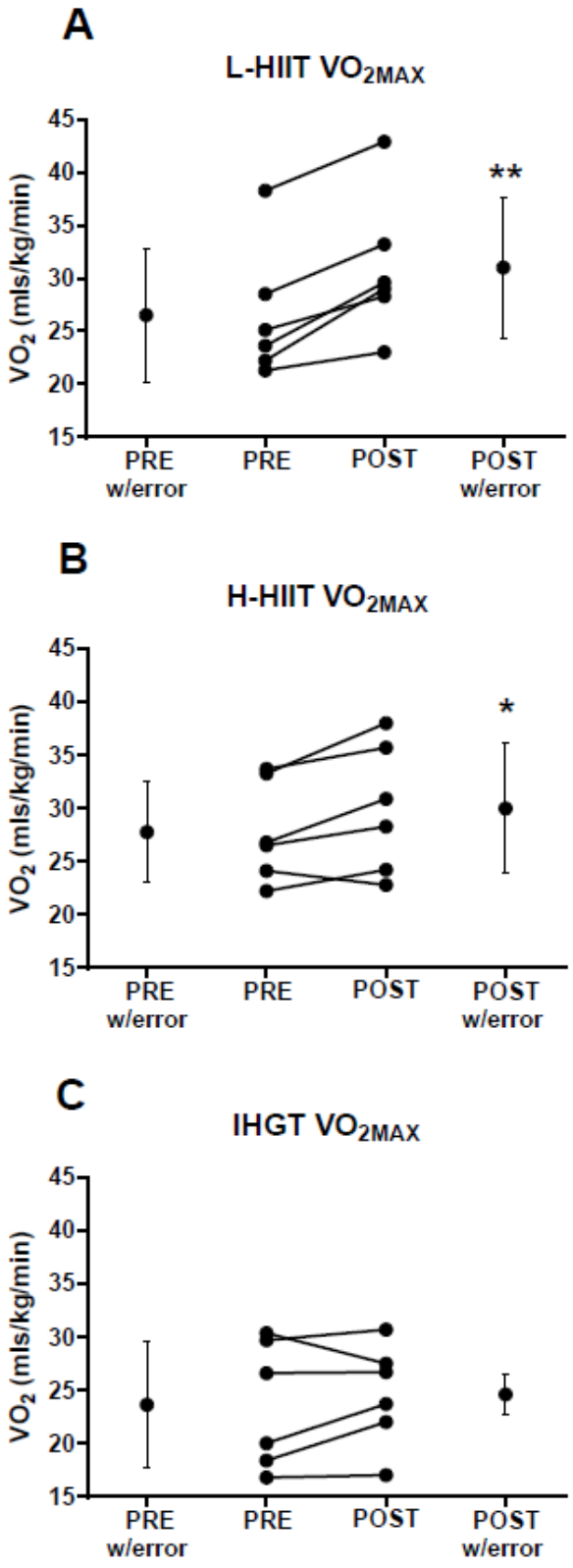


*Figure 37 - VO_{2max} before (PRE) and after (POST) 4 weeks laboratory-based high intensity interval training (L-HIIT; A), home-based HIIT (H-HIIT; B) or isometric hand-grip training (H-IHGT; C). Graphs depict mean±SD and individual changes. Analysis via paired Students t-test. *=P<0.05, **=P<0.01 vs. PRE training.*

L-HIIT elicited significantly greater improvements in AT and VO_{2max} (both $P<0.05$) when compared with H-IHGT and there were no other significant differences between the groups (Figure 38). The assumption of homogeneity of regression slopes was not violated ($p>0.05$ for interaction).

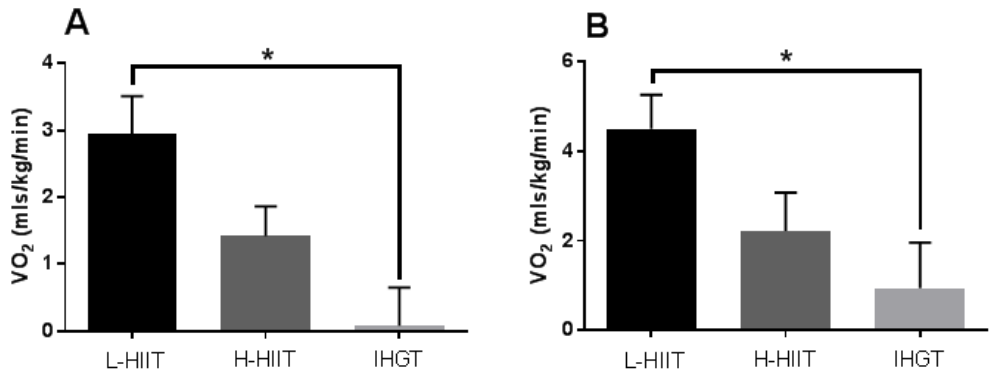


*Figure 38 – Graph A: Change in VO_{2AT} (ml/kg/min). Graph B: Change in VO_{2max} (ml/kg/min). Analysis via ANCOVA, *=p<0.05.*

4.4.3 Blood pressure results

There were no significant differences between the groups' baseline systolic (SBP) or diastolic (DBP) blood pressures. When grouping all subjects together, there was a significant negative correlation between baseline systolic and diastolic blood pressures and change in these values after training ($r=-0.72$; $P<0.05$ and $r=-0.64$; $P<0.05$, respectively). SBP (139±4 to 123±3 mmHg, $P<0.01$) and DBP (93±3 to 82±3 mmHg, $P<0.05$) decreased significantly in the H-IHGT group only, with no significant changes in the L-HIIT or H-HIIT groups (Figure 39 and Figure 40).

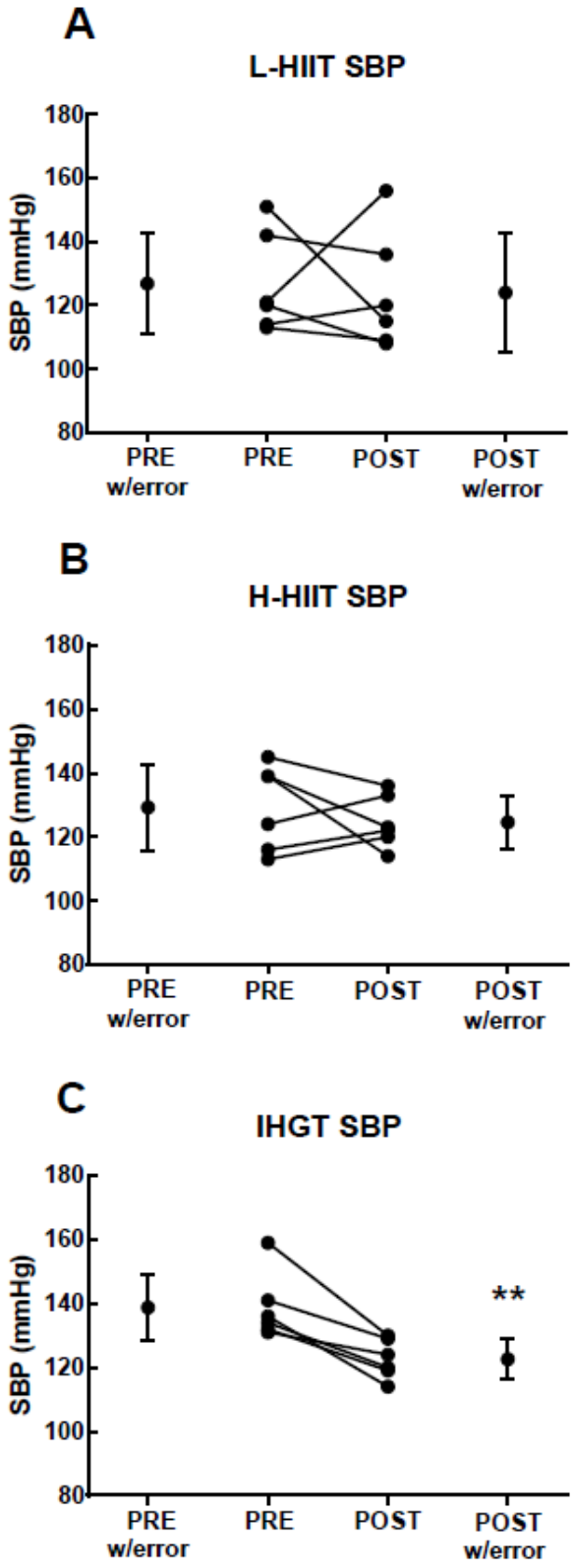


*Figure 39 - Systolic blood pressure (SBP) before (PRE) and after (POST) 4 weeks laboratory-based high intensity interval training (L-HIIT; A), home-based HIIT (H-HIIT; B) or isometric hand-grip training (H-IHGT; C). Graphs depict mean±SD and individual changes. Analysis via paired Students t-test. **=P<0.01 vs. PRE training.*

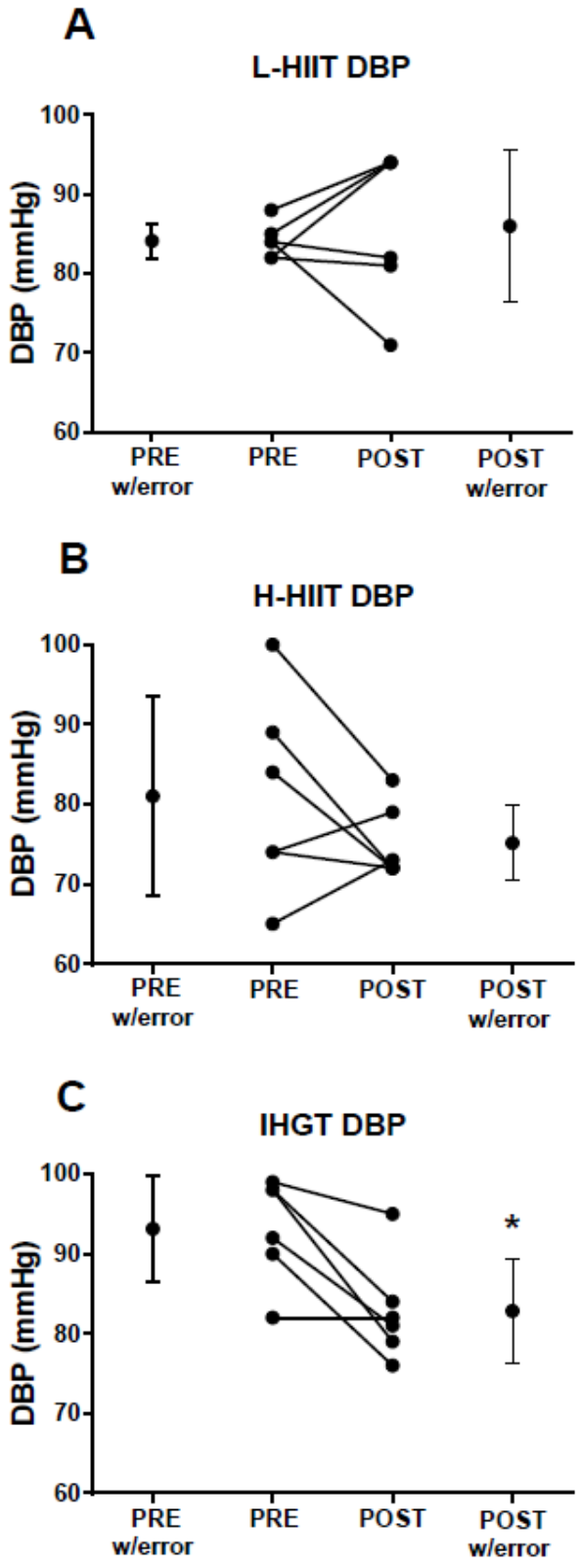


*Figure 40 - Diastolic blood pressure (DBP) before (PRE) and after (POST) 4 weeks laboratory-based high intensity interval training (L-HIIT; A), home-based HIIT (H-HIIT; B) or isometric hand-grip training (H-IHGT; C). Graphs depict mean±SD and individual changes. Analysis via paired Students t-test. *=P<0.05 vs. PRE training.*

4.5 Discussion

For the first time, both supervised L-HIIT and *unsupervised* H-HIIT have been shown to improve CRF in just four weeks using an identical work-to-rest ratio. H-IHGT did not confer benefit in CRF, but did elicit a beneficial effect on SBP in this short 4-week time frame.

As previously, and consistently shown (Boereboom et al. 2016; Little et al. 2010; Lanzi et al. 2015), L-HIIT elicited improvements in indices of CRF in just 12 sessions. However, despite this solid and expanding evidence base the mechanistic basis of HIIT-induced improvements in CRF are not fully elucidated. Increased skeletal muscle mitochondrial capacity (Little *et al.*, 2010) and (central and peripheral) vascular adaptation (Wisloff, Ellingsen and Kemi, 2009) have both been postulated to account for improvements in VO_{2max} in previous studies, whilst improvements in muscle buffering capacity (Gibala *et al.*, 2006) and reduced submaximal exercise energy expenditure (Iaia *et al.*, 2009) may account for improvements in AT. Thus, L-HIIT may represent a time-efficient method to engage sedentary middle-aged individuals, identified as at high risk for CVD (Biddle, S et al. 2010), in a regular physical activity regime with the aim of enhancing aerobic fitness and reducing BP. However, time-efficacy only combats one of the cited reasons for poor exercise adherence. Indeed, the need for specialist equipment (cycle ergometers) and supervision are notable limitations for this method of training, demanding significant time and financial commitments.

Interestingly this study demonstrates that *unsupervised* H-HIIT, without the need for specialist equipment, can also improve CRF in middle-aged sedentary individuals in just 4 weeks. With an identical time commitment to L-HIIT, H-HIIT induced significant gains in both VO_{2max} and AT, with no significant difference between the improvements made by these groups. Additionally, H-HIIT can be easily adapted to account for injury and/ or pathologies commonly occurring in middle-age (e.g. osteoarthritis, urinary stress incontinence), potentially further improving adherence.

Whilst to our knowledge the impact of H-IHGT upon VO_{2max} and other indices of CRF was unknown, here we show no effects in middle-aged sedentary adults. Perhaps, as would be predicted, in recruiting a significantly smaller muscle mass than both forms of HIIT and offering no significant

cardiorespiratory challenge, H-IHGT did not provide sufficient stimulus to promote improvements in CRF. Nonetheless, H-IHGT was able to confer significant improvements in resting BP within this cohort. H-IHGT may provide a viable alternative for those individuals who are unable to participate in dynamic exercise regimes who also have rising blood pressure not yet requiring medical management (accepted hypertension treatment threshold <140/90, (NICE, 2016a)); especially those with a tendency towards hypertension given the significant negative correlation between baseline BP and training-induced change in BP observed in this study. Potential mechanisms for this improvement include reduced endothelial dysfunction due to increased nitric oxide bioavailability as well as decreased sympathetic nerve activity, both of which lead to reduced resting arterial pressure (Garg *et al.*, 2014). With no recorded side effects, particularly versus pharmacological intervention, H-IHGT is a very attractive option to reduce BP given the striking risk reduction in both coronary heart disease events (22%) and stroke (41%) with just 10mmHg reduction in SBP or 5mmHg reduction in DBP (Law, Morris and Wald, 2009).

Advancing age, lack of time, climate and perceived effort are all negatively associated with physical activity participation (Trost *et al.*, 2002). All three of the interventions employed in this study potentially address these issues in that they are time-efficient, suitable for all ages and can be performed indoors. Indeed, previous studies have also reported HIIT to be more enjoyable and less effortful than traditional endurance exercise for both healthy individuals (Bartlett *et al.*, 2011) and patient groups (Kong *et al.*, 2016). Ongoing debate exists as to the wider public health application of HIIT (Biddle and Batterham, 2015), suggesting that, as in this study, low volume or reduced exertion HIIT (RE-HIIT) may be a more practical and tolerable solution to promote extensive uptake of HIIT, versus the earlier Wingate style HIIT (Gillen and Gibala, 2013).

Importantly, all three exercise interventions in this study required a total weekly time commitment of <45 mins. This is 30% less time than the current adult guidelines for vigorous activity and only one third of the time commitment recommended for moderate activity (WHO, 2011). As a previously identified barrier to exercise, reduction in total time commitment, would likely lead to enhanced exercise adoption and adherence (Trost *et al.*, 2002). Additionally, our findings suggest that the adaptations induced by H-

HIIT and H-IHGT have potential, particularly as adjuvant home-based strategies, to improve key aspects of CRF and BP.

Interestingly, in keeping with general findings (Allender *et al.*, 2008), there was a high drop-out rate within the H-MCT group. Two participants did not undergo baseline testing post randomisation and a further two did not return for reassessment citing 'lack of time' to complete the intervention (150mins/week) as seen previously (Trost *et al.*, 2002). As small sample size (n=2) would negate valid conclusions to be drawn regarding the efficacy of this intervention this group was removed from statistical analysis.

4.5.1 Limitations

We recognise limitations to this study design. We believe that the true potency of L-HIIT versus H-HIIT may not have been fully reflected within this study, larger sample sizes may reveal a greater effect size of L-HIIT over H-HIIT. Also the small sample size may increase type II errors, which may mask the potential of L-HIIT to improve BP given that reductions in BP have previously been shown with L-HIIT (Boereboom *et al.*, 2016). Equally the improvements in BP noted in the H-IHGT group may be reflective of regression to the mean and as such larger studies are required to remove this potential error. Lastly in relation to clinical diagnosis of hypertension, following an elevated automated NIBP reading in the clinic environment, the gold standard is now a 24 hour ambulatory reading (NICE, 2016b), further studies are required to see whether the reductions in blood pressure following H-IHGT are translatable to the home environment throughout the day. The intensity and compliance for the home-based exercise interventions was monitored by self-report, however, given the improvements in CRF in just 4-weeks, volunteers in the H-HIIT group were likely exercising at high-intensity given the improvements seen despite low total workload, as seen previously (Iaia *et al.*, 2009; Gibala *et al.*, 2012b; Gillen and Gibala, 2013).

4.5.2 Chapter Conclusions

Both L-HIIT and H-HIIT can safely produce significant gains in CRF in sedentary middle-aged individuals after just 4 weeks. Although L-HIIT clearly elicited a numerically greater improvement in VO_{2AT}/ VO_{2max} than H-HIIT, this was not statistically significant. We suspect that with a larger study there may have been a statistically significant benefit of L-HIIT over H-HIIT.

As the total volume of exercise decreases the intensity at which it must be performed increases to bring equivalent benefits in CRF following HIIT. The individuals in this study were middle aged, healthy but sedentary individuals, highly motivated and physically able to train in the laboratory setting or at home. When considering rolling this out to patients for major intra-abdominal surgery, who often have limiting co-morbidity it is essential that the most effective training method be used to see whether rapid gains in CRF are attainable within 4 weeks. Future work should include application of home based exercise modalities in these clinical groups as this would be a cost effective, generalizable way to roll out exercise prehabilitation. L-HIIT allows for true monitoring of exercise regime adherence and adherence to prescribed exercise intensity. Therefore, L-HIIT currently represents our 'gold standard' training intervention and will be employed as such within Chapters 5 and 6 to investigate HIIT's efficacy within clinical groups further.

Additionally, H-IHGT can improve BP within the same timeframe with a similar low time commitment. Larger scale studies are required to fully assess the feasibility and effectiveness of these interventions, in healthy and clinical populations, whilst also exploring the mechanistic basis of adaptation.

5 Exploring the efficacy of four weeks low volume HIIT on cardiorespiratory fitness in octogenarians with comorbid disease

5.1 Chapter focus

Chapter 2 established that HIIT is more likely to rapidly improve cardiorespiratory fitness within short time periods, within disease groups, than traditional exercise methods. Chapter 4 then investigated relative potency of supervised or unsupervised HIIT protocols in middle aged sedentary individuals, with supervised laboratory based HIIT delivering the greatest improvement in CRF over short periods. Cancer is a disease of later life, as are many chronic conditions, and the incidence of operable cancers increases with age. It is unknown whether elderly individuals with co-morbid conditions, reflective of those high risk patients presenting for major intra-abdominal surgery, would be able to make similar significant gains in cardiorespiratory fitness over a clinically relevant time period.

5.2 Introduction

As the population ages, increasing numbers of older people with chronic diseases present for major surgical resections. Indeed, the incidence of the most common cancers requiring major intra-abdominal surgery (prostate and bowel cancer) increases with advancing age, with a peak incidence at 85-89 years of age (Royal College of Surgeons, 2012; Cancer Research UK, 2015a). However, there is a marked reduction in surgical resections in older individuals across a wide range of cancer types, which is most marked over the age of 75 years (Department of Health, 2015), when fitness is often perceived to have decreased to a level that makes risks of surgery greater than benefits (Royal College of Surgeons, 2012).

Pre-operative cardiopulmonary exercise testing (CPET) can be used to stratify patients to high or low perioperative risk (cardiac mortality and postoperative morbidity), with anaerobic threshold (AT) the most commonly used metric of cardiorespiratory fitness (CRF) (West, Jack and Grocott, 2011; Older, 2013; Snowden *et al.*, 2013). Low preoperative CRF has repeatedly been shown to be predictive of poor post-operative outcome (Older, Hall and Hader, 1999; Hennis, Meale and Grocott, 2011), mortality (Snowden *et al.*, 2010, 2013; Hennis, Meale and Grocott, 2011) and length of stay (Snowden *et al.*, 2010, 2013). Whole body lean muscle mass (LMM) declines with age, with approximately 0.5–1% loss of muscle mass in over 70 years olds per year (Mitchell *et al.*, 2012). The presence of certain cancers, particularly upper gastro intestinal tract and lung cancers, accelerate LMM loss, with cachectic patients having depleted up to 80% of their LMM at diagnosis (Thomas, 2007). AT has also been correlated to LMM (Nyasavajjala *et al.*, 2015), leading to further concerns about older patients presenting for surgery, as low LMM at hospital admission is predictive of longer length of stay (Pichard *et al.*, 2004) and increased complications after surgery (Huang *et al.*, 2015). In addition, the physiological insult of surgery is known to result in increased muscle protein breakdown, leading to imbalance between muscle protein synthesis and breakdown, leading to LMM loss (Carli and Schricker, 2000). The impact of surgery on older adults, suffering from the developing processes of sarcopenia (Morley *et al.*, 2001) and dynapenia (Clark, Manini and Todd, 2012), is much greater than on younger people.

The pre-operative time period is often limited due to clinical urgency or a requirement to meet clinical waiting time targets. For cancer patients in the UK this target is not more than 31 days between decision to treat and operation (Department of Health, 2012). This short pre-operative period is the only time available to increase patient's CRF, with a view to improving peri-operative outcomes and accelerating post-operative recovery (Carli *et al.*, 2017). Post-operative outcomes can be improved following 6 weeks multi-modal (motivational interview, high intensity exercise and promotion of physical activity) prehabilitation in the comorbid elderly (American Society of Anaesthetists (ASA) grade 3-4) (Barberan-Garcia *et al.*, 2018).

Isolated exercise interventions with the potential to modulate CRF parameters in a short time-frame, such as high intensity interval training (HIIT), have been investigated in young healthy cohorts with good effect (Gibala and McGee, 2008; Gibala *et al.*, 2012b). However, despite the co-morbid elderly (ASA grade 2-3, >75 years old) representing a large proportion of patients presenting for surgical resection, it is unknown if HIIT is an effective pre-operative exercise intervention in this cohort. Studies in different specific disease states such as cardiovascular disease (Wisloff *et al.*, 2007), cancer (Devin *et al.*, 2016) and obesity (Wallman *et al.*, 2009; Trilk *et al.*, 2011) do suggest that HIIT is more potent than traditional moderate continuous exercise for improving CRF and increasing LMM (9), however, much of this literature is in younger age groups (<65 years) and delivered over a longer duration which would not comply with clinical waiting time guidelines.

5.3 Methods

5.3.1 Participants

Participants were recruited by demographically targeted postal invitations to addresses within the city of Derby. The study was approved by the University of Nottingham Medical School Ethics Committee, and written informed consent was obtained from all participants. The study was registered with Clinicaltrials.gov (NCT03138265) and complied with the Declaration of Helsinki.

A medical practitioner screened all participants prior to baseline testing. Screening consisted of a cardiorespiratory examination, resting blood pressure measurement, a 12-lead electrocardiogram and routine haematology/ biochemistry blood profiles. Inclusion criteria were: independent community-dwelling individuals aged over 75 years; ASA physical status classification system Grade 2 or 3 (Grade 2 = a patient with mild systemic disease, Grade 3 = a patient with severe systemic disease, as discussed in full in the introduction) (American Society of Anaesthesiologists, 2014). A blinded consultant anaesthetist assigned ASA grading.

Individual morbidity and regular prescribed systemic medications are shown in Table 9 in the *Results* section. Volunteers were also required to have had no change to regular medications in the month prior or during the study period, be available for the entire study period and be physically able to cycle on a static cycle ergometer. Exclusion criteria for participant safety were based on the American Thoracic Society (ATS/ ACCP) Cardiopulmonary Exercise Test (CPET) Guidelines (American Thoracic and American College of Chest, 2003). In addition, ASA Grade 1 and those already undertaking >2 exercise sessions (bouts of exercise of >10 minutes with the aim to increase aerobic fitness (WHO, 2010, 2011)) per week were excluded. Participant characteristics are shown in Table 8.

5.3.2 Experimental Design

A study schematic can be seen in Figure *41*. After baseline Assessment Session 1 a control period of 4 weeks (CON) was followed by Assessment Session 2. Participants then completed 4-weeks of HIIT and then final Assessment Session 3 (within 36 hours of the end of the 4 week HIIT period).

The control period was included to ensure no change in habitual activity level or increases in fitness occurred secondary to study participation alone. Each assessment session consisted of anthropometric measures (height and weight), *vastus lateralis* muscle architecture imaging (muscle thickness, muscle fascicle length and pennation angle) (Franchi *et al.*, 2014), CPET and blood (serum) sampling. Assessment Sessions 2 and 3 also included whole body composition imaging (DXA, GE Lunar Prodigy, UK). Participants wore a tri-axial physical activity monitor (Actiheart, CamMtech Ltd, Cambridge, UK) for a 5-day period around the mid-point of both CON and HIIT periods. At each assessment the mean of three resting heart rate and blood pressure measurements was recorded with these measures taken after 5-minutes of sitting with the arm supported at the level of the heart (British and Irish Hypertension Society, 2017).

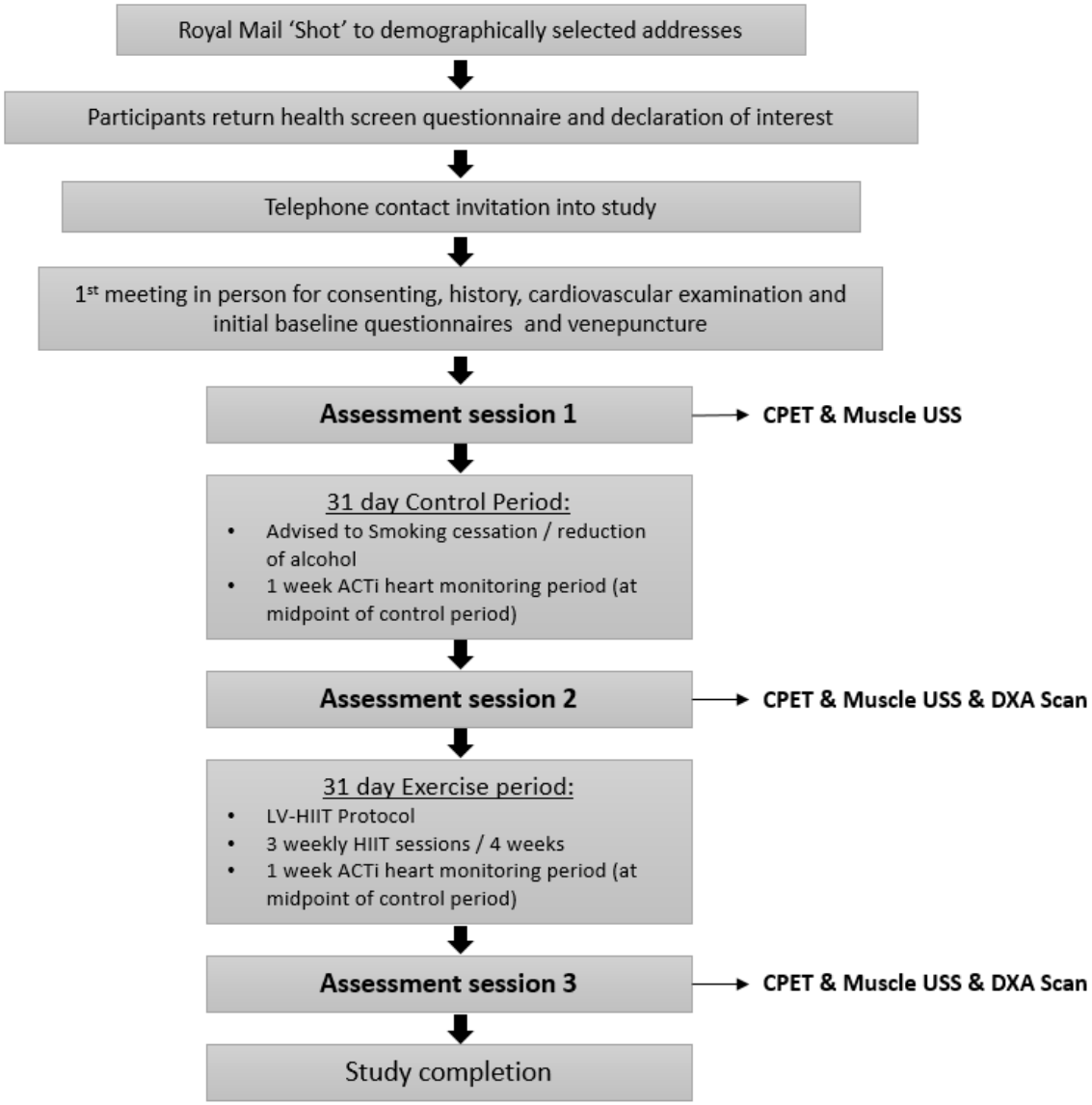


Figure 41 - Study Schematic.

5.3.3 Cardiopulmonary exercise testing

CPET was conducted in as described in detail within Chapter 3, using a 5-20W/min ramp protocol on a Lode Corival cycle ergometer (Lode Corival, Lode, Groningen) with inline gas analyser (ZAN 680, nSpire Health, Colorado, USA). For the duration of the test participants were instructed to pedal at 55 revolutions per minute (RPM) and to continue until volitional exhaustion. All CPET sessions were overseen by an advanced life support-trained doctor with termination criteria taken from the ATS statement on CPET (American Thoracic and American College of Chest, 2003). Values obtained from the CPET were: VO_{2PEAK} (litres/min); maximum heart rate (HRmax; beats per minute); heart rate recovery after 1-min (HRR1; beats) and 2-min (HRR2;

beats); and respiratory exchange ratio (RER). In addition, submaximal values for HR, VO_2 and RER at 25%, 50% and 75% maximum wattage achieved at initial CPET were recorded, with submaximal heart rate deemed indicative of exercise efficiency (Broskey *et al.*, 2015). Anaerobic threshold was derived using a modified V-slope/ ventilatory-equivalents methods (Boereboom *et al.*, 2016) (see Chapter 3), analysed by two experienced CPET assessors blinded to timeline and individual.

5.3.4 Qualitative data

In addition to our physiological endpoints, participants answered the Dukes Activity Score Index (DASI) questionnaire (Hlatky *et al.*, 1989b) to assess subjective functional status and the EuroQoL Group EQ-5D-5L standardised measure of health status questionnaire (EQ-5D-5L) (The Euroqol Group, 1990). Participants completed a HIIT acceptability questionnaire as used previously (Boereboom *et al.*, 2016). At assessment 1, participants completed both the DASI and the EQ-5D-5L questionnaire, with the EQ-5D-5L being repeated at assessment 2 and 3. Upon study completion participants completed the HIIT acceptability questionnaire.

5.3.5 HIIT Sessions

The HIIT protocol was delivered as the sole exercise intervention in this study (see Chapter 3). Each HIIT session lasted 16.5 minutes with the participants aiming to complete 12 sessions within 31 days (3 sessions/week for 4 weeks). Initial training wattage for each interval was determined at an assessment session (see Chapter 3), whilst during each exertion participants were encouraged to work at a revolution per minute (RPM) that elicited a heart rate response >85% age predicted maximum. A modified Borg scale rating of perceived exertion (RPE) (Borg, 1982) was presented to participants immediately after the final interval (no. 5) of HIIT training session 6, with individuals recording a score of 8 or less subjected to a 10% increase in training wattage for the remaining 6 HIIT sessions.

5.3.6 Statistical Analysis

5.3.6.1 Power calculation

Assuming an 18% coefficient of variation (from previous work in our laboratory), to detect a mean clinically significant increase in anaerobic

threshold of 2ml/kg/min following HIIT, with 1-β=0.8 and α=0.05 significance, we required 28 complete data sets. Assuming a 20% drop out rate (commonly seen in similar studies in our laboratory) a maximum of 34 individuals would be required.

5.3.6.2 Statistical tests

Normality of data was tested using D'Agostino and Pearson omnibus test. Paired Student's t-tests were used to test parametric data, the Wilcoxon matched-pairs signed-rank tests were used for nonparametric data. Normal data are expressed as mean ± standard deviation (SD), and nonparametric data as median ± interquartile range [IQR]. For CRF results, we report effect estimates as mean differences (MD) with 95% confidence intervals. To assess the relationship between body composition and CRF improvements we performed Pearson's correlation analysis. We report the correlation coefficient (r) with a corresponding p value for the model. Statistical significance was set at $p<0.05$. Analyses were conducted using Graphpad Prism Version 7 (GraphPad Software, CA, USA).

5.4 Results

5.4.1 Participants

Thirty-two volunteers were recruited in total providing written informed consent, 28 of whom completed the study (18 male, 10 female; aged 81.3±3.6 years; BMI: 27±3.3 kg/m^2) (Table 8). Of the volunteers who completed the study, 21 were graded as ASA Grade 2 and 7 as ASA Grade 3. Comorbidity data and prescribed regular medicines can be seen in Table 9. Notably, twenty participants had clinical diagnoses of hypertension however only 18 were medicated with anti-hypertensive drugs. The two un-medicated hypertensive individuals both stated that they had suffered unwanted side effects and had decided to stop taking the prescribed medication.

Table 8 - Participant characteristics of study completers - Descriptive statistics are represented as mean (SD) for parametric and median [IQR] for non-parametric data.

Measure	Value
Age (SD)	81.3 (±3.6) years
Gender	18 male; 10 female
BMI (+/-SD)	26.9±3.3 kg/m^2
ASA Grade (2:3)	21:7
SBP	153 [142–158]
DBP	79 (10)
Resting HR	68 (9)
VO_{2PEAK} (ml/kg/min)	22.17 (6.41)
VO_{2AT} (ml/kg/min)	13.39 (2.7)
Dominant handgrip strength	27.4 ± 8.7 kg
SPPB Score	9.8 ± 2
DASI	41.23 ± 11

Table 9 - Participants' formally diagnosed comorbidities and regular prescribed systemic medications.

System:	Pathology:	Number
Cardiovascular	Hypertension	20
	Ischaemic heart disease	6
	Heart failure	2
	Valvular disease	2
	Pacemaker	1
	Abdominal aortic aneurysm	1
Respiratory	COPD	1
	Asthma	2
	Previous Lung TB	2
Endocrine	Thyroid disorders	4
	Diabetes mellitus	5
	Dyslipidaemia	5
	Gout	2
Musculoskeletal	Osteoarthritis	8
	Large joint replacement	6
Obesity	BMI >25 (Overweight)	14
	BMI >30 (Obese Class 1)	6
Regular medications:		
Inhaled bronchodilators		3
Statins		13
Calcium channel blockers		11
Beta-blockers		3
Amiodarone / Digoxin		2
ACE-inhibitors / AT1/2 antagonists		7
Diuretics		7
Metformin		2
Thyroxine		4

Drop outs from the study can be seen in the study consort diagram (Figure 42). One volunteer was unable to cycle on the static ergometer due to knee pain (known osteoarthritis) and therefore did not undergo the initial CPET to begin the study. One participant voluntarily withdrew after the death of their spouse. One participant did not like the feeling in his legs induced by HIIT and voluntarily withdrew after one session. The last participant to not complete was withdrawn from the study as he was started on a beta-blocking agent following advice from a cardiologist. This patient had well-documented cardiovascular disease (coronary artery bypass graft, abdominal aorta repair and hypertension) and breached our safety criteria of >2mm ST depression in V5-6 during the second half of the HIIT programme (session 7) following an increase in the intensity. He was asymptomatic throughout and tolerated HIIT well despite this finding. Of the remaining participants (n=28) the primary outcome measure (VO_{2AT}) was available pre and post intervention.

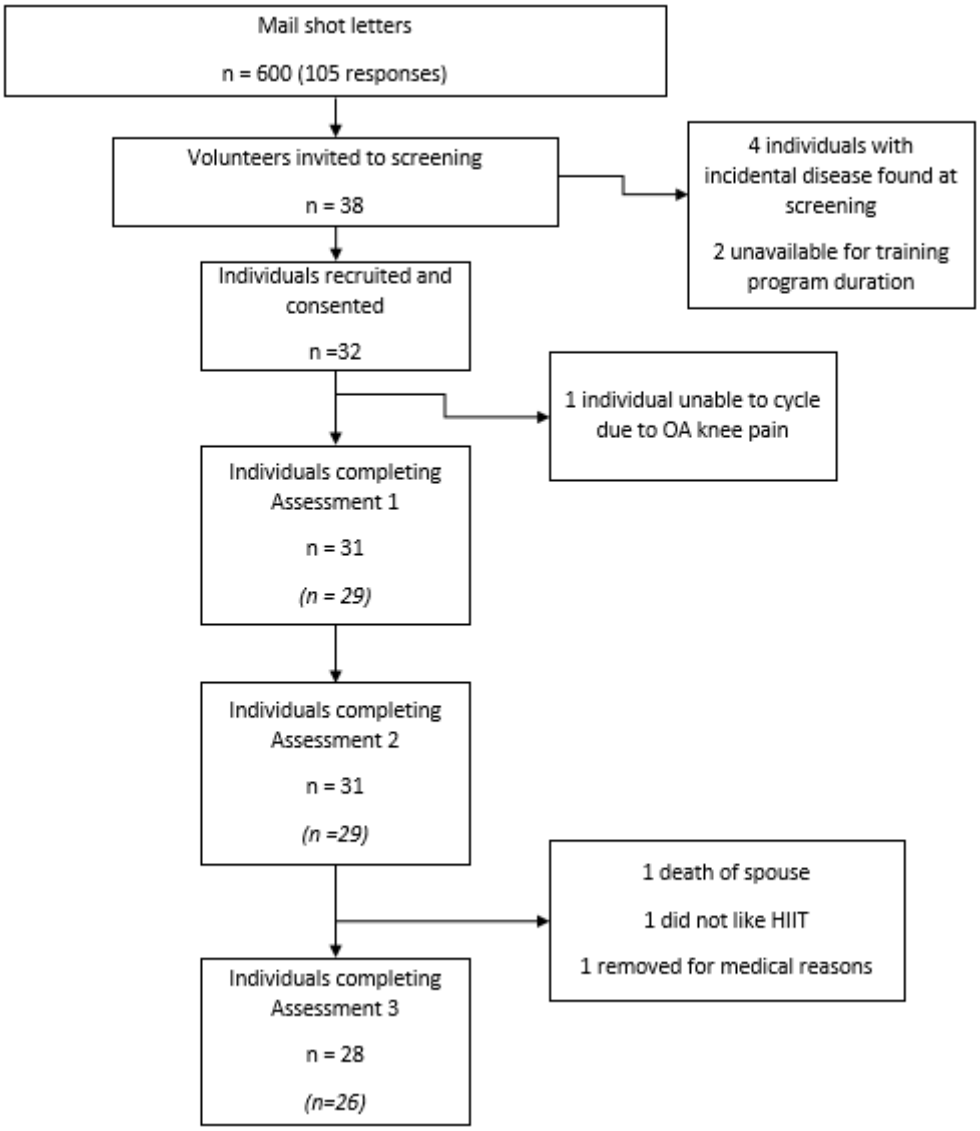


Figure 42 - Study consort diagram. Bracketed n values represent number of individuals undergoing DXA scan as part of Assessment, OA = osteoarthritis.

5.4.2 HIIT training workload and relative intensity

The number of days between assessments 1-2 and assessments 2-3 were not significantly different (28.8 ± 5.5 days vs 29.3 ± 3.8 days; p=0.87). Exercise intensity during the HIIT intervals ranged from 46-226 watts, with males exercising at a significantly higher intensity (male: 131±37 watts, female: 81.5±25 watts, unpaired t-test p=0.003). During the HIIT assessment session, 16 participants were able to exercise at 110% of maximum wattage at initial CPET, with only a single participant unable to complete 1 min at 100%. All other participants exercised at 100-105% of maximum wattage achieved at initial CPET. Mean heart rate as a percentage

of age-predicted maximum (220 beats per minute minus age in years) during training sessions 2, 6 and 10 were 96.6%, 95.7%, and 94.8% respectively, confirming that high-intensity exercise was being performed (Kravitz, 2011). Seventy-one percent of participants reached the criteria for the increase in training load by the mid-point of HIIT (session 6).

5.4.3 Cardiorespiratory fitness

HIIT significantly increased VO_{2AT} (MD) 1.21 ml/kg/min, 95% CI 0.36 to 2.07) (Figure 43 A), VO_{2PEAK} (MD 1.66 ml/kg/min, 95% CI 0.45 to 2.87) (Figure 43 B) and maximum wattage achieved at CPET (MD 12.54 W, 95% CI 8.9 to 16.1), with no increases during CON.

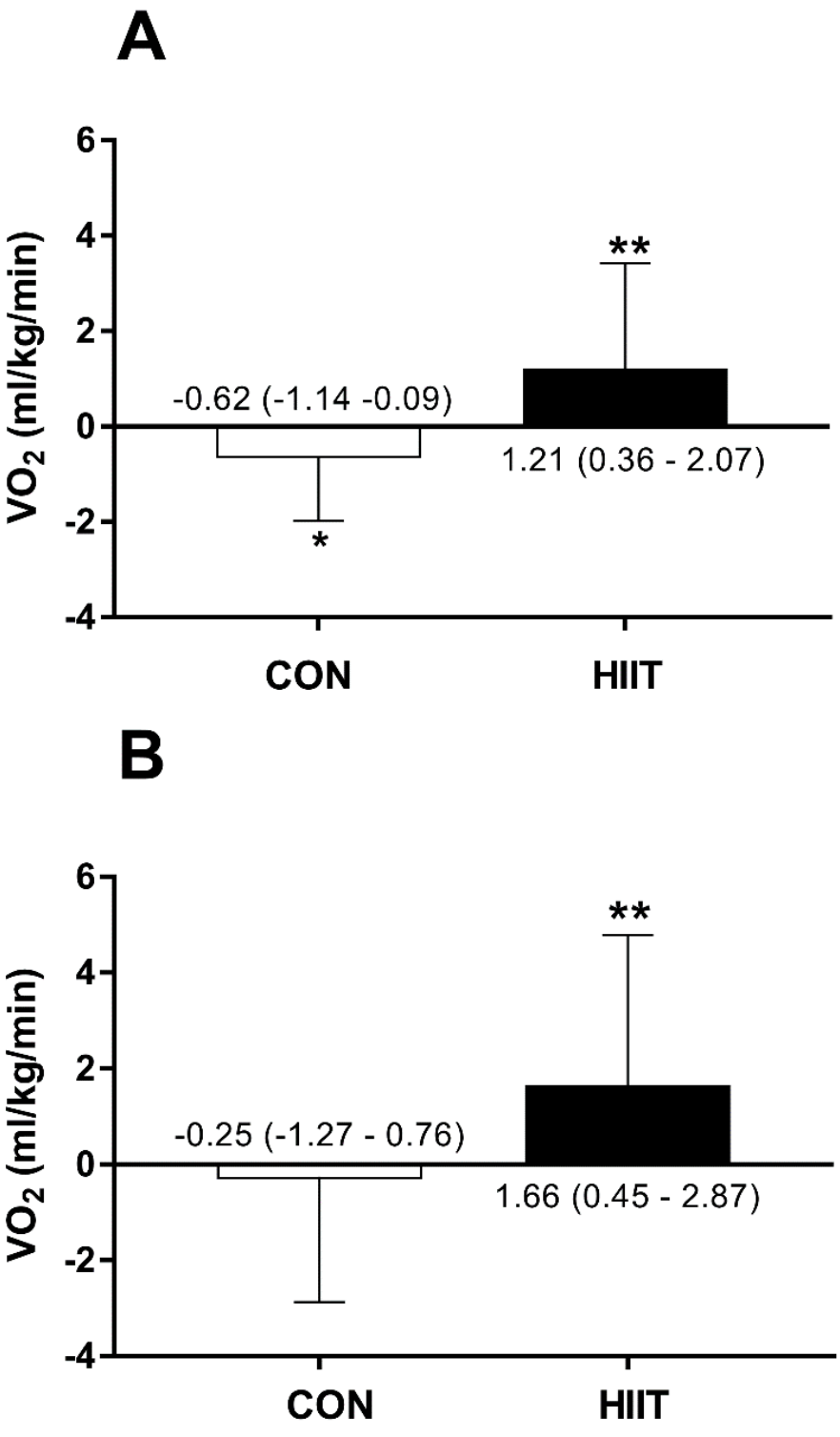


*Figure 43 - A: Change in VO_{2AT} across CON and HIIT periods, B: Change in VO_{2PEAK} across CON and HIIT periods, * = p<0.05, ** = p<0.001. Data presented as mean change (95% CI).*

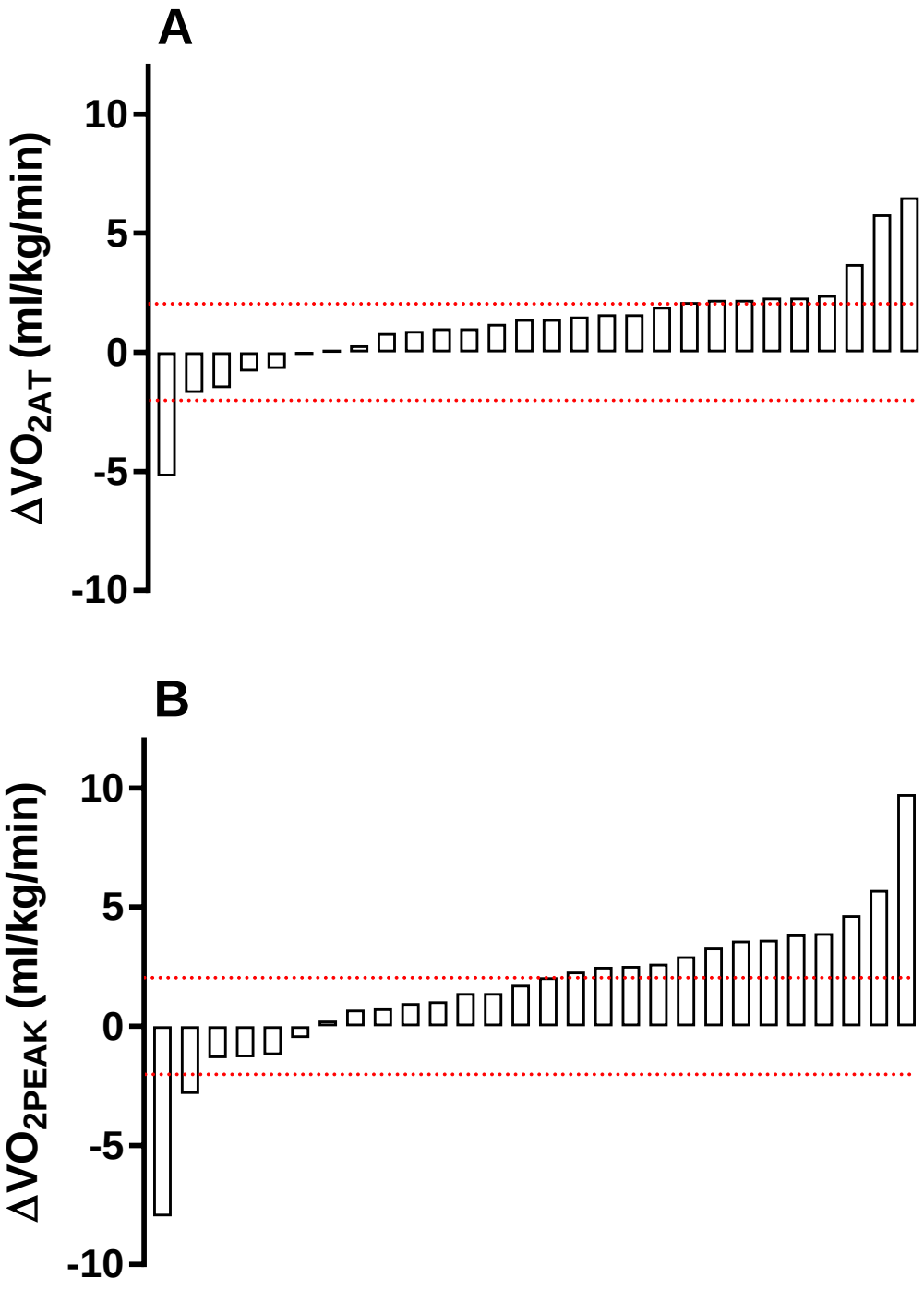


Figure 44 - Individual changes in VO_{2AT} (A) and VO_{2PEAK} (B) following HIIT (n=28). Dashed line at 2ml/kg/min.

Systolic blood pressure (SBP) and resting heart rate (RHR) both decreased following HIIT (SBP: MD -9mmHg, 95% CI -16 to -2.1); RHR: MD -4 bpm, (95% CI -6.13 to -1.8), with no significant change across CON. Full CPET data can be seen in Table 10.

Table 10 - Cardiorespiratory fitness data - descriptive statistics are represented as mean (SD) for parametric and median [IQR] for non-parametric data.

	Assessment		Change during CON		Assessment	Change during HIIT	
Parameter	1	2	1-2	p	3	2-3	p
VO_2AT (ml/kg/min)	13.39 (2.7)	12.77 (2.7)	-0.62 (1.4)	0.03	13.52 [11.8-16.3]	1.21 [0.36-2.07]	<0.01
VO_2AT (L/min)	0.94 [0.86 -1.1]	0.94 [0.79-1.04]	-0.018 [-0.14-0.03]	0.03	0.99 [0.86-1.16]	0.095 [0.01-0.15]	<0.01
VO_2peak (ml/kg/min)	22.17 (6.41)	21.9 (6.0)	-0.25 (2.6)	0.61	23.6 (6.6)	1.66 (3.1)	<0.01
VO_2peak (L/min)	1.60 [1.3-2.0]	1.63 (0.43)	-0.065 [-0.16 – 0.10]	0.31	1.78 [1.26-2.0]	0.14 [0.035-0.28]	<0.01
Wattage (W)	104 (39)	105 (37)	-0.32 (9.5)	0.86	118 (41)	12.54 (9.3)	<0.0001
SBP	153 [142-158]	147 (15)	-0.5 [-2.75-4]	0.77	139 (14)	-9.04 (18)	<0.01
DBP	79 (10)	78 (9)	-0.79 (6)	0.50	77 (10)	-1 (6.9)	0.45
Resting HR	68 (9)	66 (10)	-2 (6)	0.07	62 (9)	-4 (6)	<0.01

As seen in Figure 45, at submaximal wattages (25%, 50% and 75% maximum wattage achieved at initial CPET) heart rate was significantly lower following HIIT (25%:-5bpm, $p<0.05$; 50%: -3bpm, $p=0.05$; 75%: -5bpm, $p<0.01$) with no significant change across CON (25%:-5bpm, $p=0.01$, 50% -3bpm and 75% -3bpm both $p=>0.05$).

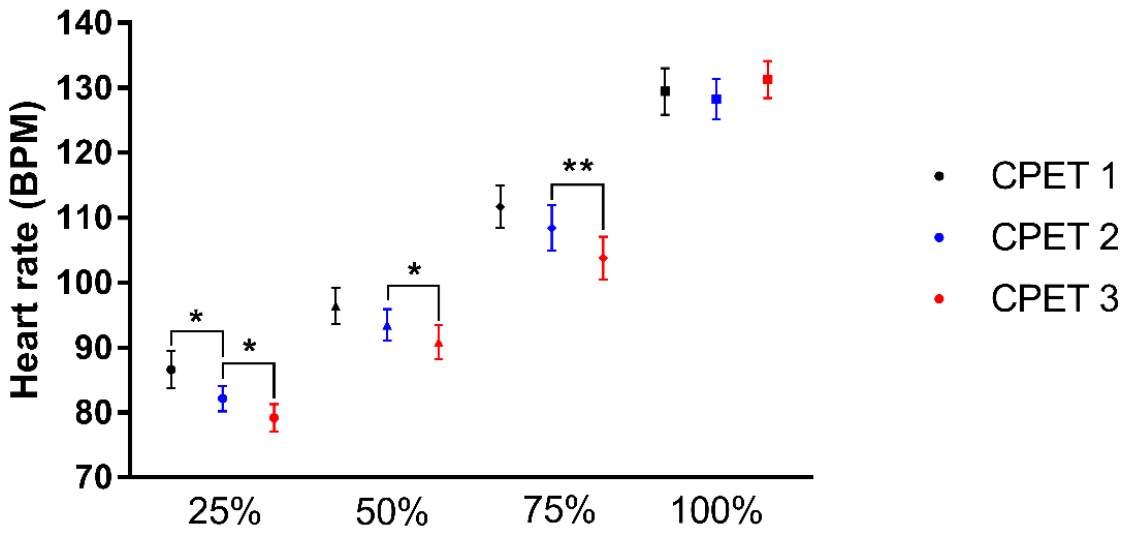


*Figure 45 - Heart rate (BPM) measures for CPET 1 (Black), 2 (Blue) and 3 (Red) at 25%, 50%, 75% and 100% of Wattage achieved at CPET 1. *=p<0.05, **=p<0.01.*

There was no significant difference in serum haemoglobin levels (g/L) across either CON (p= 0.3) or HIIT (p=0.15).

5.4.4 Body Composition

Twenty-six participants underwent DXA scan to assess body composition (one had breached the annual safe dose of radiation due to previously have a CT scan and one was due to ethical approval delay). Significant increases in whole body lean muscle mass (47.32 kg to 47.82 kg, p=0.042) and reduction in total body fat percentage (33.2% to 32.25%, p=0.004) were observed after HIIT (Figure 46). Following HIIT our three parameters of muscle architecture in the *vastus lateralis* were unaltered (muscle thickness: 1.897 ±0.32 vs 1.994 ±0.36 cm, p=0.41; muscle fascicle length: 7.079 ±0.793 vs 7.456 ±0.972 cm, p=0.19; muscle pennation angle: 13.8 ±2.4 vs 13.73 ±2.7, p=0.85). These parameters were unaltered during CON.

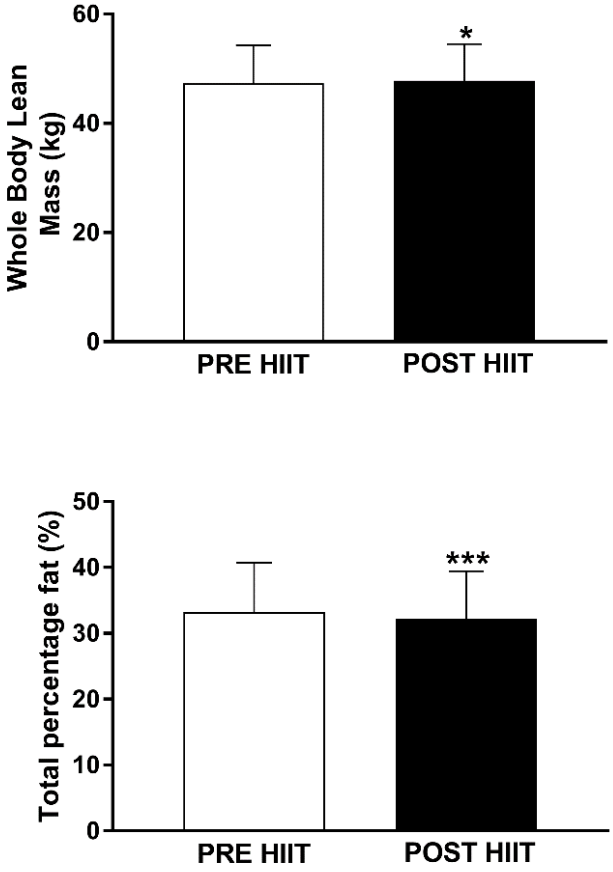


Figure 46 - Changes PRE / POST HIIT in whole body lean mass (kg) and total body fat (%) as defined by DXA Scan (n=26), data presented as mean (SD).

5.4.5 Habitual activity levels

5.4.5.1 Objective analysis

Based on our acceptance criteria of >80% of minute-by-minute physical activity data having to be available for at least three 24-hour period recordings to be accepted, only subjects (n=12) who had both CON and HIIT period recorded data were included in this analysis (Brook *et al.*, 2016). Two participants did not have activity monitoring due to a delay in ethical approval. Insufficient data was collected for 5 participants throughout both CON and HIIT periods (three participants experienced skin irritation from the electrode adhesive pads resulting in early termination, one participant did not understand that the monitor had to be worn at night and one participant broke the monitor trying to remove it for a bath). Battery life on the equipment proved unreliable, data was lost or not recorded on one of either

CON or HIIT periods for 4 participants. Subsequently 5 participants were unable to wear the monitors as they were under repair by the manufacturer. Two declined activity monitoring as it was summer and they did not want to wear the monitor (both female as worn on front of chest). There was no significant difference in the number of non-study related activity counts per day during CON vs HIIT (19367±7824 vs 17592±8677 counts per day, p=0.23). There were also no significant differences in the amount of time spent at various metabolic equivalent (MET) levels (min/day) between CON and HIIT (<1.5 METs: 1194±131 vs 1201±163.1; >1.5 to <3 METs: 128±66 vs 121±88; >3 to <6 METs: 29±36 vs 46.63±66; >6 to <10.2 METs: 0.26±0.62 vs 0.21±0.46; >10.2 METs: 0.31±0.98 vs 0.02±0.04, all p >0.05).

5.4.5.2 Subjective analysis

There was no significant increase in subjectively reported DASI questionnaire scores upon completion of the CON (median score 44.83 (38.0 – 49.4)) and HIIT (median score 45.0 (37.45 - periods (p=0.662).

5.4.6 Quality of life

HIIT increased self-rated health status using the 5EQ-5DL-5L questionnaire (85 [80 – 90] to 90 [81.25 – 90], p<0.05) with no significant change across CON (p=0.37). There was no change in weighted health state index during CON or HIIT (p>0.05).

5.4.7 Safety, feasibility and acceptability

There were no serious adverse events during assessment sessions or HIIT. Our HIIT protocol was deemed highly acceptable by this cohort (Table 11) with 89% of individuals 'Strongly agreeing' that HIIT was enjoyable. A similar number of participants reported that they would 'do HIIT again' (86% 'strongly agree') and 79% would 'recommend HIIT to others'. When asked: 'What was your favourite part of HIIT?' Forty-five percent of participants specifically stated 'social interaction with the staff' (Table 12).

Table 11 - Data from HIIT acceptability questionnaire completed by participants following HIIT protocol completion. 5 point Likert scale data represented as median (range).

Comment (n=28)	Median score (range) 5 – Strongly agree, 1 – Strongly disagree
HIIT was well explained	5 (5)
I enjoyed HIIT	5 (5)
HIIT was a time burden	1 (1-4)
I would recommend HIIT to others	5 (5)
HIIT was more demanding than expected	3 (2-5)
I would do HIIT again	5 (5)
The travelling involved with HIIT interfered with my life	1 (1-3.5)
The physical strain interfered with my life	1 (1-2.5)
I believe my fitness has improved	5 (4-5)
I would like to have exercised in a group	1 (1-3)
I would like to have exercised at home	1 (1)

Table 12 - Free text responses from the first question from the HIIT acceptability questionnaire completed by participants following HIIT protocol completion.

What has been the most challenging part of the HIT training?
No major problems
The initial and final bike tests
The cycle test but worth it
The dreaded face mask and the exercise cycle seat
The challenge was enjoyable
Doing 3 days running (without a days rest)
85% cycle reps
Cycling
Saying to myself why am I doing this? Then committing myself to keep trying to do better
Having chest stickers removed (thanks Amanda!)
On the bike - not being used to it
Spitting in the pot
The bike (the saddle)
In achieving a good standard on the cycling machine, especially on the uphill climb at my age
None
The fast periods of cycling
Wearing the mask

Table 13 – Free text responses from second question on the HIIT acceptability questionnaire completed by participants following HIIT protocol completion.

What has been the best part of the HIT training?
Staff
Seeing the results
Getting fit
Feeling fitter
All of it
Enjoy every aspect of the training
Meeting the research team
The whole experience and the medical staff
Learning about the clinical aspects of it
Providing useful data
The staff
Diversion from usual life routine. Meting others and knowing I'm not as unfit as I was
Improving fitness and interaction with staff
Social aspect
Just taking part
Insight of HIT - Loved it!
The professionalism of the training staff under Dr James Blackwell who were there at every appointment to prepare you and give you moral support whilst exercising
Pushing me to my limits
The end
Meeting pleasant staff - well looked after and the health checks. Hoping it has helped with your project
Getting fitter, stronger thighs. Meeting different members of medical staff involved and I really appreciate their encouragement when on bike, without it there were times I would have given up (in the early days)
The staff

5.4.8 Relationship between body composition and CRF improvements

There was no significant correlation between baseline LMM (DXA 1) and cardiorespiratory fitness at CPET (Assessment 2) (VO_{2AT}: r^2=0.171, p=0.40; VO_{2PEAK}: r^2=0.11, p=0.59). There was no relationship between change in VO_{2AT} or VO_{2PEAK} and gains in whole body LMM (VO_{2AT}: R^2 = 0.016, p=0.53; VO_{2PEAK}: r = 0.000035, p=0.98) following HIIT. Similarly, there was no relationship between baseline LMM and gains in CRF (VO_2AT: r=0.009, p=0.65; VO_{2PEAK}: r=0.12, p=0.082). Baseline LMM did not predict LMM gains (r=0.097, p=0.12), nor did baseline CRF predict gains in VO_{2AT} (r=0.0953, p=0.11) or VO_{2PEAK} (r=0.0056, p=0.70).

5.4.9 Correlation of CPET performance improvements, CRF improvements and training intensity

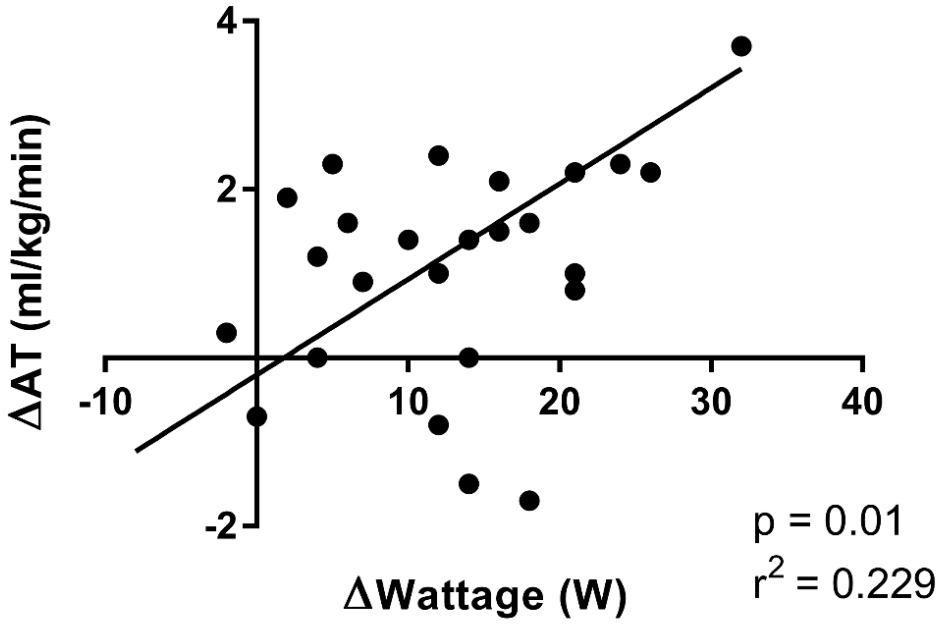


Figure 47 - Change (Δ) in Wattage achieved at CPET versus change (Δ) in VO_{2AT} following HIIT.

Improving final CPET performance (maximum Wattage achieved) was significantly correlated (r^2=0.229, p=0.01) with improvements in VO_{2AT} (Figure 47). Changes in VO_{2PEAK} following HIIT were significantly correlated with higher MET's achieved at HIIT session 12 (VO_{2PEAK}: r = 0.14, p=0.023; Wattage: r = 0.24, p=0.004) as seen in Figure 48.

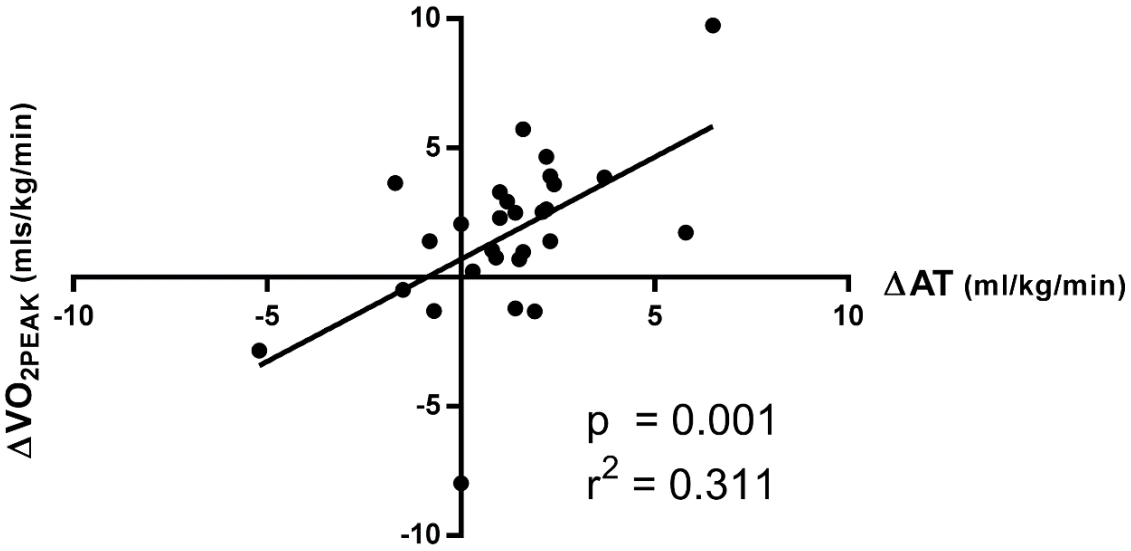


Figure 48 - Correlation of changes (Δ) in VO_{2AT} and change in VO_{2PEAK} (ml/kg/min).

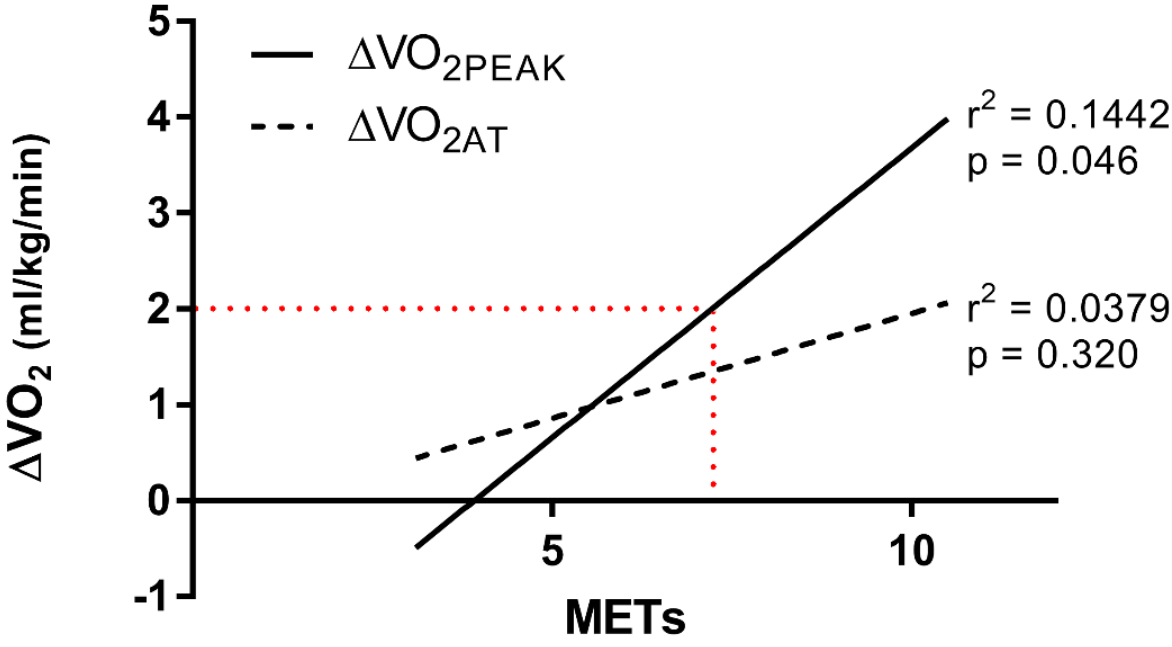


Figure 49 - Highest metabolic equivalent level reached during final HIIT session versus overall change (Δ) in VO_{2AT} (dashed black line) and VO_{2PEAK} (solid black line). Red dashed line denotes minimal clinically important improvement 2 ml/kg/min.

5.5 Discussion

The main findings of this study are that elderly co-morbid individuals are able to make significant gains in CRF within a clinically relevant time-period. After just 4-weeks HIIT, we observed statistically significant increases in both VO_{2AT} and VO_{2PEAK} in octogenarians with non-malignant disease states.

However, despite these positive findings suggesting that HIIT may be a viable, effective method to rapidly improve CRF in this cohort, the minimal effect size required to make a clinically important difference (MCID) remains controversial. This is because large-scale mortality and morbidity data following prehabilitation is lacking. However, an improvement of >1.5-2.0 ml/kg/min is considered to be of clinical importance (Kothmann *et al.*, 2009; West, Loughney, *et al.*, 2014; Boereboom *et al.*, 2016; Dunne *et al.*, 2016). In this study only 32% of individuals achieved our (statistical) *a priori* increase in VO_{2AT} of >2ml/kg/min. A previous study, using prehabilitation HIIT in patients undergoing colorectal liver metastases resection (Dunne *et al.*, 2016) looked at this in another way. They stated that by increasing the AT by >1.5ml/kg/min would move a significant proportion of their patient cohort away from the previously reported high-risk AT of 11 ml/kg/min (Older, 2013; Dunne *et al.*, 2016). Using this rationale within our own results, 46.4% of study participants would have moved away from the at risk line by a significant amount (by achieving >1.5 ml/kg/min improvement in AT). These results may have wider implications for long-term healthy ageing as improving CRF is associated with a lower risk of all-cause and CVD mortality (Lee *et al.*, 2011).

The HIIT protocol used in this study is time efficient (16.5 minutes per session, approximately 30 minutes arrival to exit time experienced within this study) which may have more attractive cost/ resource implications for clinical translation, given that two individuals could be trained within one hour on the same equipment, versus other prehabilitation HIIT protocols used previously (taking ~45 mins per individual per session). Reduced session duration may also result in increased compliance given that "lack of time" is often cited as a major barrier to exercise (Trost *et al.*, 2002). In addition, no adverse safety events occurred during this study. This adds to the evidence that HIIT is safely deliverable to people with disease (Wisloff *et al.*, 2007; Kothmann *et al.*, 2009; Gibala *et al.*, 2012b; Dunne *et al.*, 2016;

Carli *et al.*, 2017) and in older age (Guadalupe-Grau *et al.*, 2017), and is in keeping with data from a large-scale study using HIIT in cardiac rehabilitation (Rognmo *et al.*, 2012). Participants found our HIIT protocol highly acceptable and would recommend it to others. They chose to comment positively upon the social interaction with staff members and expressed enjoyment at improving their fitness levels within the free text comments. We also saw increases in self-rated health status assessed via questionnaire following HIIT.

In addition to improving indices of CRF, our HIIT protocol also reduced resting blood pressure in our elderly comorbid individuals. Prior to this study, the effect of short term HIIT on blood pressure were inconclusive (Broman *et al.*, 2006; Boereboom *et al.*, 2016), however, we have now provided supporting evidence that in older individuals short term HIIT can indeed reduce systolic blood pressure. A 10 mmHg reduction in systolic blood pressure (SBP) or 5mmHg reduction in diastolic blood pressure (DBP) can significantly reduce ischemic heart disease and cerebrovascular events (Law, Morris and Wald, 2009). Lifestyle modification is often the first line management in treatment guidelines (Herrod *et al.*, 2018), thus short term HIIT could have a place to modulate blood pressure in elderly individuals as an adjunct to first line pharmacotherapy agents. Although recently less emphasis has been placed upon modulating peri-operative blood pressure (Hartle *et al.*, 2016), the long-term risk reduction (total mortality and stroke) with lowering systolic blood pressure is well known (Staessen *et al.*, 2000) and is another example of how HIIT may improve the health of older adults in the long-term.

Our HIIT protocol also produced positive changes in body composition parameters associated with whole-body health (increased LMM and decreased body fat%) (Marriott and Grumstrup-Scott, 1990). Somewhat surprisingly given the findings of other HIIT studies (Boereboom *et al.*, 2016), this study did not show increases in lower limb muscle thickness (or other muscle architecture measures). Although the exact mechanistic basis behind improvements in CRF following HIIT remain unclear, it is likely that increased skeletal muscle mitochondrial function (up-regulation of oxidative enzymes) and content (mitochondrial density) play a significant part (Little *et al.*, 2010). In keeping with this proposition, Broskey et al. showed that chronically trained older individuals had significantly greater mitochondrial

content and function, which correlated with greater exercise efficiency (Broskey *et al.*, 2015), and this may go some way to explain the improved submaximal heart rates seen in this study. In addition, central and peripheral vascular adaptation (Wisloff *et al.*, 2007), improved muscle buffering capacity (Gibala *et al.*, 2006) and reduced submaximal energy expenditure (Iaia *et al.*, 2009) are all physiological adaptations that have been suggested to improve CRF following HIIT. Further work is required to elucidate the physiological and molecular mechanisms underlying HIIT induced gains in CRF and LMM (likely enhanced muscle protein synthesis or reduced muscle protein breakdown) (Carli and Schricker, 2000), with specific cohort studies to determine the heterogeneity of these adaptations in different clinical/ non-clinical populations, and across individuals given the growing interest in the notion of exercise "non-responders" (Phillips *et al.*, 2013).

Acknowledging that whilst this study is likely underpowered to draw firm conclusions from correlative analysis (as the study power related to change in AT alone), we do report some interesting observations regarding the relationship between aspects of HIIT and CPET performance which may warrant further research. It is not necessarily surprising, that those individuals who improve their VO_{2PEAK} the most also most improved their VO_{2AT} (Figure 48). However, the improvement in VO_{2PEAK} is significantly correlated with MET level achieved during the last HIIT session may have implications for the future implementation of HIIT. This relationship implies that there is a minimum MET level required during HIIT to evoke a significant physiological change. This could be important when assessing the suitability of patients for HIIT (or alternative exercise modalities); allowing alternatives (or perhaps an altered clinical pathway i.e., earlier operation) to be prescribed to those patients unable to generate the MET level required to elicit rapid improvements in fitness with HIIT. This observation also fits with the hypotheses surrounding the notion that a disturbance of homeostasis is required for HIIT to elicit physiological adaptations (Gibala *et al.*, 2012b). Put simply, if a patient cannot push enough Watts, then they will unlikely make clinically meaningful (denoted by the red dotted-line in Figure 49; 2ml/kg/min) CRF gains with HIIT. Based on this, it could be argued that high-risk surgical patients and the frail elderly, are the exact patients who would be unable to push high watts on a cycle ergometer, and therefore HIIT is not an appropriate, feasible intervention. However, this stance should be

adopted with caution as to not unnecessarily discount the benefit HIIT may have for certain individuals given the large inter-individual variation in exercise adaptation. Ultimately, correct patient selection for personalised prehabilitation is the goal, using exercise methodologies that are most suitable to the individual. Making even small gains in a high-risk individual may reduce their perioperative risk and enhance their functional recovery post operatively, even if the previously stated numerical clinically meaningful increase is not achieved.

5.5.1 Limitations

We acknowledge that there are some limitations to our study design. By the very nature of exercise intervention studies, it is impossible to blind against intervention. We chose to design our study with an individual controlling against them self, with the results of the initial two CPET tests providing a CON period, followed by the HIIT period and a final CPET test to measure the effect of the HIIT intervention. This was not a randomised control trial (RCT), however, we did have an equal length no-intervention CON period for all subjects, across which none of our measurement variables changed (out-with test-retest variation), leading us to believe that any changes seen across the HIIT period were truly due to the intervention. The pragmatic design of this study (including 'all comers' with a variety of co-morbidities) produced a heterogeneous cohort, which although was likely representative of community dwelling older individuals presenting for surgery, was not large enough to allow for sub-group analysis. Such analysis may have been beneficial, to define certain specific morbidities that would benefit most from HIIT (Blackwell *et al.*, 2018). An additional factor for consideration is that supervised individualised exercise training is associated with significant financial costs and resource. Therefore, in addition to the mechanistic work outlined above, future research efforts should focus on exercise interventions which are deliverable in group or community settings, both of which have previously shown benefit in healthy younger groups (Blackwell *et al.*, 2017).

5.5.2 Chapter Conclusions

In conclusion, short term HIIT delivered within a clinically relevant timeframe can produce significant improvements in CRF in certain comorbid

elderly individuals. We also saw positive changes to global body composition and other cardiovascular parameters.

Cancer is a catabolic process wherein patients are at risk of loss of both muscle mass and CRF. Low preoperative LMM and CRF are independently linked to poorer post-operative outcomes as discussed in Chapter 1. It is unknown whether elderly patients with cancer would be as 'trainable' as elderly 'healthy' (but potentially comorbid) individuals, which we have previously been able to show rapid improvements in CRF in response to our four week HIIT protocol. We have previously struggled to fit our HIIT protocol into the narrow preoperative window within the colorectal cancer management pathway, we therefore set out (Chapter 6) to ascertain whether prehabilitation HIIT could feasibly be delivered within the urological malignancy management pathway to a greater extent.

6 A randomised controlled trial of high intensity interval training in patients awaiting resection for urological malignancy

6.1 Chapter focus

Chapters 4 and 5 established that HIIT is effective at improving CRF, in certain individuals (sedentary middle aged and elderly individuals with chronic disease), over short periods in keeping with national cancer waiting time guidelines. The volunteers in Chapter 5 were elderly and had diagnoses of chronic disease, representing higher risk patients presenting to surgical outpatient clinic with new diagnoses of malignancy.

This chapter explores the effect of cancer in situ (namely urological cancers) on patients' responsiveness to HIIT and assesses the feasibility of delivering preoperative HIIT within the current UK clinical framework.

6.2 Introduction

Urological malignancy is common, with over 69,000 new diagnoses for prostate, kidney and bladder cancer in 2015 in the UK (Cancer Research UK, 2015b). Surgery for these cancers is associated with high complication rates (cystectomy 56%, nephrectomy 21%, prostatectomy 19%) (Patel *et al.*, 2016). Survivors commonly experience fatigue, reduced physical ability and reduced quality of life (Sanda *et al.*, 2008), with only 30% returning to baseline levels of physical function at 3 months (Litwin *et al.*, 1999) and 50% by 12 months (Steineck *et al.*, 2002) after radical prostatectomy (RP). This reduction in physical capacity leads to significant periods of time away from work (Bhalla *et al.*, 2014), predicts early retirement for those in work before operation (Tuomi *et al.*, 1997), and contributes to long-term reductions in health-related quality of life (HRQOL) (Steineck *et al.*, 2002; Sanda *et al.*, 2008). Success of surgery should therefore not only be measured by cancer outcomes, but also on return to preoperative levels of quality of life and physical function (Daniel Santa Mina *et al.*, 2014).

Frailty and co-morbidity increase with age, leading to increased operative morbidity and mortality. Urological cancers generally affect older people who often have diminished preoperative cardiorespiratory fitness (CRF) and are particularly at risk from major intra-abdominal surgery (Older, Hall and Hader, 1999; Moran *et al.*, 2016).

In all cancers, patients who exercise following diagnosis have a lower relative risk of cancer mortality, cancer recurrence and adverse effects from disease and treatment (Cormie *et al.*, 2017). Moreover, higher levels of physical activity preoperatively are related to better HRQOL scores post-operatively (Daniel Santa Mina *et al.*, 2014).

Cardiopulmonary exercise testing (CPET), the gold standard clinical measure of CRF (Scott *et al.*, 2015), can help to identify those least fit and therefore most at risk of complications. If poor CRF can be improved before surgery then outcomes may also improve: a pre-operative increase in oxygen consumption at anaerobic threshold (VO_{2AT}) of 2 ml/kg/min is associated with around a 40% reduction in the odds of post-surgical complications (OR 0.6, CI 0.45 – 0.80)(West, Lythgoe, *et al.*, 2014), and the minimum clinically important difference (MCID) in VO_{2AT} is suggested to be 1.5 – 2.0 ml/kg/min (West, Lythgoe, *et al.*, 2014; Dunne *et al.*, 2016).

Prehabilitation regimes aim to improve a patient's health before surgery and reduce the impact of an operation (Silver and Baima, 2013). However, in the UK the National Cancer Action Team specifies that first treatment (including surgery) should start within 31-days of the decision to treat (Department of Health, 2015), leaving only a short time-window in which to improve fitness.

Various forms of exercise training have been used to improve CRF, but most, such as moderate continuous aerobic exercise/ moderate continuous training (MCT), take too long to have an effect to be useful in patients waiting for surgery for cancer (Blackwell *et al.*, 2018). High intensity interval training (HIIT) has proven utility in healthy individuals and can safely deliver greater increases in CRF than MCT over shorter time-periods (<8 weeks) in older individuals with various chronic diseases (e.g. cardiovascular, obesity, respiratory), and certain cancers (e.g. lung, bowel and breast) (Blackwell *et al.*, 2018). There are a number of different HIIT protocols but all combine high intensity exertions with rest periods (Laursen and Jenkins, 2002). However, even though HIIT training can be delivered in just a few minutes, 3 times per week, time is often cited as a major barrier to exercise training adherence and compliance (Trost *et al.*, 2002). Therefore, shorter exercise sessions (i.e. low-volume HIIT) may be most effective in older patient groups.

The aims of this study were two-fold. Firstly, to see whether patients with urological malignancy could achieve the MCID (VO_{2AT} improvement 1.5-2 ml/kg/min) in CRF in response to HIIT, within a window compliant with UK cancer waiting time targets (31 days). Secondly, to investigate whether prehabilitation HIIT could be feasibly (by monitoring adherence to the HIIT protocol) and safely delivered for patients awaiting surgery for urological malignancy.

6.3 Methods

6.3.1 Ethical approval

Recruitment for this randomised control trial started in August 2016 and ended in June 2018. This study was granted ethical approval by the NHS research ethics committee (REC reference: 16/EM/0075, IRAS Project ID 19141) and was prospectively registered with Clinical trials.gov (NCT02671617). It was written in accordance with CONSORT guidelines (Pittler *et al.*, 2011).

6.3.2 Patient selection and recruitment

Patients were identified at a weekly multidisciplinary team (MDT) meeting where decisions to operate for urological cancer were made. Patients were approached by the research team after they had been told of the treatment plan in the outpatient clinic. To fit with the clinical service and not delay treatment, patients were only approached if the window between MDT decision to treat and the allocated operation date allowed potential for baseline assessment, 10 or more HIIT sessions and reassessment within the 72 hours before their operation. Patients in the HIIT group would be considered as having 'adhered' if they were to complete at least 10 HIIT sessions preoperatively.

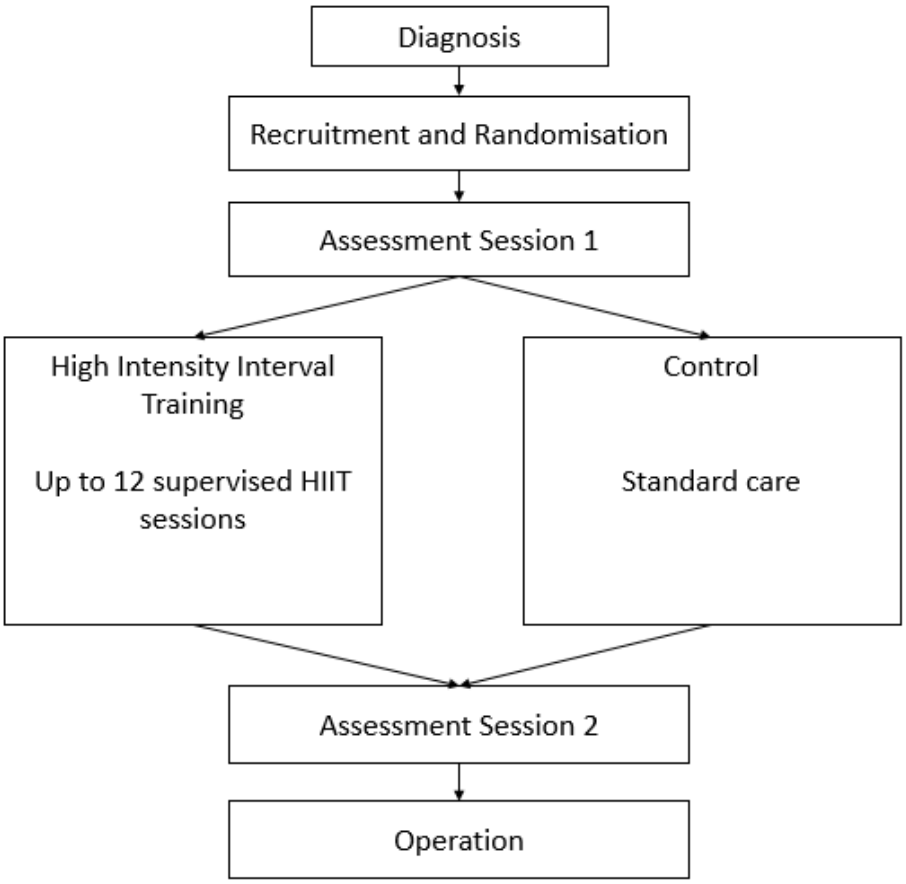


Figure 50 - Study flow chart.

Patients were provided with a patient information sheet and then invited to attend an initial study familiarisation and medical screening session. All participants provided written informed consent prior to randomisation and were screened by a medical doctor (cardiorespiratory examination, electrocardiogram, non-invasive blood pressure and blood tests comprising of full blood count, liver function tests, urea and electrolytes, C-reactive protein and a coagulation screen) in line with safety criteria for CPET testing defined by the American Thoracic Society (American Thoracic and American College of Chest, 2003).

Patients were randomised either to a control group (CON; consisting of standard care) or a four week fully-supervised HIIT intervention (HIIT) (Figure 50) using a computer-generated list of random permuted block sizes, stratified according to age and gender (to ensure a higher likelihood of equal baseline characteristics). Allocation concealment was ensured by using opaque, sealed envelopes with participant group allocation performed on the

first study visit. Due to the nature of the intervention, patients were not blinded to their group assignment, however all data collectors were.

6.3.3 Assessment Sessions

Following randomisation, all patients were invited to assessment session 1. Participants completed the following questionnaires: the Dukes Activity Status Index (DASI) (Hlatky *et al.*, 1989b), the EuroQol Group 5-level (EQ-5D-5L) (Hout *et al.*, 2012) and the Warwick Edinburgh Mental Wellbeing Scale (WEMWBS) (Tennant *et al.*, 2007). On the same assessment visit, participants whole-body composition was measured by a dual energy X-ray absorptiometry (DXA) scan, after which muscle architecture (muscle thickness, pennation angle and muscle fascicle length) of the *vastus lateralis was* measured using B-mode ultrasonography as described previously (Franchi *et al.*, 2014). Cardiopulmonary exercise testing (CPET; Lode Corival, Lode, Groningen) was performed as described previously (Boereboom *et al.*, 2016; Blackwell *et al.*, 2017), with inline breath-by-breath data collected via a metabolic cart (nSpire Zan 600, Germany). The CPET protocol was a modified Bruce ramp protocol in compliance with widely accepted guidelines (American Thoracic and American College of Chest, 2003). In brief, patients were instructed to cycle on a stationary cycle ergometer (Lode Corival, Lode, Groningen) until they reached volitional exhaustion. CPET interpretation was then conducted by two experienced assessors blinded to time-point (i.e. pre or post-intervention) and group allocation. VO_{2PEAK} (volume of oxygen consumed at the maximal exertion during the test) values were taken as the highest reading in the last 20 seconds of the test, with VO_{2AT} (volume of oxygen consumed at the anaerobic threshold) determined using a modified V-slope and ventilatory equivalents method (Boereboom *et al.*, 2016).

Following baseline assessment both HIIT and CON groups were instructed to maintain their habitual physical activity and dietary regimes for the duration of the study. The CON group had assessment sessions 1 and 2 spaced four weeks apart with no visits between. Patients randomised to the HIIT group had the same assessment sessions as the CON group and in addition were offered up to 12 HIIT sessions (3-4 times weekly, with no training at weekends) within a four-week period (i.e. less than 31 days). The HIIT protocol, performed on the same cycle ergometer as the CPET, comprised a two-minute warm-up period of unloaded cycling, followed by 5 x 1-minute

exertions at 100–115% of the maximal load (watts (W)) reached during their initial CPET (Boereboom *et al.*, 2016; Blackwell *et al.*, 2017; Phillips *et al.*, 2017), ending with a 2-minute recovery period of unloaded cycling. Immediately after completing the 6th HIIT session patients were asked to subjectively rate the difficulty of the session using a modified 1-10 Borg scale (Borg, 1982). If patients rated <8 (8= between very severe and extremely severe exertion), cycling load was increased by 10% for the reminder of the HIIT sessions.

After the second assessment session (up to 72 hours before operation), using the same protocol as assessment session 1, participants were asked to fill out a HIIT acceptability questionnaire which has previously been used to evaluate this specific HIIT protocol (Boereboom *et al.*, 2016).

6.3.4 Statistical analysis

An *a priori* sample size calculation, using data derived from previous work from our group (ANOVA; partial η^2 0.15 (effect size 0.42), for a power of 0.80 and α level of 0.05) indicated that 40 patients in total (20 Control group, 20 HIIT group) would be required to see a difference in VO_{2AT} of 2ml/kg/min, with the correlation for repeated measures assumed to be 0.7. An attrition rate of 20% was accounted for based on the drop-out rate experienced in previous similar studies in our unit. This led to a maximum recruitment number of 48 patients. Descriptive data is presented as mean (± standard deviation (SD)), median [inter-quartile range (IQR)] and number (%) as appropriate. To analyse outcomes, we used ANCOVA with pre-intervention baseline values as continuous covariates. Normality was assessed using histograms, and scatter plots were used to assess the relationship between outcomes and covariates. We assessed equality of variance using variance comparison tests. For correlations, we used Pearson's and Spearman's as appropriate. Modified intention to treat was conducted on all participants randomised and who underwent both assessment sessions and sensitivity analysis was also performed on prostate cancer patients completing a minimum of ten HIIT sessions. All analyses were conducted using STATA Version 15.1.

6.4 Results

6.4.1 Patient characteristics

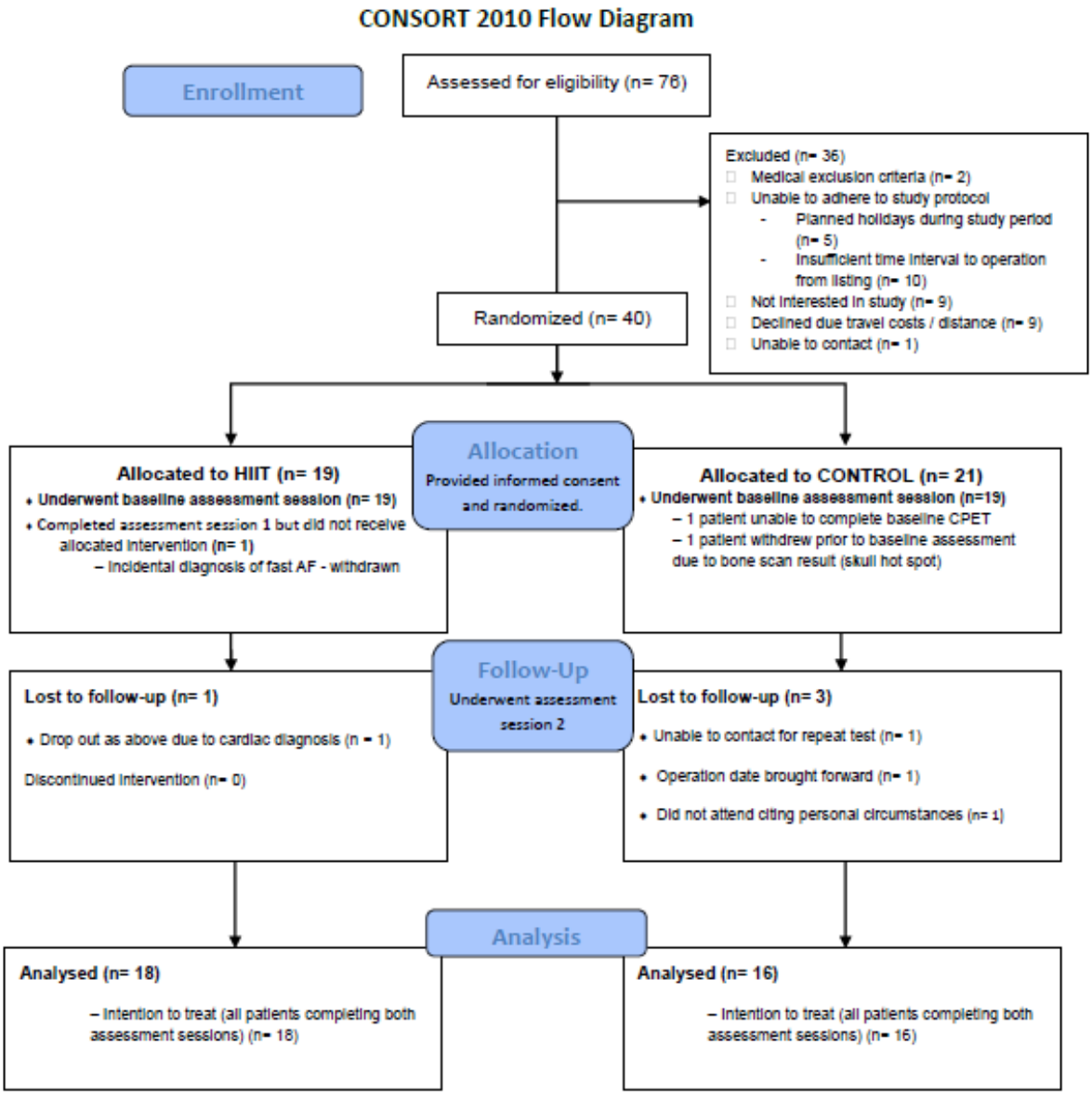


Figure 51 - Study Consort diagram (Pittler *et al.*, 2011).

Forty patients were randomised during the study period (Figure 51). Statistical analysis for the primary outcome measure (VO_{2AT}) was conducted at the end of the ethically approved study period. Baseline characteristics between groups can be seen in (Table 14).

Table 14 - Patient baseline characteristics of individuals before a <31-day control period (CON) or period of high intensity interval training (HIIT). (DASI: Dukes Activity Status Index, CPET: cardiopulmonary exercise test, SBP: systolic blood pressure, DBP: diastolic blood pressure; mean (±SD)).

Baseline characteristics	CON (n= 21)	HIIT (n=19)
Age (years)	72 (4)	71 (2)
Gender (m:f)	20:1	19:0
DASI	47.97 (9.3)	51.38 (9.6)
Weight (kg)	79.6 (14.4)	80.1 (10.4)
CPET Wattage (W)	145 (37)	137 (33)
VO_{2PEAK} (ml/kg/min)	26.4 (5.7)	24.8 (5.2)
VO_{2AT} (ml/kg/min)	13.84 (2.8)	13.15 (1.9)
SBP (mmHg)	144 (12)	139 (13)
DBP (mmHg)	82 (8)	82 (9)

Table 15 - Patient clinical characteristics of individuals before a <31-day control period (CON) or period of high intensity interval training (HIIT). RARP (Robotically assisted radical prostatectomy), Radical cystectomy includes both cystoprostatectomy and anterior exenteration and change to clinical plan after recruitment to study included no operation, watchful waiting and/ or radiotherapy.

Clinical characteristics	Control (n=21)	HIIT (n=19)
Location of malignancy:		
Prostate	17	18
Bladder	2	1
Kidney	2	0
Operation:		
RARP	14	14
Open Prostatectomy	0	1
Radical Cystectomy	2	1
Laparoscopic Nephrectomy	2	0
Change to clinical plan	3	3
Co-morbidities:		
Hypertension (medicated)	7	8
Diabetes	2	0
Musculoskeletal (osteoarthritis, rheumatoid arthritis or joint replacement)	8	8
None	4	2
Other:	Ulcerative colitis, asbestosis, gout, chronic kidney disease, asthma	Chronic fatigue, hypothyroidism (x2), chronic lymphocytic leukaemia, myocardial infarction, coronary artery bypass-grafting, asthma
Pre-op PSA (ng/ml)	9.38 [8.1 – 13.2]	9.17 [6.9 – 10.9]
D'Amico Risk Classification for Prostate Cancer (D'Amico *et al.*, 1998)		
High risk	7	6
Intermediate	10	10
Low	0	2

6.4.2 HIIT data

For those patients randomised to HIIT, adherence (10 or more HIIT sessions attended) to the exercise training protocol was 84% (16/19). Of those who did not adhere one dropped out of the study, one participant did not attend a single scheduled HIIT session, and one participant only completed 6 sessions due to a planned holiday. Patients initially trained at 100–115% of maximum wattage achieved at baseline CPET (145 (34) watts) and all but two patients had a 10% increase in wattage after 6 sessions as per protocol. The median [IQR] time between baseline and reassessment session for CON and HIIT was 28 (23-33) and 30 (28-31) days respectively. The median [IQR] number of HIIT sessions was 11 [10-12] (excluding those not adherent to the protocol).

6.4.3 Cardiorespiratory fitness

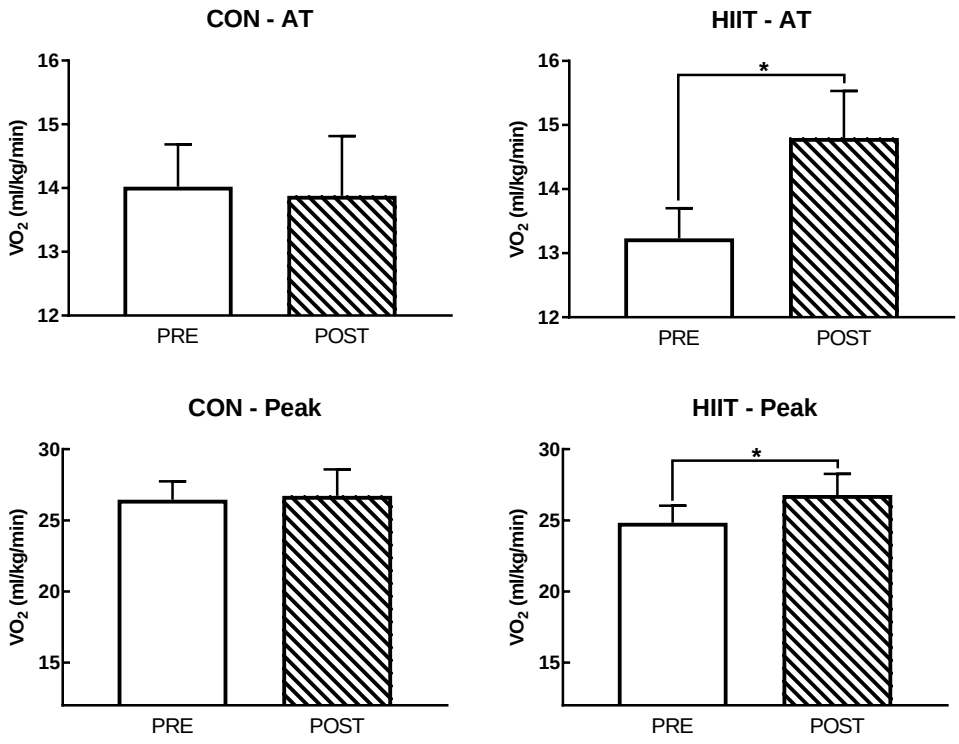


*Figure 52 - Pre (clear) and Post intervention (hatched) cardiorespiratory fitness data for individuals before and after a <31-day control period (CON; n=16) or period of high intensity interval training (HIIT; n=18). Top line graphs - volume of oxygen utilised at anaerobic threshold (VO_{2AT}) and lower line graphs - peak volume of oxygen utilisation (VO_{2PEAK}); both measured via cardiopulmonary exercise testing (CPET). *=p<0.05 vs. baseline. Analysis via ANCOVA.*

Based on all study participants who completed both pre and post intervention CPET (modified intention to treat analysis), there was a significant improvement in VO_{2AT} MD 2.26 ml/kg/min (95% CI 1.25 to 3.26) ((VO_{2PEAK} MD 2.16 ml/kg/min (95% CI 0.24 to 4.08) following HIIT (Figure 52). Similarly, there was a significant increase in CPET wattage at failure in the HIIT group (MD 12.86 W (95% CI 5.52 to 20.19)). Neither VO_{2PEAK} (r^2= 0.02, p=0.60) nor VO_{2AT} (r^2= 0.04, p=0.43) improvements were correlated with baseline values. Sensitivity analysis of prostate cancer patients alone (all 15 patients with prostate cancer adhered to the HIIT protocol) showed a significant improvement of 2.19 ml/kg/min (95% CI 1.06 to 3.32) in VO_{2AT} following HIIT.

6.4.4 Cardiovascular health

There was a statistically significant reduction in resting blood pressure parameters following HIIT (*SBP*: -8.2 mmHg (95% CI -16.09 to -0.29), *DBP*: -6.47 mmHg (95% CI -12.56 to -0.38) following HIIT (Figure 53 B) with no change in the CON group (Figure 53 A)).

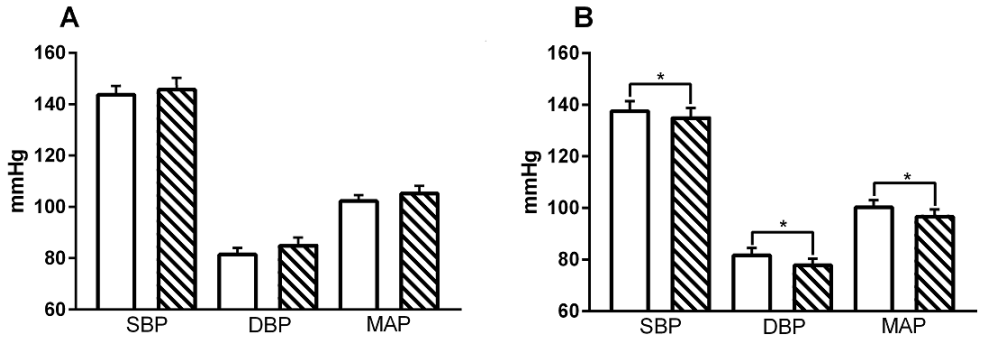


*Figure 53 - Baseline (clear) and post intervention (hatched) non-invasive blood pressure readings (SBP, DBP, MAP; mmHg) for individuals before and after a <31-day control period (CON; panel A, n=16) or period of high intensity interval training (HIIT; panel B, n=18). *=p<0.05 vs. baseline. Analysis via ANCOVA.*

6.4.5 Body composition and muscle architecture

There were no significant differences in whole-body composition between the groups as measured by DXA (total body fat (g), body fat %, total lean mass (g)) at baseline. No significant changes in whole body composition were observed after the intervention period in either the HIIT or CON groups.

Based on ultrasound of the *vastus lateralis*, there were significant increases in muscle thickness (0.22 mm (95% CI 0.02 to 0.41)) and pennation angle (2.49 degrees (95% CI 0.42 to 4.55)) in the HIIT group. Muscle fascicle length was not altered in either group.

6.4.6 Safety and acceptability

There were no adverse safety events reported. All participants were able to achieve >85% maximum predicted heart rate during the HIIT sessions.

There were no significant changes in WEMWBS (-0.88 (95% CI -4.17 to 2.4)), EQ-5D-5L Overall health score (visual analogue scale) 3.65 (95% CI -1.97 to 9.28), or 5D-EQ-5L index values ((-0.03 (95% CI -0.08 to 0.02)) scores following HIIT.

Patients found HIIT enjoyable and highly acceptable. They reported that they would recommend HIIT to others, and despite there being no significant changes in the quality of life-based questionnaires, patients were pleased to have improved their own fitness (Table 16). When asked, "What did you enjoy most about HIIT?" themes from free text comments (reported by more than two patients per comment) were as follows: a sense of achievement having completed HIIT, feeling of improved well-being and pleased to have engaged in improving their own healthcare.

Table 16 - HIIT acceptability questionnaire results.

Statement	Median score [IQR] 5: Strongly agree 1: Strongly disagree
HIIT was well explained	5 [Scored by all]
I enjoyed HIIT	5 [Scored by all]
HIIT was a time burden	1.5 [1-2]
I would recommend HIIT to others	5 [Scored by all]
HIIT was more demanding than expected	3 [2-4.5]
I would do HIIT again	5 [4-5]
The travel associated with HIIT interfered with my life	1.5 [1-2.5]
The physical strain interfered with my life	2 [1-3]
I believe my fitness has improved	5 [Scored by all]
I am pleased to have done something to improve my fitness	5 [Scored by all]
I would like to have exercised in a group	1 [1-2]
I would like to have exercised at home	1 [1-2.25]

6.5 Discussion

This study shows that patients awaiting surgery for urological cancer can make clinically meaningful improvements in CRF (VO_{2AT} and VO_{2PEAK}) in less than 31 days, via a safe and enjoyable programme of HIIT. Physiological principles support the implementation of either unimodal or multimodal preoperative interventions in patients diagnosed with cancer requiring surgical intervention (Carli *et al.*, 2017), and this study provides a feasible and efficient exercise protocol that is effective within urological (predominantly prostate cancer) patients before surgery.

We successfully improved CRF within the UK cancer target waiting times of 31 days from decision to treat. This is important for feasibility and generalisability as 93.2% of urological cancer patients receive first definitive treatment within 31-days of decision to treat (data for the second quarter of 2018) (NHS England, 2018). However, supervised laboratory-based HIIT is a resource dependent intervention (equipment and staffing), but allows monitoring of adherence to the prescribed HIIT sessions and confirmation that high-intensity (>85% heart rate maximum) was achieved during every individual session. The intensity of HIIT likely contributed to the significant gains in CRF seen within this study (Little *et al.*, 2010), but this intensity and compliance is hard to deliver in unsupervised exercise studies (Bosworth, 2010).

In addition to improvements in CRF, we also report significant reductions in BP following just one-month of HIIT, with this method of exercise training appearing to be more potent than traditional exercise aerobic exercise training, which produces reductions of 5mmHg in SBP and 3mmHg in DBP over a three month period (Herrod *et al.*, 2018).

It has previously proved difficult to improve $VO_{AT,}$ (as measured by CPET) by the minimum clinically important difference of 1.5-2.0 ml/kg/min for all comers for major benign (Tew *et al.*, 2017) and malignant intra-abdominal surgery (Banerjee *et al.*, 2015; Dunne *et al.*, 2016; Boereboom *et al.*, 2018) using supervised exercise regimes. Less objective measures of functional fitness (e.g. improved six-minute walk test (6-MWT) and increased muscle leg power) have been shown to improve within a 31 day timeframe in patients with cancer (Jensen *et al.*, 2016; Chen *et al.*, 2017). Previous prehabilitation studies in urological populations have largely been aimed at

reducing specific urological complications (e.g. urinary incontinence) and this has been successfully achieved with pelvic floor muscle training (Davie, Cook and Rochester, 2009). Given the well-reported post-operative decline in physical functioning and reduced HRQOL scores following prostatectomy (Litwin *et al.*, 1999; Steineck *et al.*, 2002; Sanda *et al.*, 2008), this study's findings of improved CRF, reduced BP and positive adaptations in muscle architecture has the potential to reduce peri-operative morbidity and mortality, and pre-operative improvements in strength and fitness are thought to improve time to return to baseline function after surgery (Carli *et al.*, 2017).

Exercise prescription as a unimodal intervention has produced a range of outcomes for patients with cancers at different primary sites (Kim *et al.*, 2009; Dronkers *et al.*, 2010; Timmerman *et al.*, 2011; Dunne *et al.*, 2016), resulting in a lack of consensus on the optimal training modality and regime. As prehabilitation is often multimodal (Carli *et al.*, 2017), the efficacy of different aspects of these regimes can be difficult to ascertain. Patients awaiting radical prostatectomy showed improvements in 6-minute walk test before surgery and a more rapid return to pre-operative walk test distances after surgery compared to control using a home-based mixed-modality (aerobic exercise, resistance exercise training and pelvic floor training) prehabilitation regime (Santa Mina *et al.*, 2018). Although this study used different outcome measures (6-MWT vs. VO_2 parameters), it would seem that the presence of prostate cancer does not inhibit positive physiological adaptations to exercise training, adaptations which may be blocked by the presence of other types of cancer (Phillips, B E. *et al.*, 2013).

Previously, we have failed to elicit similar gains in CRF using an identical HIIT protocol in colorectal cancer before surgery ('Surgical Academic Research Society abstracts 2017', 2018). It is unclear why patients with certain cancers would be less responsive to HIIT. There is a degree of anabolic blunting (reduced mitochondrial enzyme activity and muscle protein synthetic responses to nutrition) with colorectal cancer in situ (Phillips, B E. *et al.*, 2013), which may be less pronounced with prostate cancer. There is also growing evidence that HIIT mitigates the pro-inflammatory environment induced by cancer (Papadopoulos and Santa Mina, 2018) by reducing systemic interleukin six (IL-6) (Fu *et al.*, 2013) and moderating increases in reactive oxygen species (ROS) associated with inflammation

(Mitranun *et al.*, 2014). Future work should investigate these hypotheses which may lead to tailored prehabilitation programs for the specific cancer types and/ or individuals likely to respond positively to this training method.

We failed to show improvements in whole body composition which have been previously achieved with HIIT (Boereboom *et al.*, 2016). Utilising multimodal exercise training, reductions in body fat % (measured by bio impedance electrical analysis) have been reported after prehabilitation prior to radical prostatectomy. However, this may be explained by the aerobic exercise element being of moderate intensity (traditionally associated with fat utilisation) and a longer average exercise period (45 days) (Santa Mina *et al.*, 2018).

We did show favourable changes in muscle architecture of the *vastus lateralis* that were similar magnitude to those previously seen in healthy older individuals in response to both resistance exercise training (Aagaard *et al.*, 2001) and HIIT (Boereboom *et al.*, 2016). These improvements are consistent with data showing increases in muscle cross sectional area (CSA) following 9 sessions of HIIT (over 3 weeks) in obese adults (Blue *et al.*, 2018), reflecting the relatively rapid adaptations in muscle architecture that are produced by HIIT. Increasing muscle CSA (to which muscle thickness contributes) and pennation angle, increases the potential maximal force generating capacity of the muscle (Aagaard *et al.*, 2001), which may aid rehabilitation and promote a quicker return to baseline physical function after surgery. Again, more work in larger groups is required.

Lack of time is one of the most commonly cited barriers to exercise, but this is addressed by HIIT training, using which we demonstrate significant improvements after a matter of a few minutes of exercise per week over 4 weeks. Our HIIT protocol is highly acceptable and enjoyable for urological cancer patients. Many of our patients brought along family members or spouses to the HIIT sessions and it is known that quality of life scores in prostate cancer survivors are significantly associated with the degree of outcome satisfaction among both the patients and their spouses or partners (Sanda *et al.*, 2008).

6.5.1 Limitations

The primary limitation of this study relates to the homogeneity of the sample, with the majority of patients having prostatic adenocarcinoma, and being

Caucasian males. This specific group of men are clearly trainable, making significant gains in a range of cardiorespiratory parameters comparable to healthy counterparts of a similar age (Boereboom *et al.*, 2016), yet still suffer significant post-operative declines in physical functioning (Steineck *et al.*, 2002) and reduced quality of life (Sanda *et al.*, 2008). The large proportion of male patients awaiting robotic assisted prostate operations was because it was these patients who could adhere to the protocol by having long enough between decision to treat and their operation. There was a possible selection bias as subjects had to be willing to be randomised to the HIIT arm of the study, potentially excluding more sedentary individuals, although subjectively reported physical activity levels at baseline showed no difference between groups. In addition, referrals to our secondary care specialist centre come from a wide geographical area, and as such eligible patients cited travel time and potential financial cost incurred by travelling from home to the exercise laboratory as barriers to participation.

6.5.2 Chapter Conclusions

Preoperative HIIT improves CRF, cardiovascular health and measures of muscular architecture, and represents a clinically meaningful and achievable improvement in the health status of urological (primarily prostate) cancer patients in the time available before surgery. Further work is required to investigate the generalisability of this finding to different cancer types. Large randomised trials are required to investigate the effect of prehabilitation upon post-operative complications, socio-economic impact and long-term survival following radical prostatectomy.

7 Discussion

Systematic review and meta-analysis performed in Chapter 2, showed that high intensity interval training (HIIT) improves objective measures of cardiorespiratory fitness (CRF) in diseased cohorts within 8-weeks, compared with no intervention. When compared with moderate-intensity continuous training (MCT), HIIT delivers significant additional improvements in measures of CRF, with clinically important additional improvements in cardiovascular patients in one of these measures (VO_{2peak}).

In light of this HIIT was chosen as the exercise intervention for studies in this thesis. This HIIT regime has shown similar gains in CRF across different cohorts (i.e. sedentary middle aged, octogenarians with chronic disease and urological cancer patients), for both mean improvement and the number of 'positive responders', compared to alternative HIIT regimes used previously in patient groups. This is despite our protocol requiring substantially less total time commitment from the patient compared to many other HIIT protocols.

As our HIIT protocol takes only 16.5 minutes for the entire HIIT session (other common HIIT regimes take >30 mins), it may improve adherence (Trost *et al.*, 2002) and may also allow for a financially economical delivery of exercise sessions.

Our ***first study*** *(Chapter 4)* showed that supervised (in the laboratory) high-intensity interval training (L-HIIT) improves CRF in sedentary middle aged individuals to a greater extent than unsupervised home-based HIIT (H-HIIT) of the same exercise volume. Improvements in CRF were however seen in the H-HIIT programme and as such this regime does offer a practical, time-efficient way of improving CRF (albeit to a lesser extent than L-HIIT). For a large scale roll out of exercise prehabilitation to wider surgical and/ or patient groups H-HIIT shows promise, as it is much less costly than L-HIIT. One issue with unsupervised HIIT is ensuring that high intensity targets are reached (i.e. achieving >85% maximum heart rate). It may be the case that individuals are less likely to maintain high intensity when unobserved, and, if this is true, exercise regimes may need to be of a higher volume at lower intensity to compensate. This study also demonstrated that static exercise regimes, such as isometric hand grip training, may be useful adjuncts or alternatives to HIIT to improve cardiovascular parameters (blood pressure) in those patients unable to perform whole body exercise and is an area for future work.

The importance of preoperative exercise regimes for older adults with comorbidity is gaining wider interest from healthcare professionals and is amongst current research topics suggested by leaders within perioperative care (Carli *et al.*, 2017) and from national bodies (National Institute for Academic Anaesthesia, 2015). In the ***second study*** *(Chapter 5)* we showed that HIIT can be safely delivered to independent community-dwelling octogenarians with morbidity as a method of significantly improving both (CRF) and lean muscle mass (LMM), with 32% of individuals achieving clinically important improvements. Indeed, that HIIT improves these parameters in such a short time-frame (<4-weeks), suggests that it may be a useful medium to improve CRF and LMM (both predictive of post-operative mortality) of high-risk elderly individuals within cancer target timeframes.

Our findings of a significant improvement in CRF in these older adults (1.21 ml/kg/min) is contrary to that previously reported in patients awaiting elective abdominal aorta repair (Tew *et al.*, 2017) where they only achieved a mean group improvement in anaerobic threshold of 0.7 ml/kg/min following HIIT (vs. 0.5 ml/kg/min in their control group). Despite this lack of mean improvement versus control, the authors of this study comment on marked inter-individual variation in exercise 'trainability' and propose that one-third of participants are 'possibly to very likely being' positive responders (defined as an improvement of > 1.5 ml/kg/min). This heterogeneity in exercise responder status is something that is becoming more commonly reported in the literature, and is something that we have also seen in the studies within this thesis (discussed further in Chapter 5). However from a clinical point of view when considering exercise as prehabilitation, the challenge remains of how to preselect these 'high responders' who may benefit significantly from exercise training, whilst concurrently deselecting those unlikely to benefit from any delay associated with completing a preoperative exercise program.

Having shown the potential for older adults with chronic disease to rapidly improve CRF with our HIIT protocol, the ***third study*** *(Chapter 6)* sought to understand whether patients with urological cancer in situ are able to make similar CRF gains to 'healthy' counterparts. We recruited 40 patients awaiting curative cancer surgery for urological malignancy (predominantly prostatic cancer) to a randomised clinical trial of standard care versus HIIT. The intervention group showed clinically significant improvements in CRF

following HIIT within clinically relevant timeframes. A median number of 11 HIIT sessions per patient over four weeks was achieved, proving both the feasibility and efficacy of the HIIT protocol in this cohort. Our centre has previously failed to show similar CRF gains in patients before colorectal resection following HIIT (Boereboom *et al.*, 2018). Notably however, within the above study, initiation of preoperative exercise did not 'stop the clock' in relation to 31-day cancer waiting targets. The local colorectal cancer clinical pathway only allowed for a mean number of 8 HIIT sessions over 19 days, providing a mean AT benefit of only 0.48 ml/kg/min (vs. 2.26 ml/kg/min in the urological cohort). These findings may be due to the reduced number of HIIT sessions delivered per individual, or may be due to the difference in pathological and systemic effect between colorectal and prostate cancers. It has previously been shown that colorectal cancer causes anabolic blunting and reduced CRF whilst remaining in situ, with restoration following surgical resection (Hossain *et al.*, 2012; Williams *et al.*, 2014). This basic science data is not available for urological cancers, however, it may be that if this 'metabolic impairment' is not apparent in urological cancer patients (perhaps due to the aforementioned differences is systemic disease burden) then this may be underlying the 'exercise resistance' in colorectal cancer patients.

As alluded to above, our HIT protocol is feasibly deliverable within the current clinical, diagnostic and management frameworks at the Royal Derby Hospital for certain patients; as such further collaboration with the multidisciplinary team could lead to more patients being offered exercise prehabilitation prior to surgery without affecting waiting time targets. Only 3% of eligible patients breached the inclusion criteria for the study (as per ATS/ACCP CPET safety criteria (American Thoracic and American College of Chest, 2003)) and a further 12% were 'not interested' in the study; which may decrease in the future if exercise prehabilitation comes with the full support and promotion by the clinicians and wider MDT.

Published outputs, including conference proceedings and symposia, would suggest that exercise 'prehabilitation' is gathering momentum and is becoming a recognised field within clinical medicine. This should not be wholly surprising, given that the preoperative period is well-recognised as an area for optimisation of physical fitness, nutritional status and psychological well-being to improve post-operative outcomes. Exercise

prehabilitation has also received attention at a national level with new societies being formed to raise awareness, generate research interest and provide clinical guidelines within the field (e.g., the Perioperative Exercise Testing and Training Society (POETTS) (POETTS, 2016) and the Preoperative Association (The Preoperative Association, 2004)).

Despite the proven benefit of HIIT as an exercise-for-health tool in both healthy and comorbid individuals, there remain concerns from the media and general public about its safety profile. During the studies within this thesis, whilst adhering to the American Thoracic Society guidelines on CPET (and using their inclusion/ exclusion criteria as participant suitability for HIIT training) there were no serious adverse events (American Thoracic and American College of Chest, 2003). This profile is in keeping with the literature on HIIT in both healthy and disease groups.

Given the variable response to HIIT training in both healthy and comorbid individuals, it is important to try and fully understand the mechanistic basis behind improvements in exercise parameters so that future interventions, and perhaps patient selection, can be based on this. Therefore, although out with the scope of this thesis, human tissue (muscle) and plasma samples from the studies in this thesis will be analysed in a molecular metabolism laboratory to further elucidate the mechanisms behind group and individual responses to HIIT and how comorbidity interacts with the normal response. Using novel deuterium (D_2O) stable isotope methods refined in the host laboratory for this thesis, we will be able to assess both myofibrillar and mitochondrial muscle protein synthesis rates in response to our HIIT protocol. Coupled to this, samples obtained during work done for this thesis will also be used to probe changes in (anabolic, vascular and mitochondrial) cell signalling pathways and muscle oxidative enzyme activity in response to HIIT. Analysis of systemic and muscle level inflammation will allow exercise adaptation (exercise performance, lean muscle mass and muscle protein synthetic rates) to be correlated to the degree of inflammation.

However, we do not yet know whether improving fitness before surgery improves clinical outcomes. The large patient numbers required for the assessment of clinical outcomes (such as post-operative length of hospital stay, complications or return to baseline functional status), precluded such analysis in the studies within the thesis. However, one such study currently recruiting is the SupPoRtive Exercise Programmes for Accelerating REcovery

after major ABdominal Cancer surgery (PREPARE-ABC) study (Swart, 2016). This is a multi-centre, 3 arm, parallel randomised control trial which aims to recruit a target sample size of 1146 patients all awaiting curative colorectal cancer resection. The primary outcomes of this study are two-fold; one short-term and one long-term. The first is morbidity (30 day measure of Clavien-Dindo complications) in standard care versus i) hospital-based and ii) home-based exercise. The second, longer term outcome, is health-related quality of life (HRQoL; as measured by SF-36) at 12-months post randomisation. The results of this study will be eagerly awaited by contributors to the growing scientific literature on exercise prehabilitation, especially those who have shown effective exercise regimens within small cohorts, but without sufficient power to analyse post-operative clinical outcomes. Should large studies such as PREPARE-ABC show tangible benefit on post-operative outcomes following exercise prehabilitation, then the studies within this thesis (especially Chapter 5 in prostatic cancer patients), suggest a ready-made cohort who are truly trainable within current clinical time-frames.

Another large study currently recruiting is the WES-Fit study (Jack, 2018) with a primary outcome length of stay for cancer patients having curative operations. Interestingly, in addition to an exercise intervention, some patients in this study will also receive psychological support preoperatively and as such the psychological measurement tools used are more rigorous than in previous studies. This may reveal an extra benefit of exercise prehabilitation, making patients more psychologically robust prior to major surgery, which may have been achieved to date but studies so far have not been suitably designed to pick up subtle changes in psychological status which may profoundly affect post-operative outcomes and patient satisfaction reporting.

In conclusion this thesis has established HIIT training improves fitness in the diseased elderly, can be delivered at home (although with less improvement than supervised training), and can improve fitness by a clinically significant margin in a group of patients in a relevant timeframe.

8 Appendices

8.1 Outreach / Public Engagement

8.1.1 Screen shot from BBC Website



Figure 54 - Image taken from BBC website publication (Blackwell and Phillips, 2016).

8.1.2 Time for HIIT?



TIME FOR A HIIT?

HIIT (high intensity interval training) is the latest fitness trend to, ahem, hit the gym. We found out what is so good about it and got volunteers to try it out at home

Even the most dedicated of us can find it hard to fit exercise into our day, but in a BBC documentary, *The Truth About Getting Fit*, Dr Michael Mosley demonstrated how we could fit just five minutes of high-intensity interval training (HIIT) into our day — without even changing into sportswear!

We spoke to Dr James Blackwell, a clinical research fellow at the University of Nottingham, who has researched HIIT's efficacy, to find out whether just five minutes, three times a week, can really deliver health benefits.

It's recommended to do 150 minutes per week of moderate aerobic exercise. So is five minutes of HIIT sufficient for all health benefits?

"HIIT is an increasingly popular method of exercise which has a growing research base to suggest rapid improvements can be made in certain exercise parameters. This is with the well-known caveat that there simply isn't a 'one size fits all' exercise method to tackle all of the fitness measures that regular exercise can modify.

"For example, low-intensity endurance training [e.g. jogging, swimming, cycling] may be great to reduce cardiovascular risk and fat mass, however may do little to improve muscular strength and power which is key to functional independence as we age. I would always advocate a multi-modal exercise plan with variety in the week if you're aiming to improve whole body health.

"Noteworthy, is the addition made to the WHO exercise guidelines which reflects the benefit seen with higher-intensity exercise, they now read: Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity."

If five minutes of HIIT is beneficial, is there any point to other aerobic exercises if one's goal is fitness?

"The answer to this question again comes down to what you might class as 'fitness'. Some gym goers might consider themselves very 'fit' because they can squat 150 kg yet cannot run a sub-20 minute 5 k. Another interesting example is in super trained athletes who actually suffer reduced immune function — does this make them too 'fit'?!

"Perhaps another way to look at this is what could HIIT offer me? Our research has shown that it can be used as a great way to kick start exercise in sedentary individuals. HIIT isn't necessarily a great way to lose weight in the short term; we tend to see that people stay relatively weight neutral given loss of fat mass but increase in muscle, which actually weighs more.

"Life is busy nowadays, previous research

would suggest that time is the biggest barrier to exercise, HIIT is compact and can easily be scheduled into the working day with minimal equipment requirement. More specifically in relation to fitness parameters, we have shown that both the lactate threshold (or anaerobic threshold) and the maximum exercise capacity (VO2max) can be significantly improved in a short period (just four weeks) across a range of ages from 40–85 years old."

Is HIIT recommended for people who do not usually exercise?

"HIIT has been shown to be safe and feasibly delivered in a wide spectrum of people. This ranges from sedentary healthy individuals to elite athletes.

"A large proportion of the clinical research base exploring HIIT has actually been conducted in patients following heart attack and numerous other disease groups including cancer.

"If you do not normally do any exercise at all it is always sensible to 'start low and go slow' in the first few weeks. This is of course whilst remembering that if you experience any untoward symptoms during any type of exercise (such as chest pain or tightness, dizziness, palpitations, undue shortness of breath etc.) you should seek medical advice prior to carrying on and certainly before pushing yourself too hard."

Who would benefit the most from five minutes of HIIT?

"Most individuals... Like all exercise programmes, motivation and effort levels play an important part in who is likely to improve their fitness. We have correlated the amount of watts pushed (during a one minute exertion) to improvement in fitness (anaerobic threshold) following our HIIT protocol. This finding is in agreement with others in the field that believe there is likely a minimal exertion level required to get the desired benefit. Work has been done to suggest that even a one minute blast at high wattage causes enough stimulus at a cellular level to provoke positive change. This is quite remarkable and really raises questions about the molecular basis behind the often vast improvements seen with HIIT."

What if I don't notice any difference?

"There are a few things to consider here. HIIT by definition has to achieve >85 per cent maximal predicted heart rate to be classed as 'high intensity'. Broadly, maximal predicted heart rate can be worked out as (220 – your age) x 0.85 (i.e. 220 – 31 years old = 189 x 0.85 = 160 bpm [beats per minute]). So this means that I would need to achieve >160 bpm during each repetition to be sure that I had actually completed 'HIIT' — this can be pretty hard work, but if you're not actually doing HIIT then the reduction in volume (i.e. only five minutes exercise) might be why you aren't reaping the benefits! It's difficult to measure your pulse during a session by hand at these kinds of rates so invest in a reasonably priced heart rate watch to be sure you're training in the right heart rate zone.

"The second factor to mention would be that there is likely a strong genetic basis behind which types of exercise you will respond to and others that you won't. Rat models show this clearly, and work is ongoing to investigate this further in humans... two people can go to the gym and lift weights, one gets huge muscles (hypertrophy) and the other, despite their best efforts, just doesn't get any bigger — this is probably genetics in action! If you find no benefit from HIIT then it just might not be for you.

"The easiest way to know if you are improving your fitness level is probably to stringently count the repetitions of each exercise you are able to complete in one minute. This will give you an objective number to match or beat each session. If you start finding the exercises easy or aren't able to achieve the required heart rate then you will need to adapt those exercises to maintain intensity which is the key element to low volume HIIT."

The Truth About Getting Fit:
www.bbc.co.uk/programmes/p05w69pz

We asked a random group of volunteers to follow the five-minute routine as demonstrated by Dr Michael Mosley, for however long it appealed to them, and to feed-back their experiences. Ours was an informal 'review' of the five-minute HIIT routine, with no stats taken. The aim was for people of different ages and fitness levels to try the routine, and report back on whether it inspired them to be more active on a regular basis.

One comment from women was the need for a sports bra — so whilst Mosley only needed to change into trainers, this was not the case for most women. Another comment from some women was that because of the impact of having given birth on bladder control, it may be necessary to wear pads. Other comments included:

"I liked it as an option for when the weather made it difficult to get outside."

"I tried it! I liked it especially as I was able to do the star jumps without completely wetting myself. But I wanted to keep up with my stretches that I need to keep my shoulder and knees mobile, so I combined the bits I really liked with my stretches — that means each morning I do my stretches and include 40 squats. I left out the star jumps as my bedroom wasn't quite big enough, and the running as well as I feel like a plonker running on the spot. I also find that it just adds that extra time which means I get later and later each day for leaving the house."

"I felt I got something out of it — I had a minute timer and found it incredibly hard the first couple of times. In fact, the first time I had to stop half-way through. I liked the fact that I could fit it in to my day and it gave me no excuse not to exercise. But then I took up Couch to 5 k. I think the HIIT was probably the catalyst for that. Since then, despite my good intentions, I haven't done the HIIT routine. I clearly need to schedule it into my week!"

"I didn't realise the break between each minute was only 90 seconds, so was sitting down and playing Candy Crush between each minute of exercise."

"Loved it. Still doing it. Modified it to suit my ability (i.e. run on mini trampoline, squats, star jumps on trampoline, stationary bike, cool down with walking on the spot.) I cycle daily too. Overall, I do feel better. More muscle definition and fitness level improving — can feel that with the endurance ability."

"I started doing it with my teenage daughter so we could do it together, but often when I get home she has already done it and I don't feel motivated to do it by myself, so I don't do it very often. I prefer to do exercises with somebody so a work colleague has said that maybe we can do it together in our lunch break."

"I started off as I wanted to get fit. I did the session twice and, physically, did not find it that tough. However, I really did not enjoy it, in fact hated it. It did make me realise that I was not as unfit as I thought. So it motivated me to start Couch to 5 k. I am really enjoying exercising outdoors and the sense of the achievement once a session is done. So all in all, my experience of the five minute HIIT has been really positive."

Figure 55 - Optimum Nutrition Magazine publication (Blackwell, 2018).

8.2 Chapter 2 Appendices

8.2.1 Training regimes HIIT versus CON

Author	Year	HIIT	CONTROL
Andersen et al.	2017	10 intervals; 30sec (low intensity):20sec (middle high intensity): 10sec (maximal intensity), 3min break after 5 intervals	Non-intervention control
Dolan et al.	2015	Number of intervals unknown, Weeks 1-2: 2min (80% VO_{2peak}):4-2min active recovery, Weeks 2-6: 2min (close to maximal effort):4-2min active recovery	Non-intervention control
Dunne et al.	2016	6 intervals, alternating moderate (<60% VO_{2peak}) & vigorous (>90% VO_{2peak}) intensity, (work: rest durations not provided - 30 mints total)	Non-intervention control
Flemmen et al.	2014	4 intervals; 4 min (90-95% HRmax):3min (~70% HRmax)	Non-intervention control
Freese et al.	2014	4-8 intervals; 30sec:4min	Non-intervention control
Heggelund et al.	2011	4 intervals; 4min (>85% HRpeak):3min (70% HRpeak)	Computer game training, equal time duration to HIIT group.
Hermann et al.	2011	Number intervals unknown, 4min (80% VO_{2peak})/2min (85% VO_{2peak})/30sec (90% VO_{2peak}):1-2min rest periods. Plus 10min staircase running (80% VO_{2peak}): recovery walking downstairs (50% VO_{2peak}), 42min total.	Non-intervention control
Hwang et al.	2012	Number of intervals unknown, 2-5min (80% VO_{2peak}/RPE 15-17):active recovery (60% VO_{2peak}/RPE 11-13), Total time 30-40 min.	Non-intervention control

Licker et al.	2017	40 intervals, 15sec (80-100% peak W):15sec rest, 4 min rest between sets, 2 sets	Non-intervention control
Mobius-Winkler et al.	2016	Number of intervals unknown, intervals up to 95% exercise capacity: recovery at 70% exercise capacity, 30mins total time.	Non-intervention control
Monk-Hansen et al.	2014	Number of intervals unknown, 4min (80% VO_{2peak}):3min / 2min (85% VO_{2peak}):1min / 30sec (90% VO_{2peak}):30sec, followed by 10min running upstairs (80% VO_{2peak}), 42 min total time.	Non-intervention control
Smith-Ryan et al.	2016	Either 10 intervals, 1min:1min (90% peak power output), or 5 intervals, 2min:1min (undulating intensities 80-100% VO_{2peak})	Non-intervention control
Trilk et al.	2010	4-7 intervals, 30sec (sprints vs 5% body mass resistance):4min active recovery between sprints.	Non-intervention control
Wallman et al.	2009	Number of intervals unknown, 1min (90% VO_{2peak}):2min (30% VO_{2peak}), 30mins total time.	Dietary advice only.

8.2.2 Training regimes HIIT versus MCT

Author	Year	HIIT	MCT
Angadi et al.	2015	Week 1: 8 intervals, 2min (80-85% HRmax):2min (50% HRmax), Week 2-4: 4 intervals, 4min (85-90% HRmax):3min (50% HRmax).	Week 1: 15 min (60% HRpeak), Week 2: 30 min (70% HRpeak)
Baekkerud et al. - 4x4	2015	4 intervals, 4min (85-95% HRmax):3min (70% HRmax)	45min (70% HRmax)
Baekkerud et al. 10x1	2015	10 intervals, 1min (90% HRmax):unknown rest period (active recovery walking)	45min (70% HRmax)
Boyne et al.	2016	Number of intervals unknown, 30sec (max walking speed):30-60sec recovery periods, 20min total time.	Week 1: 20min (45 +/-5% HRR), Week 2: 20min (50 +/-5% HRR).
Coppoolse et al.	1999	9 intervals, 3min (90% peak work rate):2min (45% peak work rate)	Duration unknown, (60% peak work rate)
Devin et al.	2016	4 intervals, 4min (85-95% HRmax): 3min (50-70% HRpeak)	(50-70% HRmax)
Dolan et al.	2015	Number of intervals unknown, Weeks 1-2: 2min (80% VO_{2peak}):4-2min activy recovery, Weeks 2-6: 2min (close to maximal effort):4-2min activy recovery.	3.22 km (55–60 % VO_{2peak}) progressed to 4.02 km (70 % VO_{2peak}) by the end of week 5.
Fisher et al.	2015	Number of intervals unknown, 30sec (85% max anaerobic power):4min (15% max anaerobic power).	45-60min (55-65% VO_{2peak})
Freyssin et al.	2012	12 intervals, 30sec (80% max power):1min (complete rest)	45min (HR at ventilatory threshold)

Gloeckl et al.	2012	Number of intervals unknown, 30sec (100% PWR):30sec (0% PWR), 12 to 36 minutes in interval training.	10 to 30 min (60% PWR)
Higgins et al.	2016	Week 1-2: 5 intervals, 30sec ('all out'):4min (minimal resistance pedalling), Week 3-4: 6 intervals 30sec ('all out'):4min (minimal resistance pedalling), Week 5-6: 7 intervals, 30sec ('all out'):4min (minimal resistance pedalling)	20-30 min (60-70% HRR)
Jaureguizar et al.	2016	30 intervals, 20sec (all out at 50% max work load):40 sec (10% max work load).	40min (HR below ventilatory threshold)
Jung et al.	2015	4 intervals, Week 1: 1min (~90% HRmax):1min (low intensity), by day 10: 10 intervals (~90% HRmax):1min.	Week 1: 20min (~65% HRmax), by day 10: 50min (~65% HRpeak)
Kim et al.	2015	4 intervals, 4min (walking 85-95% HRR):3min (50-60% HRR).	25min (70-85% HRR)
Kong et al.	2016	Maximum 60 intervals, 8sec (sprinting):12sec (passive rest)	40min (60% VO_{2peak})
Lanzi et al.	2015	10 intervals, 1min (90% HRmax):1min (50W)	40-50min (individual Fatmax)
Mador et al.	2009	7 intervals, 1min (150% cycle/treadmill speed for control group):2 min (75% cycle/treadmill speed for control group).	Duration unknown (50% Watt max achieved in incremental exercise test).
Matsuo et al.	2015	3 intervals, 3min:(80-85% VO_{2peak}):2mins (50% VO_{2peak})	40min (60-65% VO_{2peak})
Moholdt et al.	2009	4 intervals, 4min (90% HRmax): 3min (70% HRmax)	46 min walking (70% HRmax)
Puhan et al.	2006	Number of intervals unknown, 20sec (90-100% max capacity):40sec (10% max capacity)	20mins (70% max capacity)
Robinson et al.	2015	4 intervals, 1min (85-90% HRpeak):1 min rest. Increased to 10 intervals by day 10.	20min (60-65% HRpeak), increased to 50min by day 10.

Sawyer et al.	2016	10 intervals, 1min (90-95% HRmax):1min (low intensity)	30 min (70-75% HRmax)
Schmitt et al.	2016	8 intervals, 1min (>95% HRmax):2min (slow walking)	60 min (walking outdoors) and 15min cycling (60% HRmax). Total time 75min.
Skleryk et al.	2013	8-12 intervals, 10 secs ('all out' sprint loaded at 0.05kg/body mass):80 secs rest.	30 minutes (65% VO_{2peak})
Slordhal et al.	2005	8 intervals, 2min (80% VO_{2peak}):3min (sat down)	30min (60% VO_{2peak})
Uhleman et al.	2016	Number of intervals unknown, intervals up to 95% exercise capacity:recovery at 70% exercise capacity, 30mins total time.	6-8 sessions per day, 20 min each (up to 60% angina free capacity).
Wallman et al.	2009	Number of intervals unknown, 1min (90% VO_{2peak}):2min (30% VO_{2peak}), 30mins total time.	Cycled at a power that equated to 50% of individual VO_{2peak} for a duration that resulted in the same amount of energy as HIIT group.

8.3 Chapter 5 Appendices

8.3.1 Nottingham University Ethics Approval

The University of Nottingham

Faculty of Medicine and Health Sciences

Research Ethics Committee
School of Medicine Education Centre
B Floor, Medical School
Queen's Medical Centre Campus
Nottingham University Hospitals
Nottingham
NG7 2UH

Direct line/e-mail
+44 (0) 115 8232561
Louise.Sabir@nottingham.ac.uk

17th August l2015

Dr James Blackwell
Clinical Research Fellow/PhD Student
Medical Sciences and GEM
Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3DT

Dear Dr Blackwell

Ethics Reference No: A14072015 SoM MSGEM – please always quote
Study Title: Improvements in aerobic performance following a four-week period of high intensity interval training in the elderly – A pilot Study.
Chief Researcher/Academic Supervisors: Dr John Williams, Associate Clinical Professor in anaesthesia and pain medicine Metabolic, School of Medicine.
Researchers/Supervisors: Mr Jon Lund, Clinical Associate Professor and Consultant Colorectal Surgeon, Dr Bethan Phillips, Assistant Professor Clinical, Metabolic and Molecular Physiology, Miss Catherine Boereboom Surgical Research Fellow, MRC-ARUK Centre of Excellence for Musculoskeletal Ageing Research, Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital Campus.
Lead Researcher/Student: Dr James Blackwell, Clinical Research Fellow & PhD Student, Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital Campus
Duration of Study: 01/08/2015-31/07/2017 24 mths **No of Subjects:** 34 (70+ yrs)

Thank you for submitting your responses to the comments made by the Committee and the following documents were received:

HIIT in the Elderly:
- FHMS REC Application form version 1.0, Date 26/06/2015
- DXA Scan/UoN IRMER Radiation Practitioner Sign off 28/07/2015
- Protocol Final Version 1.3, 07/08/2015
- Participant Information Sheet Final Version 1.0 date 24/06/15
- Consent Form Final Version 1.0: 07/08/2015
- Letter to GP informing of abnormal result or Adverse event dated 26/06/2015

These have been reviewed and are satisfactory and the study is approved.

Approval is given on the understanding that the Conditions of Approval set out below are followed.

1. You must follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. This study is approved for the period of active recruitment requested. The Committee also provides a further 5 year approval for any necessary work to be performed on the study which may arise in the process of publication and peer review.

4. An End of Project Progress Report is completed and returned when the study has finished (Please request a form).

Yours sincerely



Dr Clodagh Dugdale
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

University of Nottingham
UK | CHINA | MALAYSIA

Email: FMHS-ResearchEthics@nottingham.ac.uk

Faculty of Medicine & Health Sciences
Research Ethics Committee
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School of Medicine Education Centre
B Floor, Medical School
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4 May 2017

Dr James Blackwell
Clinical Research Fellow/PhD Student
Medical Sciences and GEM
Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3DT

Dear Dr Blackwell

Ethics Reference No: A14072015 SoM MSGEM – please always quote
Study Title: Improvements in aerobic performance following a four-week period of high intensity interval training in the elderly – A pilot Study.
Chief Researcher/Academic Supervisors: Dr John Williams, Associate Clinical Professor in anaesthesia and pain medicine Metabolic, School of Medicine.
Researchers/Supervisors: Mr Jon Lund, Clinical Associate Professor and Consultant Colorectal Surgeon, Dr Bethan Phillips, Assistant Professor Clinical, Metabolic and Molecular Physiology, Miss Catherine Boereboom Surgical Research Fellow, MRC-ARUK Centre of Excellence for Musculoskeletal Ageing Research, Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital Campus.
Lead Researcher/Student: Dr James Blackwell, Clinical Research Fellow & PhD Student, Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital Campus
Duration of Study: 01/08/2015-31/12/2017 30 mths
No of Subjects: 34 (70+ yrs) 32-40 (40-60yrs)

Thank you for notifying the Committee of amendment no 3: 02/05/2017 as follows:

- Amendment: Extension of ethics deadline by 6 months to 31/12/2017.
- Reason: Study recruitment has gone well and is on track considering the delay in starting the project initially. We believe that this extension will make the project fully deliverable within this time.

These have been reviewed and are satisfactory and amendment no 3: 02/05/2017 has been given a favourable opinion.

A favourable opinion is given on the understanding that the conditions set out below are followed:

1. You should follow the protocol agreed and inform the Committee of any changes using a notification of amendment form (please request a form).

2. You must notify the Chair of any serious or unexpected event.

3. An End of Project Progress Report is completed and returned when the study has finished (please request a form).

Yours sincerely

Professor Ravi Mahajan
Chair, Faculty of Medicine & Health Sciences Research Ethics Committee

8.3.2 Consent form

Division of Medical Sciences and GEM
School of Medicine

The University of Nottingham

Human Tissue Act Management:
Healthy Volunteer Consent Form (HVCF)

Premises covered	Clinical Physiology, Derby	This is version	6
Document Created	15.7.2009	Document issued in	August 2015
Review Period	Every two years	To be reviewed in	August 2017

Project Title: Improvements in aerobic performance following a four-week period of high intensity interval training in the elderly.
Names of Researchers: Dr James Blackwell, Mr Jon Lund, Dr Bethan Phillips, Miss Catherine Boereboom, Dr John Williams, Dr M Sherwin.
REC Ref: A14072015 SoM MSGEM

Please read this form and sign it once the investigator above-named, or their designated representative, has explained fully the aims and procedures of the study to you

Please Initial Box

- I voluntarily agree to take part in this study. ☐
- I confirm that I have been given a full explanation by one of the above named investigators and that I have read and understand the information sheet version number 1.2 dated 15.03.16 for the above study and have had the opportunity to ask questions. ☐
- I understand that I am free to withdraw from the study at any time, without having to give a reason for withdrawing. ☐
- I agree to the above investigators contacting my general practitioner to make known my participation in the study where relevant. ☐
- I agree to comply with the reasonable instructions of the supervising investigator and will notify him immediately of any unexpected unusual symptoms or deterioration of health. ☐
- I understand that relevant sections of data collected in the study may be looked at by responsible individuals from the University of Nottingham, other than the research team, where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand my personal details will be kept confidential. ☐
- I understand that information about me recorded during the study will be kept in a secure database. If data is transferred to others it will be made anonymous. Data will be kept for 7 years after the results of this study have been published. After this time it will be disposed of in line with University policy. ☐
- I authorise the investigators to disclose to me any abnormal test results. ☐
- I understand that the tests or procedures are carried out for research only and not for clinical diagnostic purposes. However, if the study investigator should feel it necessary to inform my GP of an adverse event or abnormal test result, I understand am giving my consent to do so. ☐
- I confirm that I have disclosed relevant medical information before the study. ☐
- There will be no inconvenience allowance paid for this study. ☐

8.3.3 Patient information sheet

Participant Information Sheet

Final version 1.2: 15.03.2016

Title of Study: Improvements in aerobic performance following a four-week period of high intensity interval training in the elderly.

Study ID – eHIIT

Name of Researcher: Dr James Blackwell, Clinical Research Fellow, BMBS Bsc

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

We are investigating whether a short term high intensity exercise program can improve elderly people's physical performance. Elderly people often become increasingly frail and this negatively affects their chances of having a major operation and indeed increases the risks associated with any operation. Medical standards state that operations for cancer should be performed within 31 days of the decision being made that surgery is the best treatment option for an individual. We want to see whether similar increases in physical performance, over this short time period, can be achieved in over 70 year olds as we have previously shown in younger ages. Our exercise program is less time intensive than traditional methods and may result in a suitable alternative for elderly people.

Why have I been invited?

You are being invited to take part because you are over the age of 70 years old. We are inviting 34 participants like you to take part, both male and female.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

If you agree to take part in the project you will be required to attend to fill out a consent form and have some initial baseline tests. There will be a number of parameters measured and also a blood sample will be taken at this time. You will have an ultrasound of your heart and muscle in your leg. Also you will have a DXA scan which uses a very small dose of x-ray.

We will then perform an exercise test from which we can personally tailor a training plan for you. Four weeks later you will repeat this exercise test prior to starting the High intensity training protocol. This consists of three visits a week with approximately 20 minutes exercising each time. After completion of 12 sessions over 4 weeks we will then repeat all of the initial visit tests and perform one final exercise test to measure any improvement.

During the study period (8 weeks per individual) you will be required to attend every scheduled training session, these can be quite flexible within the week to fit in with your daily life. The study will run for 2 years however your commitment will only be for the 8 week period. During this period you will also be asked to fill out a number of questionnaires. For two separate weeks of the study you will be asked to wear an Actiheart monitor. This is a chest strap that monitors your heart rate and movement. It can be taken off to bath or shower. During this week you will also be asked to record your dietary intake via a diet diary over a four day period.

Some of the volunteers will be asked to provide a muscle biopsy sample, if you don't wish to consent to this you can still be included in the study. Three days prior to the first biopsy you will ingest 150mls of D_2O or 'heavy water'. This stable isotope tracer, even in tiny amounts, is incorporated into your cells and muscle proteins. We need to 'top up' the amount of D_2O once weekly for the duration of your involvement in the study to ensure there is enough D_2O present. The way that we monitor the amount of D_2O is via saliva samples; therefore you will need to provide a small saliva sample immediately prior to D_2O ingestion and then 3 hours afterwards (you can bring this second sample with you to the next visit). The procedure involves the use of local anaesthetic to numb the skin before a small cut in the skin on the outer aspect of your thigh, the muscle sample will be taken and a single stitch will be placed to close the wound. This may cause you to have some additional pain and bruising afterwards as well as a small risk of superficial infection. Should you choose to consent for this a further detailed discussion of the procedure will take place with the medically qualified and trained person who will perform the biopsy.

Expenses and inconvenience allowance

Participants will not be paid (an inconvenience allowance) to participate in the study. Car parking expenses will be offered for any visits incurred as a result of participation.

What are the possible disadvantages and risks of taking part?

As mentioned above there will be bloods tests and the possibility of a muscle biopsy if you decide to participate in the study. There are separate exclusion criteria for the muscle biopsy as detailed below, you will also have the chance to opt out of having a muscle biopsy during the consenting procedure – this will not affect your further participation within the study in any way.

Being over the age of 70 years there is a higher risk that you could experience an adverse event whilst participating in this study. In particular we may uncover abnormality with your heart and its function. If this is the case we would treat you as necessary at the time and would also inform your GP of any findings. We have developed a list of conditions which would exclude you from participating in this study; these conditions could put you at undue risk whilst exercising close to your maximum.

Inclusion criteria:

1. Aged over 70 years.
2. Sufficient mobility to be able to exercise on a static exercise bike.
3. Availability for the entire 8 week period.
4. Sufficient capacity to consent for the trial.

Exclusion criteria: (these can be further explained if necessary)

5. Individuals under the age of 70 years.
6. Individuals with a significant past medical history of:
7. Myocardial infarction (within last 6 months)
8. Unstable Angina
9. Heart failure (NYHA class III/IV)
10. Uncontrolled Hypertension (BP>160/100)
11. Previous stroke/TIA
12. Severe respiratory disease inc. known pulmonary hypertension(>25 mmHg), Forced Expiratory Volume in 1 second <1.5l.
13. Brittle asthma/exercise induced asthma
14. Known cerebral aneurysm or abdominal aortic aneurysm.
15. Cognitive impairment, which may reduce individuals' ability to provide informed consent.

If you have been a subject in any other research study in the last three months which involved: taking a drug; being paid a disturbance allowance; having an invasive procedure (eg blood sample >50ml) or exposure to ionising radiation.

Exclusion criteria pertaining specifically to muscle biopsies:

Current use of anticoagulation (i.e. Warfarin/Clopidogrel/Rivaroxaban)

Any pre-existing clotting disorders known to the patient (i.e. haemophilia).

Family history of severe bleeding requiring medical intervention.

Any musculoskeletal deformity or skin conditions making the taking of a biopsy unsuitable as deemed by the medical practitioner taking that sample.

Lack of capacity to fully consent for the procedure.

<u>DXA Scan:</u>

All volunteers will undergo two whole body DXA scans (Lunar Prodigy, GE Healthcare) for the estimation of body composition, including total lean body and lean leg mass which are required for our analysis of muscle protein synthesis. Alternative methods of assessing body composition without the use of x-rays, such as bioimpedance, air-displacement plethysmography, or skin-fold thickness cannot provide accurate regional lean mass measures, and as such are not viable alternatives for this study. As we are assessing the effect of HIT training over a period of time these DXA scans are required at week 0 (at the initial assessment visit) and week 8 (after training is completed at the reassessment visit). In the event the initial scan is

interrupted e.g. by subject moving or similar, only 1 repeat scan will be carried out and we will not perform a total of more than 4 scans as per ethical approval. The performance of the DXA equipment (Lunar Prodigy; GE Medical) will be monitored using daily QA checks and weekly assessment of a spine phantom to ensure that the X-ray tube and all the machines' safety features are functioning correctly. The DXA is also checked by the University of Nottingham Safety Office and serviced annually by the manufacturer. The estimated dose per examination is calculated by the lead IRMER Radiation Practitioner - Mrs. Aline Nixon, University of Nottingham Radiation Practitioner.

In real terms a single DXA scan contains less radiation as you would be exposed to in a long haul flight or the equivalent of 3 days normal background radiation. Also this test is widely used in healthcare to screen for osteoporosis and it is even used in pregnant women so it is generally considered very safe for the participant.

CPEX:

CPEX stands for Cardio-pulmonary exercise testing and is a good way of assessing someone's physical fitness in a standardised manner. It is widely used in healthcare and research. The specific test we will be using within this study is performed on a static exercise bike, you will have monitors attached to your chest and also a face mask, this allows us to monitor your heart and lungs whilst safely performing the test. During the study you will perform three exercise tests which are designed to be quite hard and to take you to above 85% of your maximum. This will cause you to sweat and become tired; also you will feel tiredness in your legs. You will have a recovery period after the test where we will ensure that you have fully recovered before we would let you go home.

If you do not perform regular exercise normally you may feel some muscle tiredness after each HIT training session. This will usually be self-limiting within 48hours. During a HIIT session you will have continuous12 lead ECG monitoring and intermittent non-invasive blood pressure monitoring during all sessions.

The training will be stopped immediately if you experience any of the following adverse reactions to the exercise including:

- Chest pain or tightness,
- Faintness,
- Sudden pallor,
- Loss of co-ordination,
- Confusion,
- Dizziness,
- Signs of respiratory failure,
- Palpitations,
- Ischaemic changes (>2mm ST depression) on ECG,
- Arrhythmias on ECG (multiple ectopics, heart block,

- Blood pressure drops by greater than 20mmHg from maximum or >250mmHg systolic or >120mmHg diastolic,
- Sudden onset bradycardia with a drop in heart rate of >10bpm from previous,
- Desaturation with a SpO_2 <80%

The American Thoracic Society Statement of Cardiopulmonary Exercise Testing (CPET) confirms that the CPEX test you will undergo is the most widely used test in clinical practice. Clinical indications for CPET testing are broad and include evaluation of exercise tolerance, evaluation of patients with cardiovascular disease, evaluation of patients with respiratory disease, pre-operative evaluation and pulmonary rehabilitation. This test is used widely in patients with other health concerns and long term conditions. There are however risks with any procedure or test. We have performed over 100 CPEX tests in our laboratory with no adverse events. At all times during the exercise and for a period afterwards (until return to baseline) there will be an ALS (Advance Life Support) certified medical practitioner present as well as another research member to assist. The expert consensus is that CPEX is a relatively safe procedure giving a risk of death for all comers during CPET 2 – 5 per 100,000 tests.

<u>High intensity interval training (HIIT):</u>

HIIT is a lot shorter than other types of exercise however you do work harder during this period. Once we have completed the first CPEX test (as above) we will create a personalised exercise program for you designed to work you hard during your training sessions. During a session you will work hard for one minute then have some rest, this is repeated numerous times during the session. After six sessions if you are responding well to the training we may increase the difficulty slightly to ensure that you continue at high intensity throughout the training period. Each training session takes approximately 20 minutes and each visit should take approximately 45 minutes. There would be three visits a week for four weeks, although we can arrange this for a mutually convenient time.

<u>Blood samples:</u>

We will take blood samples during the study. These are exactly the same as blood samples you may have had in the past and will be performed by a suitably trained medical professional or nurse. They should not hurt unduly; you may have a small bruise and some tenderness for a day or so after the sample. We will only take a small amount of blood each time.

<u>D_2O ingestion:</u>

D_2O or 'heavy water' has been shown to be very safe in previous research studies. We only aim to use a small total quantity of D_2O when compared to the total body pool of water. Some people have experienced dizziness after drinking D_2O. We have sought to minimise this risk by splitting the initial dosage into two 75ml doses which are taken a few hours apart. Any dizziness should be self-limiting. To monitor the level of D_2O in the body you will be required to provided saliva samples prior and three hours after D_2O ingestion. You can take this second sample at home and store it in your fridge until your next training session.

<u>Muscle Biopsy:</u>

We would like to take muscle biopsies in a subgroup of participants within the study. These may allow us to understand more clearly what affect high intensity training has upon the body and in particular if this type of training has beneficial effects on your muscle growth. The procedure entails numbing the skin with local anaesthetic (on the outside of your thigh), making a small (1cm) incision and taking a small bite of muscle with specialised muscle biopsy forceps. The wound would then be sutured closed with a stitch which would be removed after 5-7 days. There is a small risk of infection and bleeding and very occasionally some nerve damage associated with the patch of skin although this can heal itself over time. You can also be left with a small scar on the skin. You will have a thorough consenting process in relation to the biopsy should you decide to agree to the procedure. Opting out of this procedure will not affect your participation within the study in any way.

All procedures will be carried out by suitable qualified medical practitioners (doctors/ nurses). There will always be an Advanced Life Support (ALS) qualified doctor present during the exercise testing and HIIT sessions.

What are the possible benefits of taking part?

The information we get from your participation in this study may help direct future advice given to patients about their physical fitness and may help us to develop exercise programs for those patients undergoing major surgery. This in turn may improve patient outcomes following major surgery.

Will my taking part in the study be kept confidential?

During the study you will be allocated a unique number. From this point onward your data will be anonymised. Any recordings made or questionnaires filled out will be kept under lock and key within the medical school building, they will also be transcribed into electronic format and stored on our secure network. The procedures for handling, processing, storage and destruction of your data will meet the requirements of the Data Protection Act 1998.

Your data will be used for the purpose of this study only. It may be used for future studies only if directly relevant, for example should this initial study lead to future studies your data may be analysed again in the future against a new group of volunteers. Future studies would also have to be ethically approved just as this study has been. Only members of the research team who will have access to view identifiable data. We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the institution will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for 1 year after the end of the study so that we are able to contact you about the findings of

the study *and possible follow-up studies* (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason.

Involvement of the General Practitioner/ Family doctor (GP)

We will not routinely tell your GP that you are taking part in the study. We will however inform them of any abnormal findings that we might make as a result of the investigations which are part of the study.

What will happen to any samples I give?

We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to you and securely at the University of Nottingham under the universities Human Tissue Research Licence (no 12265).

Some of these future studies may be carried out by researchers other than current team of Dr Williams who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authorities codes of practice.

What will happen to the results of the research study

We aim to publish our findings widely in scientific and health literature. This may involve presenting it at conferences in the UK and abroad.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the University.

Who has reviewed the study?

All research in the University of Nottingham is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Faculty of Medicine & Health Sciences (FMHS) Research Ethics Committee.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you should then contact the FMHS Research Ethics Committee Administrator, c/o The University of Nottingham, School of Medicine Education Centre, B Floor,

Medical School, Queen's Medical Centre Campus, Nottingham University Hospitals, Nottingham, NG7 2UH. E-mail: louise.sabir@nottingham.ac.uk.

Further information and contact details

Dr James Blackwell (BMBS BSc) Email: james.blackwell@nhs.net

Dr John Williams MBChB, FRCA, PhD Phone: 01332 724641

Email: john.williams7@nottingham.ac.uk

8.4 Chapter 6 Appendices

8.4.1 East midlands (Derby) research ethics committee approval

NHS
Health Research Authority
East Midlands - Derby Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

22 March 2016

Dr John Williams
Consultant Anesthetist and Clinical Associate Professor
University of Nottingham
University of Nottingham Medical School
Royal Derby Hospital
Uttoxeter Road, Derby
DE22 3DT

Dear Dr Williams,

Study title:	**A randomised control trial to assess efficacy of preoperative high intensity interval training in older patients scheduled for oncological abdominal surgery.**
REC reference:	**16/EM/0075**
Protocol number:	**16011**
IRAS project ID:	**199141**

Thank you for your letter of 17 March 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Victoria Strutt, NRESCommittee.EastMidlands-Derby@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Covering Letter]	V1.0	27 January 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor Insurance]	V1.0	28 January 2016
GP/consultant information sheets or letters [GP Letter]	V1.0	27 January 2016
IRAS Checklist XML [Checklist_17032016]		17 March 2016
Letter from sponsor [Sponsor Letter]	V1.0	28 January 2016
Non-validated questionnaire [HIIT Acceptability Questionnaire]	V1.0	27 January 2016
Other [Supervisor CV 2]	V1	03 February 2016
Other [Additional Supervisor CV 3]	V1	03 February 2016
Participant consent form [Consent Form eHIITCa]	V1.1	16 March 2016
Participant information sheet (PIS) [Participant Information Sheet]	V1.1	16 March 2016
REC Application Form [REC_Form_29012016]		29 January 2016
Research protocol or project proposal [Protocol]	V1.0	27 January 2016
Response to Request for Further Information		17 March 2016
Summary CV for Chief Investigator (CI) [CI CV]	V1.0	28 January 2016
Summary CV for student [Student CV]	V1.0	28 January 2016
Summary CV for supervisor (student research) [Supervisor CV]	V1.0	28 January 2016
Validated questionnaire [DASI]	V1.0	27 January 2016
Validated questionnaire [IPAQ]	V1.0	27 January 2016
Validated questionnaire [EQ-5D-5L]	V1.0	27 January 2016
Validated questionnaire [WEMWBS]	V1.0	27 January 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/EM/0075	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

J. Parliament

pp
Mr Peter Korczak
Chair

Email:NRESCommittee.EastMidlands-Derby@nhs.net

Enclosures: "After ethical review – guidance for researchers" *SL-AR2*

Copy to: *Sponsor - Ms Angela Shone*
R&D Contact - Miss Teresa Grieve

8.4.2 Consent form

Derby Teaching Hospitals NHS
NHS Foundation Trust
Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3NE
Tel: 01332 340131
Minicom Users: 01332 785566
www.derbyhospitals.nhs.uk
Follow us on Twitter @DerbyHospitals

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

CONSENT FORM
(Final Version 1.2 / 16.03.16)

Title of Study: **A randomised control trial to assess efficacy of preoperative high intensity interval training in older patients scheduled for oncological abdominal surgery.**

REC ref: ***16/EM/0075***

Name of Researcher:

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number V1.2 dated 16.03.16 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand and agree that the following samples will be taken for analysis: ☐
   i. A blood sample will be taken for analysis of major organ function and markers of chronic health. ☐
   ii. A blood sample will be taken for future gene analysis.

In addition for participants consenting to muscle biopsies and D_2O ingestion (Optional):
   iii. I understand and agree that saliva samples will be taken for analysis of bodily D_2O levels. ☐
   iv. I understand and agree that a muscle sample (biopsy) will be taken for analysis of muscle protein content and intracellular mechanisms. ☐

5. Consent for storage and use in possible future research (Optional) ☐
   I agree that the samples I have given and the information gathered about me can be stored by the University of Nottingham at the Graduate Entry Medical School building, Royal Derby Hospital, for possible use in future studies. I understand that some of these studies may be carried out by researchers other than the current team who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and I will not be identified in anyway.
6. I agree to my GP being informed of my participation in this study. ☐
7. I agree to take part in the above study. ☐
8. I would like to receive a lay summary of the results following completion of the study. ☐
9. I understand that all activities herein will be undertaken within University of Nottingham premises onsite at Royal Derby Hospital and as such the hospital emergency care team does not cover this study directly. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

3 copies: 1 for participant, 1 for the project notes and 1 for the medical notes

8.4.3 Letter to General Practitioner

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Faculty of Medicine and Health Sciences

School of Medicine

Division of Medical Sciences & Graduate Entry Medicine

University of Nottingham

Royal Derby Hospital Centre

Uttoxeter Road

Derby

DE22 3DT

t: +44 (0)1332 724618

www.nottingham.ac.uk/gem

Head of Division:

Professor John Alcolado DM, BM(Hons) FRCP

Dear Dr,

Research Study - A randomised control trial to assess efficacy of preoperative high intensity interval training in elderly patients scheduled for oncological abdominal surgery.

I am writing to inform you that your patient,

Name: XXXXX DoB: XXXXXX

Has provided informed consent to participate in the above research study that we are conducting within the department of clinical physiology, Nottingham University, Royal Derby Hospital. This research study aims to see whether a preoperative high intensity exercise protocol can rapidly and significantly improve the fitness of elderly patients prior to operations for cancer. Their usual NHS care will not be affected in any way due to participation within the study.

This is NOT a drugs trial.

This study has been approved by The University of Nottingham Research Ethics Committee

In addition to their usual care, by participating in our trial, your patient will undergo a thorough screening assessment which is likely to be far in excess

of their usual screening. This will involve pre and post venous blood samples, DXA scans, ECHO scan, cardiopulmonary exercise testing and muscle USS. Depending upon which group they are randomised to they may be required to attend for exercise sessions 3-4 times per week.

They will also have two muscle biopsies and ingest a stable isotope tracer (D_2O) to enable us to undertake work to quantify the mechanistic basis behind the effect of high intensity training. They will however be allowed to continue with the study should they not wish to provide consent for the muscle biopsy.

If you have any questions about the participation of your patient in the study then please do not hesitate to contact us using the details below.

A copy of the participant information sheet is included for your information.

Yours sincerely,

Dr John Williams

Chief investigator, Consultant anesthetist and clinical associate professor.

8.4.4 Study Protocol



A randomised control trial to assess efficacy of preoperative high intensity interval training in older patients scheduled for oncological abdominal surgery.

20.01.2016

Short title: Preoperative HIIT in older cancer patients.

Acronym: eHIITCa

Trial Registration: www.clinicaltrials.gov reference: application underway.

IRAS Project ID: 199141

Trial Sponsor: University of Nottingham

Sponsor reference: 16111

Funding Source: Personal research funds of Dr John Williams, Mr Jon Lund and Dr Bethan Philips

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor: University of Nottingham

Contact name Ms Angela Shone

Head of Research Governance

Research and Graduate Services

King's Meadow Campus

Lenton Lane

Nottingham

NG7 2NR

Email: sponsor@nottingham.ac.uk

Chief investigator: Dr John Williams MBChB, FRCA, PhD

Associate Clinical Professor,

Honorary Consultant Anaesthetist and Divisional Director.

Phone: 01332 724641

Email: john.williams7@nottingham.ac.uk

Co-investigators:

Mr Jon Lund, DM FRCS,

Clinical Associate Professor,

University of Nottingham,

Division of Graduate Entry Medicine and Health, School of Medicine and Consultant Colorectal Surgeon,

Royal Derby Hospital.

Email: Jon.Lund@nottingham.ac.uk

Dr Bethan Phillips, BSc (Hons), PhD,

Research Fellow,

Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham.

Email: beth.phillips@nottingham.ac.uk

Dr Kenneth Smith BSc, PhD.

Principal Research Fellow.

MRC/ARUK Centre for Musculoskeletal Ageing Research, Graduate Entry Medical School, Faculty of Medicine & Health Sciences, University of Nottingham.

Email: Ken.Smith@nottingham.ac.uk

Dr James Blackwell. BMBS BSc. (PhD Student)

Clinical Research Fellow,

Division of Graduate Entry Medicine and Health, School of Medicine, University of Nottingham

Email: james.blackwell@nhs.net / mzxjb2@nottingham.ac.uk

Clinical radiation expert:

Dr Dominic Clarke.

Consultant Radiologist.

Royal Derby Hospital, Derby. DE22 3NE

Tel: 01332 340 131 X88569

Email: dominic.clarke2@nhs.net

Medical Physics Expert:

Simon Evans.

Consultant Healthcare Scientist,

Royal Derby hospital, Derby, DE22 3NE.

Tel: 01332 340131.

Email: simon.evans1@nhs.net

Trial / Study Statistician: Dr Brett Doleman.

Clinical Fellow, Royal Derby Hospital, Derby. DE22 3NE

Email: dr.doleman@gmail.com

Trial / Study Coordinating Centre:

Royal Derby Hospital – School of Graduate Entry Medicine

Uttoxeter Road, Derby, DE22 3NE

SYNOPSIS

Title Improvements in aerobic performance in older patients following a high intensity interval training program in a short timeframe prior to major oncological intra-abdominal surgery.

Acronym eHIITCa

Short title Preoperative HIIT in older cancer patients.

Chief Investigator Dr John Williams

Objectives Primary Aim: To assess whether our short term HIIT protocol can increase anaerobic threshold (VO2AT) in older individuals with abdominal cancer.

Secondary Aims:

To assess whether a short term HIIT protocol can increase aerobic fitness (VO_{2PEAK}) in individuals over the age of 65 prior to surgery for cancer.

Assess feasibility and acceptability of this HIIT protocol in the clinical environment.

Measurement of mitochondrial function and turnover (through muscle biopsy) via tracer incorporation and enzymatic assays to explore the mechanistic basis of HIIT-induced changes of aerobic performance.

To see whether there is an apparent different response to training between different abdominal cancer types.

Trial Configuration Multi-centre randomised control trial.

SettingRoyal Derby Hospital (NHS).

Department of Clinical Physiology, University of Nottingham, Graduate Entry Medicine School building onsite at Royal Derby Hospital.

Sample size estimate The study design will be a randomised control trial. Sample size calculations were performed for a repeated measures ANOVA with between subject factors (2 repeated measures of AT and 2 independent groups). We used data derived from a previous study we have conducted on

HIT. The partial eta squared was 0.15 (effect size F 0.42), for a power of 0.80 and a 0.05 level of statistical significance. The correlation for repeated measures was assumed to be 0.7. This indicated a sample size of 40 would be required. A dropout rate of 20% as experienced previously leads us to believe that a total number of 48 participants would be required.

Number of participants 48

Eligibility criteria Patients aged over 65 years old who have been scheduled for major abdominal cavity surgery for cancer.

Description of interventions After consenting and randomisation, baseline measures of heart rate, blood pressure, height, weight and a 12 lead ECG will be recorded. Also a screening blood test will be taken. Participants will undergo initial physiological testing including a cardiopulmonary exercise test (CPET), echocardiography (ECHO), leg muscle ultrasound and a DXA scan. CPET provides assessment of the integrative exercise responses involving the pulmonary, cardiovascular and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function and is being used increasingly in a wide spectrum of clinical applications for evaluation of undiagnosed exercise intolerance and for objective determination of functional capacity1.

There will be a control group (non-exercise) who will follow 'current best practice' which entails smoking and alcohol cessation advice. The exercise group (HIIT) will have a window to train before their planned operation, during this period a minimum of 8 HIIT sessions and reassessment 24-48 hours prior to surgery will be scheduled. These HIIT sessions are individualised 18 minute training sessions on a static exercise bike with medical supervision. Participants will complete 3-4 sessions per week.

Throughout the study participants will be required to fill out personal activity sheets and subjective questionnaires.

We aim to consent all participants for two muscle biopsies to investigate the mechanistic basis of high exercise intensity induced muscle protein synthesis changes, this will involve ingestion of a stable isotope tracer (D2O). To monitor the quantity of whole body D2O participants will be required to provide saliva samples pre and 3 hours post ingestion of the D2O, they can take the second sample pot home and bring it with them at the next visit.

Duration of study March 2016 – August 2018

Participants will be involved for their entire preoperative period from when the decision to offer surgical resection has been made until hospital discharge date postoperatively. We anticipate this time frame to be close to one month however there may be some individual discrepancy between cases (estimated range 2 weeks – 6 weeks).

Randomisation and blinding Randomisation will be conducted using www.sealedenvelope.com. A member of the research team who is not involved in the data collection or recruitment of participants will generate the randomisation codes and keep these securely. Block randomisation using random permuted block sizes of two and four will be used. Participants will be stratified according to age and sex to ensure a higher likelihood of equal baseline characteristics. Allocation concealment will be ensured by using opaque, sealed envelopes with participant group allocation performed on the first visit. Due to the nature of the intervention, patients will not be blinded

to the intervention or control group. However, data collectors will be blinded to the participant's group assignment.

Outcome measures Primary:

Anaerobic threshold.

Secondary:

VO_{2PEAK}

Acceptability of the HIIT protocol.

Blood pressure, heart rate.

Blood profile changes inc. Hb, Wcc, CRP, HBA1c, Lipid profiles.

Muscle thickness and pennation angle.

DXA body composition assessment.

Cardiac function via ECHO scan.

Subjective questionnaire data and physical activity recording via questionnaire.

Muscle oxidative enzyme activity and mitochondrial/sarcoplasmic functional synthetic rate.

Saftey:

Adverse event monitoring during CPET.

Adverse event monitoring during HIIT protocol.

Statistical methods

Data will be analysed with Prism and GraphPad by the research team.

ABBREVIATIONS

AE Adverse Event

CI Chief Investigator overall

CPET Cardiopulmonary exercise testing

CRF Case Report Form

DASI Dukes Activity Score Index

DXA Dual energy X-ray absorptiometry

ECHO Echocardiography

GCP Good Clinical Practice

HIIT High intensity interval training

ICF Informed Consent Form

IPAQ International Physical Activity Questionnaire

NHS National Health Service

PACES Physical Activity Enjoyment Scale

PI Principal Investigator at a local centre

PIS Participant Information Sheet

RDH Royal Derby Hospital

REC Research Ethics Committee

R&D Research and Development department

SAE Serious Adverse Event

SPBT Short Performance Battery Test

USS Ultrasound scan

UoN University of Nottingham

WEMWBS Warwick-Edinburgh Mental Well-Being Scale

TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

The prevalence of many conditions requiring major surgery increases with age. This in conjunction with improved perioperative care, surgical techniques and the ageing population has led to increased numbers of older patients undergoing major surgery in recent years. Despite this, rates of surgery for major surgical procedures still decline with age as highlighted in the National Cancer Intelligence Network report: Major surgical resections England, 2004-2006 and more recently reiterated in both Dunhill Medical Trust & Royal College of Surgeons joint reports – Access all ages and Access all ages 22,3. These reports highlight a stark decline in access to surgical procedures after the age of 65. The reasons for this disparity between increasing health need on the one hand and a decline in potentially life enhancing treatments on the other with increasing age are complex and varied2. One of the reasons proposed for this reduction in surgical access is the decrease observed in physical function with advancing age. Limitations in aerobic capacity have repeatedly been shown to affect outcome after major surgery, with diminished peak oxygen uptake (VO_{2PEAK}) and oxygen uptake at anaerobic threshold (AT), as assessed by cardiopulmonary exercise testing (CPEX), increasing the risk of post-operative mortality and morbidity4-15. Chronological age is however not an exact measure of physical performance or health11,16-18. Moreover, physical function is often erroneously evaluated by the surgical team, and judged by non-objective assessment of physical performance and/or chronological age7,19. This in turn commonly leads to the view that older individuals are unable to withstand the rigours of major surgery and its aftermath20,21. These factors may well influence access to surgery in this age group and contribute to the steep decline in survival rates after the age of 65 years seen in most cancers; for example bowel cancer 5-year survival is 65% in 60-69 year-olds, while in the over 80 year old age group 5-year survival drops to 43%22.

Patients who undertake exercise training preoperatively ('Prehabilitation') regain baseline fitness post operatively more rapidly than the untrained23. However, although recent studies have shown a positive effect of prehabilitation on postoperative outcomes24, robust data with regard to

outcomes is lacking25 and the optimal form of training programme yet to be clarified26.

Exercise programmes directed at improving physical fitness and modulating these risks in the preoperative period are an attractive option27,28, with increases in AT of 2ml/kg/min or greater considered to be of clinical benefit29. However, The Department of Health policy (2011) Improving Outcomes: A strategy for cancer30, mandates that operations for cancer should be completed within 31 days of decision to treat. This provides a narrow window to optimise patients' aerobic performance prior to their operation date.

Traditional methods of exercising to increase 'fitness' involve long periods of moderate intensity exercise, which can be time consuming. High intensity interval training (HIIT) is a safe way of rapidly improving cardiovascular fitness in older individuals28,31, it has been shown to be more effective than performing the same total work at lower intensity.28,32 It has also been shown to increase skeletal muscle oxidative capacity and induce specific metabolic adaptations during exercise that are comparable to traditional exercise training33. Given the less time intensive nature of HIIT vs traditional methods it may increase adherence to training protocols. Perioperative management of surgical patients has evolved with enhanced recovery programmes now being common place, the Enhanced Recovery After Surgery society recommends that increasing exercise preoperatively may be of benefit but highlights that the research base is inconsistent and further work is needed to elucidate its usefulness in relation to post-operative patient outcomes.34

We have recently shown that significant increases in cardiovascular fitness, as measured by VO_{2PEAK} and VO2AT, can be achieved by HIIT in healthy older individuals in a time period as short as four weeks35 in accordance with literature citing similar gains during 2 – 8 week HIIT protocols36,37,38,. What is unclear is whether these gains can be replicated in an older age group over the age of 75 suffering from co-morbid health conditions which include cancer. Demonstration of an ability to improve aerobic performance in a truncated time frame in such a population could, coupled with advancements in perioperative care and surgical techniques, allow for access to surgery for older patients becoming more readily available. HIIT training provides a significant opportunity to increase the aforementioned 'fitness for surgery' in comparison to current best advice or more traditional methods of exercise. Another key question is whether patients with cancer are able to make the same gains as aged matched 'healthy' individuals. Lastly it is important to assess whether the potential gains made are acceptable and feasible to both the patient and the clinician within the time constraints of the clinical environment.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

To see whether older patients with cancer can rapidly improve their fitness in a short time period using HIIT. To assess if this approach is an acceptable and practically viable health intervention, in this demographic group.

PRIMARY OBJECTIVE

To determine whether an improvement in aerobic fitness, as judged by a 2ml/kg/min increase in VO2AT, can be achieved via a short term HIIT protocol, in a group of older patients with abdominal cancer.

SECONDARY OBJECTIVES

To determine whether an improvement in aerobic fitness, as judged by a 2ml/kg/min increase in VO_{2PEAK}, can be achieved via a short term HIIT protocol, in a group of older patients with abdominal cancer.

To assess whether this programme would be acceptable to the group studied, through determination of subject compliance and adherence to the training programme and self-reported enjoyment.

To elucidate the mechanistic basis behind aerobic gains in response to HIIT via tracer incorporation (D2O) and enzymatic assays (using muscle biopsies).

To compare any change in fitness over this time period within the control group (smoking cessation and reduction of alcohol advice) versus that of the HIIT group.

To measure any changes body composition (fat, muscle, bone) and amount of muscle content during the study via DXA scans and muscle ultrasound scans.

DETAILS OF PRODUCT(S)

Description

D2O (95% deuterium oxide) will be given to participants undergoing muscle biopsies. This is purchased from Sigma-Aldrich, Poole, UK. It is premixed and stored in locked medical storage cupboard within the Clinical Physiology department, Nottingham University, Royal Derby Hospital. D2O is water containing one "heavy" deuterium atom in the place of hydrogen. This, novel method has been used successfully in our previous studies in our laboratory to quantify protein turnover without the need for radioactive labelling or invasive monitoring of participants. D2O is incorporated as a tracer into amino acids such as alanine. The fractional synthetic rate of D2O bound to for example, alanine, in the muscle vs. the total alanine body pool can then be measured giving rates of muscle protein synthesis. It can be assumed that pre study D2O levels are zero, this will be confirmed using plasma protein from the blood sample on the baseline visit. The participants will be 'loaded' with 150mls of D2O initially prior to the first biopsy and then they will have 50mls 'top up's' every seven days until operation date to ensure body pool enrichment. At each top up visit 2ml saliva will be collected in a non-sterile, sealed saliva collection tubes immediately before and three hours after the D2O dose is given. These samples in combination with the muscle biopsy (outlined below) allow us to measure the incorporation (and therefore rate of muscle protein synthesis) in our participants after the training programme.

Manufacture

Sigma-Aldrich, Poole, UK

Storage, dispensing and return

It is premixed and stored in locked medical storage cupboard within the Clinical Physiology Unit (Graduate Entry Medicine building, Royal Derby

Hospital). Each participant will be witnessed taking each dose which will be measured out by a member of the research team.

Placebo

There is no placebo used.

Known Side Effects

D2O is very well tolerated and the majority of people have no side effects at all. Self-limiting dizziness is the commonest side effect which resolves spontaneously44, however we have previously minimised this effect by splitting the initial 150mls dosage into two 75ml doses which are taken apart, this method will be followed in this study. The side effect profile is thought to be dose dependent (total body pool enrichment) and we will aim for an enrichment level of 0.4% which is within safe limits as shown previously44.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

Multi-centre randomised control trial.

Primary endpoint

VO_{2AT} (measured at Assessment visit 2).

Secondary endpoint

Questionnaire data relating to feasibility and acceptability of HIIT training protocol.

Mechanistic basis of cellular level effects of HIIT via muscle biopsies.

Safety endpoints

Safety variables:

Screening - results of physical examination by qualified doctor, vital signs (pulse rate, BP, O2 saturations), 12 lead ECG. Baseline blood results as interpreted by medically qualified doctor.

Whole study - AEs spontaneously reported during the study, discontinuations due to AEs.

Please see exclusion criteria below for medical conditions inhibiting inclusion in the study.

Abnormal results of screening blood tests.

Abnormal screening ECG

Abnormal clinical measurements eg. Blood pressure

Abnormal echocardiogram

Cardiorespiratory variables during VO_{2PEAK} testing sessions or any exercise training session.

Side effects of D2O ingestion.

Stopping rules and discontinuation

Any participant may withdraw from the study at any point, without giving reason.

Participants will be able to decline consent to allow muscle biopsy but will continue unaffected within the rest of the trial.

Screening tests to indicate renal failure, liver failure, significant anaemia, abnormal coagulation.

Abnormal screening ECG, to show arrhythmia, 2nd or 3rd degree heart block.

Screening blood pressure of greater than 160/100mmHg

CPET test termination criteria: as per ATS/ACCP Statement on CPET testing42.

The training will be stopped immediately if a volunteer complains of any adverse reaction to the exercise including:

- Chest pain or tightness,
- Faintness,
- Sudden pallor,
- Loss of co-ordination,
- Confusion,
- Dizziness,
- Signs of respiratory failure,
- Palpitations,
- Ischaemic changes (>2mm ST depression) on ECG,
- Arrhythmias on ECG (multiple ectopics, heart block)
- Blood pressure drops by greater than 20mmHg from maximum or >250mmHg systolic or >120mmHg diastolic,
- Sudden onset bradycardia with a drop in heart rate of >10bpm from previous,
- Desaturation with a SpO2 <80%

HIIT training termination criteria: as previously used in the same centre, HIIT training will be terminated in accordance with the same guidance provided above for termination of a CPET test.

RANDOMIZATION AND BLINDING

Randomisation will be conducted using www.sealedenvelope.com. A member of the research team who is not involved in the data collection or recruitment of participants will generate the randomisation codes and keep these securely. Block randomisation using random permuted block sizes of two and four will be used. Participants will be stratified according to age and sex to ensure a higher likelihood of equal baseline characteristics. Allocation concealment will be ensured by using opaque, sealed envelopes with participant group allocation performed on the first visit. Due to the nature of

the intervention, patients will not be blinded to the intervention or control group. However, data collectors will be blinded to the participant's group assignment.

Independent reviewers of CPET data and muscle USS will be blinded to both group and pre / post results.

Maintenance of randomisation codes and procedures for breaking code

Participants will not be blinded to intervention.

TRIAL/STUDY MANAGEMENT

Data will be inputted to a secure database with encryption. Consent forms and hard copies of data will be kept securely under lock and key in a locked office (Room 3008 Graduate Entry Medicine Building, RDH).

Dr James Blackwell (clinical research fellow / PhD student) will be responsible for recruitment and overall conduct of the study including screening, CPET testing and exercise training, data collection in both the University and clinical (NHS) environments and the taking of muscle biopsies.

Any data will be inputted to a secure database with encryption. Consent forms and hard copies of data will be kept securely under lock and key in a locked office (Room 511 Graduate Entry Medicine Building, RDH).

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: Enrolment will begin as soon as ethical approval has been granted and will run until a sufficient number of participants have been recruited. We anticipate that this project may take up to two and a half years to complete in total (March 2016 - August 2018).

Participant Duration: Individual participants will be required to be involved within the study from the date they are informed about the option to have definitive surgical treatment for their cancer until their post-operative hospital discharge date. In accordance with national guidelines this process should be no longer than 31 days from MDT decision to treat plus in hospital recovery time. Usual recovery times for uncomplicated intraabdominal surgery are now approximately 3-7 days. Patients who experience a complicated post-operative period however may take longer to go home. This leads us to believe that a single participant would be unlikely to be involved with the study for more than 6 weeks.

End of the Trial:

The end of the study will be the last post-operative hospital discharge date of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Participants will be recruited at the earliest point in their management pathway when there is sufficient evidence, as per expert opinion (specialty

consultant), to tell the participant they more than likely have a cancer and will likely require an operation to remove it.

Using Urology as an example specialty; participants with certain lesions (i.e. bladder tumours) seen during investigation (i.e. flexible cystoscopy) will have a very high likelihood of being offered surgical resection and a histological diagnosis is not obtained until postoperatively.

This would be the earliest opportunity to recruit participants and will allow for maximum benefit to be gained from the exercise program as they will be able to complete more HIIT sessions prior to operation.

Another example within urology would be that for renal cell carcinomas (RCC) the diagnosis is a radiological one, there is no preoperative histological diagnosis. So therefore at point of expert recommendation (consultant radiologist) that a given lesion is likely malignant we would try to recruit this participant. Post-operative histology will be checked to confirm the presence of cancer, in the unlikely event that the lesion were benign this participant's data would be removed from the final analysis and this would be highlighted in the final write up. A theoretical example of this might be within colorectal surgery where a lesion looks malignant, is surgically removed, and then is found to be an adenoma (as opposed to an adenocarcinoma or cancer) on histology. Our proposed study would not affect the decision to operate in this participant; they would just not be included as a patient with cancer in analysis.

In the event that a participant is recruited prior to a staging scan which shows widespread metastases therefore either making their operation a palliative procedure or removing surgical resection as a possible option, we would continue to offer HIIT sessions to this person as per the usual protocol. We would however remove the participant from the trial should they be offered / decide to undergo adjunctive chemotherapy or localised radiotherapy. Metastasis per se should not be an exclusion criteria as some patients, in colorectal cancer for example, will undergo primary bowel resection followed by liver metastectomy with curative intent.

Participants will be recruited in the surgical outpatient setting at Royal Derby Hospital. This large secondary referral centre accepts referrals from a wide area and as such has a high volume of cancer specific surgery within the surgical domains of Colorectal, Upper Gastrointestinal, Hepatobiliary and Urology. All departments have cancer nurse specialists who provide expertise and counselling support for patients with new diagnoses of cancer.

The initial approach will be from a member of the patient's usual care team (which may include the investigator).

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time

but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

There will be certain cancer types which only effect one gender (i.e. prostatic cancer in males or endometrial cancer in females) therefore these will be treated as subgroups within the analysis should these cancers be recruited.

Eligibility criteria

Inclusion criteria

Aged over 65 years (no upper age limit).

Histologically proven, radiologically or direct visualisation leading to high clinical suspicion of cancer.

Sufficient mobility to be able to exercise on a static exercise bike.

Ability to give informed consent.

Ability to travel to RDH to complete the HIIT sessions (may also rely upon dependents/relatives to provide transport).

Exclusion criteria

Adjuvant systemic chemotherapy / radiotherapy treatment for this cancer.

Participants with a significant past medical history of:

Myocardial infarction (within last 6 months)

Unstable Angina

Heart failure (NYHA class III/IV)

Uncontrolled Hypertension (BP>160/100)

Previous stroke/TIA

Severe respiratory disease inc. known pulmonary hypertension(>25 mmHg), Forced Expiratory Volume in 1 second <1.5l.

Brittle asthma / exercise induced asthma

Known cerebral aneurysm.

Inclusion in a recent (within 3 months) study which included any form of exercise, taking a drug or ionising radiation.

Exclusion criteria pertaining specifically to muscle biopsies:

Current use of anticoagulation (i.e. Warfarin/Clopidogrel/Rivaroxaban)

Any pre-existing clotting disorders known to the patient (i.e. haemophilia).

Family history of severe bleeding requiring medical intervention.

Any musculoskeletal deformity or skin conditions making the taking of a biopsy unsuitable as deemed by the medical practitioner taking that sample.

Lack of capacity to fully consent for the procedure.

Expected duration of participant participation

Study participants will be participating in the study for 4-6 weeks (depending upon lead time to operation and post-operative recovery time to discharge).

Removal of participants from therapy or assessments/Participant Withdrawal

Patients will be withdrawn from the study if they lose capacity for consent or if they wish to voluntarily withdraw consent.

Patients will be withdrawn from the study if the suffer any adverse effects of exercise on the exercise bike. These include symptoms of myocardial ischaemia (chest pain/tightness, faintness, palpitations), arrhythmias (prolonged runs of multiple ectopic beats, atrial fibrillation, heart block) or ischaemic ECG changes (>2mm ST depression with symptoms or >3mm ST depression without symptoms).

Patients will be withdrawn from the study if they have any adverse effects which are attributed to the ingestion of deuterium oxide (e.g. nausea, vomiting or abdominal pain). This is very unlikely given that only one dose of D2O will be given. Should this occur we will refer the patient to hospital for further tests and treatment (intravenous normal saline).

Patients will be withdrawn from the study if they fail to complete a minimum of 8 exercise sessions prior to operation date.

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Key for schematic diagram: Blue boxes represent standard NHS care to which you would routinely be exposed; this will take place in Royal Derby Hospital. Red boxes represent additional contacts for the purposes of the research study, other than the initial 'Recruitment', all of these visits will be to the Nottingham University Graduate Entry Medical School building on site at Royal Derby Hospital. S = Saliva sample (pre D2O ingestion and 3 hours post in all cases), MB = Muscle biopsy, CPET = cardiopulmonary exercise testing, Baseline measurements: Cardiovascular parameters (HR, BP),

bloods (FBC, UE, LFT, lipid profile, TFT, CRP, HBA1c, glucose), SPBT (Short performance battery tests), DXA scan, muscle USS, ECHO scan, hand grip strength, Subjective Assessments: Validated questionnaires (DASI, IPAQ, EQ-5D-5L).

Participants will be recruited from surgical outpatient clinics following initial introduction to the exercise trial by their primary care team. At this point they will be talked through the participant information sheet and given a copy to take away with them. They will then be contacted by telephone and invited to come for a consenting and initial screening session. This would entail a detailed description of all study elements and answering of any questions prior to signing the study consent form. Once the patient provides informed consent they will undergo a full cardiovascular medical examination by a medically qualified research member and will have a set of screening bloods taken.

Baseline physiological measurements will be taken at Assessment 1 via a CPET test, the Short Performance Battery Test (SPBT) and hand grip strength. Participants will also undergo DXA scan, muscle USS and ECHO scan at this point, investigations which are additional to routine NHS care. Participants will also fill out a number of questionnaires (Validated questionnaires (EQ-5D, Duke Activity Status Index (DASI), International Physical Activity Questionnaire (IPAQ), Warwick Edinburgh Mental Wellbeing Scale (WEMWBS). Echocardiography will be used to assess the central cardiovascular adaptations to HIT (end diastolic volume, stroke volume (therefore cardiac output), ventricular ejection fraction and ventricular wall thickness will be measured). This will be compared to peripheral mitochondrial adaptations assessed from the muscle biopsy.

VO_{2PEAK} and anaerobic threshold will be measured using a 15 – 30Watt/min ramp protocol on a stationary exercise bike (Lode Corival cycle ergometer, ZAN 680, nSpire Health). In brief, flow and gas composition will be calibrated before each test and the exercise protocol explained to the subject. Subjects will be seated on the ergometer and the position adjusted to fit. Subjects will be fitted with a face mask from which inspired and expired gases will be sampled during exercise. In order to ensure accurate gas analysis masks will be checked for any leaks prior to exercise. Following a two minute warm-up period, cycling workload will be increased in a ramp-wise manner of 10-30W per minute, with individuals encouraged to maintain a cadence of 50-60 rpm. Subjects will be verbally encouraged to exercise to 85% or more of predicted maximal heart rate and to a respiratory exchange ratio (VCO2/VO2) above 1.1. The test will be terminated when the subject indicates that they have reached their maximum possible effort. A 12 lead ECG will be measured continuously throughout the test (CardioCollect12S, DelMar Reynolds) and non-invasive blood pressure collected every 2 minutes.

Exercise will be stopped immediately if a volunteer complains of any adverse reaction to the exercise including:

- Chest pain or tightness
- Faintness
- Sudden pallor
- Loss of co-ordination
- Confusion

- Dizziness
- Signs of respiratory failure
- Palpitations
- Ischaemic changes (>2mm ST depression with symptoms or >3mm without symptoms) on ECG
- Arrhythmias on ECG (prolonged runs of multiple ectopics, heart block)
- Blood pressure drops by greater than 20mmHg from previous reading or >250mmHg systolic or >120mmHg diastolic
- Sudden onset bradycardia with a drop in heart rate of >20bpm from previous reading
- Desaturation with a SpO2 <80%

(Termination guidelines adapted from ATS/ACCP Statement on CPET testing42)

The American Thoracic Society Statement of Cardiopulmonary Exercise Testing (CPET)42 confirms that the maximal incremental cycle protocol (ramp protocol) that we intend to use is the most widely used in clinical practice. The work rate increments can be altered to allow for difference in volunteer's usual activity status to aim for a VO_{2PEAK} test of 8 – 12 minutes. Clinical indications for CPET testing are broad and include evaluation of exercise tolerance, evaluation of patients with cardiovascular disease, evaluation of patients with respiratory disease, pre-operative evaluation and pulmonary rehabilitation. This test is used widely in a variety of co morbid patients. Whilst they acknowledge that patient safety is of paramount importance the ATS/ACCP state that CPET is a relatively safe procedure and give a risk of death for all comers during CPET 2 – 5 per 100,000 tests.

Participants will then enter the 'training' phase wherein they will complete a minimum of eight individual HIIT sessions at a frequency of three to four per week. We do not train people at the weekend so this provides two natural rest days each week. Participants will complete a maximum of twelve sessions before retesting prior to their surgery. Should their operation be delayed for any reason which did not preclude them from continuing in the study (i.e. personal choice of date, list cancellation etc), and they had completed the twelve HIIT sessions we would ask that their Assessment session 2 (and muscle biopsy if applicable) be brought forward from the operation date to ensure all repeat measurements are comparable by number of HIIT sessions completed. In this event the biopsy would be taken in our clinical room in the Graduate Entry Medicine building on site at RDH under local anaesthetic. If individual participants wanted to continue training we would do so for up to 6 weeks or until their operation date if sooner.

HIIT sessions consist of a 2 minute lightly loaded pedalling (15W) warm up phase followed by 5 x 1 minute intervals with 90 seconds rest in between. A 3 minute warm down period follows the final interval. The first training session will comprise of 5 x 60second intervals set at 95%, 100%, 105%, 110% and 115% Watt max. The intervals at the following training sessions will be set at the highest completed interval from this initial assessment session.

After 6 training sessions the interval training level will be increased by 10% of the initial baseline maximum power output providing:

- The participants assess their effort on a modified Borg scale at 8 or below
- No adverse cardiovascular signs during the first 6 training sessions
- Fully completed all training sessions

E.g. A volunteer who achieves 200W at their baseline exercise test will undergo assessment session at 190W, 200W, 210W, 220W, 230W (95 – 115%Watt max). If they completed the 220W interval but not the 230W interval they would train at 220W intervals up to and including training session 6. If the above criteria were met they would then increase to 240W (additional 10% of 200W) for the remaining 6 training sessions.

All sessions will be supervised by medically qualified research staff trained in Advanced Life Support. Participants will be monitored by 12 lead ECG, pulse oximetry and non-invasive blood pressure cuff during all cycling sessions.

The muscle biopsy will be taken from the mid belly of m. vastus lateralis using a conchotome biopsy technique40. Biopsies will be taken by medically qualified doctors trained in this procedure. The procedure will be performed under aseptic conditions. A 5-10mm incision will be made in the skin and underlying fascia and a sample of muscle will be taken (approximately 60mg). Direct pressure will be applied to achieve haemostasis. A single non-soluble suture will be placed to allow skin apposition and healing. A sterile dressing and compression bandage will be applied to remain in place for the duration of the day. The suture will be removed around 5-7 days after the biopsy is taken.

Muscle biopsy consented participants only: Participants willing to provide a muscle biopsy will have one additional visit (D2O Visit) in which they will have a serum blood sample to measure protein (5mls), ingest 150mls of D2O (2 x 75ml doses) and then will provide a saliva sample pre and three hours after initial ingestion of D2O. The control group will then have a muscle biopsy followed by a second at operation date. Participants in the HIIT group would have their first biopsy prior to starting the training phase. During the training phase participants will ingest 50mls 'top up's' of D2O every seven days to main total body pool enrichment. They will be required to provide a saliva sample immediately before and three hours after taking each D2O dose.

Following the final HIIT session prior to surgery participants will undergo Assessment visit 2 which mirrors Assessment visit 1, this would be >24 hours prior to operation date. In addition to the previous questionnaires a final HIIT acceptability questionnaire will be filled out as well as the PACES questionnaire (Physical Activity Enjoyment Scale). Muscle biopsy two will (unless brought forward as above, or at patients request) be taken on operation day whilst the participant is under general anaesthetic to minimise distress to the participant. Local anaesthetic will also be infiltrated as usual to provide analgesia. A research member will visit the ward on day five to remove the single stitch placed at biopsy. Should the patient have discharged by day 5 they will be advised to see their district nurse for stitch removal.

As detailed above, in addition to their normal treatments, patients will undergo the following invasive or potentially harmful tests (risks outlined in

Risk section): two CPET tests, two DXA scans, blood tests and two optional muscle biopsies.

Compliance

Compliance with the HIIT protocol will be monitored by the member of the research team present at every supervised session.

Acceptable compliance will defined as attendance at a minimum of 8 HIIT sessions, lower than this would lead us to believe that there may be minimal beneficial gains and therefore the participant would not undergo Assessment 2.

Criteria for terminating trial

The study will only be terminated should there be a complete lack of recruitment to the study/willing participants. Terminating the whole study may be as a result of a formal or informal interim analysis (data to be analysed after ten participants) and based on overwhelming evidence of efficacy/inefficacy, major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). Individual CPET tests and HIIT sessions are individually scrutinised for saftey by the responsible medical doctor present at the time of the test/session.

In the event of trial termination, any research data already collected would be kept as outlines in the archiving section below, the participants are consented for data storage at the beginning of the trial.

RADIATION EXPOSURE

All volunteers will undergo two whole body DXA scans (Lunar Prodigy, GE Healthcare) for the estimation of body composition, including total lean body and lean leg mass which are required for our analysis of muscle protein synthesis (expressed per 100g lean leg/ body). Although these do carry an ionising radiation burden (approx. 0.1 μSv per scan) it is considered very small compared to other imaging techniques such as CT scans (up to 400 times less). Their widespread use in screening for osteoporosis and even in pregnant women leads us to believe that our participants would not be exposed to a dangerously high level of ionising radiation. Scans will not be performed if the individual has received an x-ray dose of >6mSv in the previous year. Alternative methods of assessing body composition without the use of x-rays, such as bioimpedance, air-displacement plethysmography, or skin-fold thickness cannot provide accurate regional lean mass measures, and as such are not viable alternatives for this study. As we are assessing the temporal effect of HIT training these DXA scans are required at week 0 (Assessment Visit 1) and after the final HIIT training session (Assessment 2). In the event the initial scan is interrupted e.g. by subject moving or similar, only 1 repeat scan will be carried out and we will not perform a total of more than 4 scans (as per NRES approval). The performance of the DXA equipment (Lunar Prodigy; GE Medical) will be monitored using daily QA checks and weekly assessment of a spine phantom to ensure that the X-ray tube and all the machines' safety features are functioning correctly.

The DXA is also checked by the University of Nottingham Safety Office and serviced annually by the manufacturer. The estimated dose per examination is calculated by Simon Evans (Medical Physics Expert) and clinical evaluation performed by Dr Dominic Clarke (Clinical Radiation Expert) as named above.

Details of diagnostic or therapeutic ionising radiation

The dose from Dual Energy Absorptiometry is generally very low compared to other types of x-ray examination, but is dependent on the type of scanner and the scan method to be used. Participants in this study will all be older adults.

The effective dose DXA body composition scans is published by the National Osteoporosis Society (NOS) and are used for the assessment below.

The study protocol requires participants to undergo a body composition scan on up to four occasions. A dose per scan is quoted, along with the maximum dose from the study

1.1.1.1 Doses per scan for GE Prodigy scanner

Effective Dose in microsieverts: Body Composition Study Total

Adult 0.1 0.4

*Source: National Osteoporosis Society

1.1.1.2 Total dose from study and equivalences

Effective Dose in microsieverts: Per Scan Total for 4

Scans Equivalent background radiation Equivalent Chest X-rays

Adult 0.1 0.4 1.5 hours 1/50th

Note that the background equivalent is based on the average for the UK and the extra dose from this study is well within the natural variability of background.

Whilst there is no safe level of radiation for induction of stochastic effects such as cancers and leukaemia, the risk to the research subjects will be indistinguishable from background populations levels, and is therefore negligible.

Participants will undergo two DXA scans, if there is insufficient quality of a scan (e.g: due to movement) the scan will only be repeated once, making the maximum possible number of scans four per person.

Details of radioactive materials and dose

No radioactive materials are to be used.

ARSAC research certificates

Not required.

Clinical Assessment

As clinical director of imaging at Royal Derby Hospital I have reviewed the above protocols and I am in agreement with the MPE that the clinical exposures (for use of DXA) are justified as part of this trial protocol (CRE Dr Clarke).

TRANSPORT AND STORAGE OF THE TISSUES

Samples will be stored in linked anonymised format at the Clinical Physiology department at the University of Nottingham. This department is part of MRC-AR UK Centre of Excellence for Musculoskeletal Ageing Research and is based within the Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, Royal Derby Hospital Centre. All samples will be labelled using

a combination of study identifier, initials, date of birth and study number to permit accurate linkage to clinical data and the consent form.

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Blood serum samples will also be centrifuged to allow extraction of plasma samples which as well as muscle biopsy samples will be stored in aliquots, both at -80 degrees centigrade and in paraffin wax blocks.

The master database will be held by Dr James Blackwell in a password encrypted file.

The analysis of samples will take place at the University of Nottingham within the Department of Medicinal Sciences and Graduate Entry Medicine (Derby).

Samples stored for future research will be stored at the research tissue bank at the MRC-AR UK Centre of excellence for musculoskeletal research, clinical, metabolic and molecular physiology research group, division of medical sciences and graduate entry medicine, School of Medicine, Royal Derby hospital only if participants are agreeable and sign the optional clause on the consent form (DI Prof William Dunn – HTA Licence number 12265).

Where participants do not agree to the future use of the samples they will be destroyed in accordance with the Human Tissue Act, 2004.

LABORATORY ANALYSES

Blood samples will be sent to clinical chemistry within RDH to be analysed for a number of baseline health measures (FBC, UE, LFT, COAG, TFT) and also other markers of improved health (HBA1c, lipid profile, CRP, glucose, protein). Labelling of body water with deuterium will be assessed by extraction of the water from the saliva samples, to be analysed using direct liquid injection TC/EA-IRMS41. Muscle samples will be prepared to separate out; myofibrillar, sarcoplasmic, lipid, satellite cell and DNA fractions according to established procedures in our lab. These fractions will then be analysed via GC-pyrolysis-IRMS and GC-MS for deuterium labelling; this combined with the body water labelling will allow the calculation of rates of synthesis for each fraction using the standard precursor-product model,

Fractional Synthesis Rate (% / day) = [(APEAla)] / [(APEP) × t] × 100

Where APEAla = deuterium enrichment of protein-bound alanine, APEP = mean precursor enrichment over the time period, and t is the time between samples.

For additional insight in to the mechanisms regulating control of muscle mass and muscle protein metabolism we will measure a number of target proteins within muscle by western blotting.

As well as the above blood tests taken for medical screening a venous blood sample will be taken and stored to allow gene analysis in the future, this will not however entail whole genome screening. Whole blood will be stored in a pax gene tube for analysis once candidate genes have been identified.

Saliva samples will be collected from the participants during all D2O visits. These samples will be handed to the research fellow who will place them in a refrigerator within the clinical skills lab. These samples will have the unique participation number of the patient printed upon them.

Muscle biopsies will be collected by the research fellow and placed into liquid nitrogen. This sample, stored in a portable liquid nitrogen container will be handed to the clinical physiology study group for analysis.

STATISTICS

Methods

Objective and subjective measures of aerobic performance (VO2AT) will be analysed for differences between control group vs HIIT in changes seen pre and post training as the primary outcome.

Upon study completion data will be analysed using GraphPad Prism, v5.0, (La Jolla, Calif. US) and SPSS version 19 (IBM, US), with no interim analysis planned. Data will be analysed in house by members of the research team and with statistical advice provided by the University of Nottingham.

Distribution of the data will be tested using the Kolmogorov-Smirnov test, with normally distributed data expressed as mean (SD) and non-normally distributed data as median +/- interquartile range. Repeated measures ANOVA with between subject factors (2 repeated measures of AT and 2 independent groups) will be used to compare Control vs HIIT. T-tests will be used to assess control vs HIIT in relation to muscle mass and function. The correlation between continuous variables will be tested using Pearson or Spearman's correlation coefficient as appropriate. Categorical variables will be compared using the Fisher's exact test. SPSS v19 software will be used and the significance level will be set at 0.05.

Analysis of data will be on UoN computers and backed up to the UoN servers.

Sample size and justification

Sample size calculations were performed for a repeated measures ANOVA with between subject factors (2 repeated measures of AT and 2 independent groups). We used data derived from a previous study we have conducted on HIT. The partial eta squared was 0.15 (effect size F 0.42), for a power of 0.80 and a 0.05 level of statistical significance. The correlation for repeated measures was assumed to be 0.7. This indicated a sample size of 40 would be required.

Assessment of efficacy

Primary efficacy endpoint: mean increase in VO_{2PEAK} (as measured via CPET) in each group (control vs HIIT).

Secondary efficacy endpoints:

- Mean increase in AT (as measured via CPET 2) in each group (control vs HIIT).

- Mean differences in baseline measures such as BP, resting HR, blood tests.

- Muscle thickness & pennation angle changes.

- Muscle mitochondrion quantity, FSR, oxidative enzyme activity.

See study regime above for timings.

Assessment of safety

All sessions will be supervised by medically qualified research staff trained in Advanced Life Support along with another individual experience in exercise testing. All blood samples and biopsies will be taken by medically qualified, trained individuals. Volunteers will be monitored by 12 lead ECG, pulse oximetry and non-invasive blood pressure cuff during all cycling sessions.

The American Thoracic Society Statement of Cardiopulmonary Exercise Testing (CPET)42 confirms that the maximal incremental cycle protocol (ramp protocol) that we intend to use is the most widely used in clinical practice. The work rate increments can be altered to allow for difference in volunteer's usual activity status to aim for a VO_{2PEAK} test of 8 – 12 minutes. Clinical indications for CPET testing are broad and include evaluation of exercise tolerance, evaluation of patients with cardiovascular disease, evaluation of patients with respiratory disease, pre-operative evaluation and pulmonary rehabilitation. This test is used widely in a variety of co morbid patients. Whilst they acknowledge that patient safety is of paramount importance the ATS/ACCP state that CPET is a relatively safe procedure and give a risk of death for all comers during CPET 2 – 5 per 100,000 tests.

Any complication that may occur will be dealt with in accordance with standard NHS practice.

Procedures for missing, unused and spurious data

Participants will be removed from the study if significant amounts of data is missing eg. greater than 4 exercise sessions missed.

Definition of populations analysed

Safety set: All randomised participants who receive at least one HIIT session.

Full Analysis set: All randomised participants, who participated in at least 8 HIIT sessions and for whom at least one post-baseline assessment of the primary endpoint is available.

Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

Dr James Blackwell will screen participants for violations of eligibility criteria during the consenting procedure. Deviations from the protocol will be assessed by members of the research team, primarily by Dr James Blackwell as adherence and compliance to the protocol is monitored by attendance to the HIIT sessions.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

5. Muscle biopsy- pain, bleeding and infection. Should the patient be concerned with any of the following then we will refer the patient on to the correct NHS clinical team for analgesia or antibiotics (standard NHS policy).

6. Blood tests- Bruising. Should the patient be concerned with any of the following then we will place a pressure dressing and observe for 5 minutes (standard NHS policy).

7. Cardiorespiratory or neurological complications occurring due to exercise.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the treatment or intervention that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Eg. Cardiac, respiratory or neurological complications due to exercise.

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment / intervention administration which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation. This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment / intervention administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment / intervention is not the cause. The Chief Investigator shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

In the event of a pregnancy occurring in a trial participant or the partner of a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring. Where it is the partner of a trial participant consent will be obtained for this observation from both the partner and her medical practitioner.

All treatment related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Trial Treatment / Intervention Related SAEs

A serious adverse event that is unexpected in its severity and seriousness and deemed directly related to or suspected to be related to the trial treatment or intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment or intervention.

- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.

- If the event is deemed related to the trial treatment or intervention shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.

- Shall, within a further eight days send any follow-up information and reports to the REC.

- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent

regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

All case report forms will be kept in the chief investigators file. This file will be locked within a cupboard in a locked office on site.

Each participant will be assigned a trial identity code number with the prefix 'eHITCa', allocated at randomisation if appropriate, for use on CRFs other trial documents and the electronic database. Each participant will be assigned a trial identity code number for use on CRF's (Case report forms), other trial documents and the electronic database. The documents and database will also use the study acronym, initials, date of birth and sequential study number eg: eHIITCaAB11.04.65_01. Back up electronic file will exist in a password protected program on a password protected computer within the chief investigators office.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. The documents and database will also use the study acronym (eHITCa, initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy) in accordance with the Human Tissue Authority Codes of Practice.

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

Paper records will be filed and placed into locked cupboards within a locked office in the department of Clinical Physiology, University of Nottingham, Royal Derby Hospital. Electronic data will be placed on password protected databases (secure network) on a Nottingham University password protected computer within a locked office in the same department.

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Information about the trial in the participants medical records / hospital notes will be treated confidentially in the same was as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator/Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

This study will for part of the research fellow's thesis. No identifiable information will be used at all. The results will be published within a peer reviewed journal and international presentations will be made.

USER AND PUBLIC INVOLVEMENT

A recent study undertaken by our unit assessed the effectiveness of the same HIT training programme in an older healthy volunteers group (mean age 68). Following the study all volunteers completed a training feedback form. This was designed to assess the acceptably of the intervention to the volunteers and provide a mechanism for making the training more acceptable if necessary. The volunteers all said that the HIT programme was enjoyable, it was not a significant time burden, it did not interfere significantly with other aspects of their life and they would recommend HIT to others.

We will use the same training feedback form to assess the acceptability of the training to the cancer patients, as well as the PACES questionnaire as outlined in the protocol.

STUDY FINANCES

Funding source

This study is funded by personal research funds of Dr John Williams and Mr John Lund.

Participant stipends and payments

Participants will not be paid to participate in the trial.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)Dr John Williams

Signature:_____

Date: _____

Co- investigator: (name) Dr James Blackwell

Signature:_____

Date: _____

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8.4.5 Patient information sheet

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Participant Information Sheet

(Final Version 1.2 16.03.16)

Title of Study: **A randomised control trial to assess efficacy of preoperative high intensity interval training in older patients scheduled for oncological abdominal surgery.**

Name of Researchers: Dr James Blackwell; Dr John Williams; Mr Jon Lund; Dr Beth Phillips, Miss Catherine Boereboom

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

We are investigating the effects of cancer on fitness and whether a short term high intensity exercise program can improve physical performance in older people with cancer. Frailty increases with age and this can negatively affect a patient's chance of having a major operation and indeed increases the risks associated with any operation. Medical standards state that operations for cancer should be performed within 31 days of the decision being made that surgery is the best treatment option for an individual. We are investigating whether similar increases in fitness, over this short time period, can be achieved in over 65 year olds with cancer as we have previously shown in younger healthy participants. We also want to investigate whether our exercise program can significantly improve fitness in people with cancer compared with advice to stop smoking and reduce alcohol intake which is current best practice during this period. Our exercise program is less time intensive than traditional methods and may result in a suitable alternative for older people, especially in a short time frame from diagnosis to surgery.

Why have I been invited?

You are being invited to take part because you are over the age of 65 years old, you have recently been told by your surgical specialist that they believe you have a cancer and it is likely you will require an operation to remove it. We are inviting 48 participants like you to take part, both male and female.

From today onward, any appointments relating to this study, including the tests outlined below will be undertaken within the Nottingham University Graduate Entry Medicine building on site but separate to Royal Derby Hospital.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

A diagram of the following description can be found at the end of this document.

If you agree to take part in the project you will be required to attend to fill out a consent form.

This study is a randomised control trial. This means that willing participants are completely randomly allocated to one of two groups. Unfortunately you are not allowed to choose which group you would like to be in and therefore would have to consent to be in either group as the randomisation process occurs after consenting. This allows us to have the most scientifically correct method which will ultimately allow us to make sound deductions about our exercise protocol after the study finishes.

Group 1 will receive 'current best practice' which is largely advice about stopping smoking (if you do smoke) and reducing alcohol intake. This group will allow us to quantify the effect an active cancer has on your fitness over this time frame. There would be two assessment sessions, one immediately after diagnosis and a second immediately prior to operation. Your normal NHS treatment will not be affected in any way.

Group 2 will be required to attend the Graduate Entry Medicine building (Nottingham University) at the Royal Derby Hospital site 3-4 times per week to undergo the high intensity interval training (HIIT) protocol. This can be thought of as the 'exercise' group. There is obviously much more time commitment involved however again there will be no change to your normal NHS treatment.

Once you have been fully consented and randomised a medical history, examination of your heart and lungs and a blood sample will be taken. Both groups will be invited to an initial assessment session. At each assessment session there will be a number of parameters measured. You will have an ultrasound of your heart and muscle in your leg. Also you will have a DXA scan which uses a very small dose of x-ray. You will then perform an exercise test on a static bicycle to assess your current level of fitness.

Group 2 will then have a personally tailored training plan created from the results of their initial cycle test. You need to complete a minimum of 8 HIIT sessions prior to your operation, but ideally we will aim for 12 sessions before retesting 24-48 hours before your operation. All of our testing and exercise training sessions are completed on a static exercise bike. We are investigating the effectiveness of HIIT as a newer method of training which is much less time intensive than traditional methods but has shown very good improvements in fitness over a short period. Each HIIT session consists

of less than 20 minutes exercise. After completion of 12 sessions, or less if the operation is sooner, we will then repeat all of the initial visit tests and perform one final exercise test to measure any improvement.

The study will run for 3 years however your commitment will only be for the period from diagnosis to discharge from hospital following surgery. During this period you will also be asked to fill out a number of questionnaires about your activity levels, general health and mental wellbeing.

All participants will be asked to provide optional consent for a muscle biopsy sample at the beginning of the study and then immediately prior to the operation. The second biopsy can be taken on the day of surgery whilst you are anaesthetised if you would prefer. Both Group 1 and 2 will undergo muscle biopsy if consent is provided. Three days prior to the first biopsy you will ingest 150mls of D_2O or 'heavy water'. This stable isotope tracer, even in tiny amounts, is incorporated into your cells and muscle proteins. We need to 'top up' the amount of D_2O once weekly for the duration of your involvement in the study to ensure there is enough D_2O present. The way that we monitor the amount of D_2O is via saliva samples; therefore you will need to provide a small saliva sample immediately prior to D_2O ingestion and then 3 hours afterwards. Should you decided not to provide consent for the muscle biopsies you will still be able to continue with the study.

Expenses and payments

Participants will not be paid (an inconvenience allowance) to participate in the study. Car parking expenses will be offered for any visits incurred as a result of participation.

What are the possible disadvantages and risks of taking part?

As mentioned above there will be blood tests and the possibility of a muscle biopsy if you decide to participate in the study. There are separate exclusion criteria for the muscle biopsy the researcher will advise whether these are applicable to you, you will also have the chance to opt out of having a muscle biopsy during the consenting procedure – this will not affect your further participation within the study in any way.

Being told you more than likely have cancer can understandably be a difficult time for you and your family. To participate in this study there would be an additional time commitment during this period as you would have to visit the Royal Derby Hospital campus three or four times a week to train. Previous participants have found this training very beneficial and have commented that the time commitment was manageable.

Being over the age of 65 years there is a higher risk that you could experience an adverse event whilst participating in this study. In particular we may uncover an abnormality with your heart and its function. If this is the case we would treat you as necessary at the time and would also inform your GP of any findings. We have developed a list of conditions which would exclude you from participating in this study; these conditions could put you at undue risk whilst exercising close to your maximum.

Those unaccustomed to exercise may feel some muscle tiredness after a HIIT training session. This will be self-limiting. You will be monitored during your training sessions and medically trained staff will be present. Exercise will be stopped immediately if you feel unwell or experience any chest tightness or pain, light headedness, palpitations or other feelings of discomfort. Your heart tracing and blood pressure will also be monitored

every time you use the exercise bike and your session will be stopped if the medical team have any concerns with these. These sessions will be take place in the University of Nottingham Medical School building (attached to but not technically part of the Royal Derby Hospital) if the medics supervising your sessions deemed it necessary or in an emergency you would be accompanied to the hospital for further investigations or an ambulance would be called.

Body Scans:

All participants will undergo two DXA scans, one at each assessment session. This is an additional exposure to radiation that you would not normally be exposed to in most routine preoperative assessments for a new cancer. You may have already had imaging such as a CT scan to investigate your cancer which carries a much larger radiation burden in comparison to DXA. In real terms a single DXA scan contains less radiation as you would be exposed to in a long haul flight or the equivalent of 2 days normal background radiation. Also this test is widely used in healthcare to screen for osteoporosis and it is even used in pregnant women so it is generally considered very safe for the participant.

Exercise fitness test:

CPEX stands for Cardio-pulmonary exercise testing and is a good way of assessing someone's physical fitness in a standardised manner. It is widely used in healthcare and research. The specific test we will be using within this study is performed on a static exercise bike, you will have monitors attached to your chest and also a face mask, this allows us to monitor your heart and lungs whilst safely performing the test. During the study you will perform three exercise tests which are designed to be quite hard and to take you to above 85% of your maximum heart rate. This will cause you to sweat and become tired; also you will feel tiredness in your legs. You will have a recovery period after the test where we will ensure that you have fully recovered before we would let you go home.

A doctor qualified in advanced life support (ALS) will always be present when you perform a CPEX test.

If you do not perform regular exercise normally you may feel some muscle tiredness after each HIIT training session. This will usually be self-limiting within 48hours. During a HIIT session you will have continuous 12 lead ECG monitoring and intermittent non-invasive blood pressure monitoring during all sessions.

The training will be stopped immediately if you experience any of the following adverse reactions to the exercise including:

- Chest pain or tightness,
- Faintness,
- Sudden pallor,
- Loss of co-ordination,
- Confusion,
- Dizziness,
- Signs of respiratory failure,

- Palpitations,
- Ischaemic changes (>2mm ST depression) on ECG,
- Arrhythmias on ECG (multiple ectopics, heart block)
- Blood pressure drops by greater than 20mmHg from maximum or >250mmHg systolic or >120mmHg diastolic,
- Sudden onset bradycardia with a drop in heart rate of >10bpm from previous,
- Desaturation with a SpO_2 <80%

The American Thoracic Society Statement of Cardiopulmonary Exercise Testing (CPET) confirms that the CPEX test you will undergo is the most widely used test in clinical practice. Clinical indications for CPET testing are broad and include evaluation of exercise tolerance, evaluation of patients with cardiovascular disease, evaluation of patients with respiratory disease, pre-operative evaluation and pulmonary rehabilitation. This test is used widely in patients with other health concerns and long term conditions. There are however risks with any procedure or test. We have performed over 100 CPEX tests in our laboratory with no adverse events. At all times during the exercise and for a period afterwards (until return to baseline) there will be an ALS (Advance Life Support) certified medical practitioner present as well as another research member to assist. The expert consensus is that CPEX is a relatively safe procedure giving a risk of death for all comers during CPET 2 – 5 per 100,000 tests.

<u>High intensity interval training (HIIT):</u>

HIIT is a lot shorter than other types of exercise however you do work harder during this period. Once we have completed the first CPEX test (as above) we will create a personalised exercise program for you designed to work you hard during your training sessions. During a session you will work hard for one minute then have some rest, this is repeated 5 times during the session. After six sessions if you are responding well to the training we may increase the difficulty slightly to ensure that you continue at high intensity throughout the training period. Each training session takes approximately 20 minutes and each visit should take approximately 45 minutes. There would be 3-4 visits a week during the available time period, although we can arrange this for a mutually convenient time.

<u>Blood samples:</u>

We will take blood samples during the study. These are exactly the same as blood samples you may have had in the past and will be performed by a suitably trained medical professional or nurse. They should not hurt unduly; you may have a small bruise and some tenderness for a day or so after the sample. We will only take a small amount of blood each time.

<u>Muscle Biopsy:</u>

We would like to take muscle biopsies from participants within the study. These may allow us to understand more clearly not only the effect cancer has on our muscles but also what affect high intensity training has upon the body and in particular if this type of training has beneficial effects on your muscle growth. The procedure entails numbing the skin with local anaesthetic (on the outside of your thigh), making a small (1cm) incision and taking a small bite of muscle with specialised muscle biopsy forceps.

The wound would then be sutured closed with a stitch which would be removed after 5-7 days. There is a small risk of infection and bleeding and very occasionally some nerve damage associated with the patch of skin although this can heal itself over time. You can also be left with a small scar on the skin. You will have a thorough consenting process in relation to the biopsy should you decide to agree to the procedure. Opting out of this procedure will not affect your participation within the study in any way.

Drinking 'Heavy water':

We have developed a new method of assessing changes in muscle turnover and new protein formation within muscle. This involves participants drinking small amounts of 'heavy water' in which one of the elements which makes up water has been changed to a similar but distinct element which we can then measure in our laboratory. This is called a stable isotope tracer. The amount of heavy water only constitutes a very small amount of your whole body water pool, however it becomes incorporated into new proteins made and therefore we can quantify this later in the laboratory. This method has proven to be safe, the commonest side effect is a temporary dizziness in some people which self resolves.

All procedures will be carried out by suitably qualified medical practitioners (doctors/nurses).

What are the possible benefits of taking part?

The information we get from your participation in this study may help direct future advice given to patients about their physical fitness and may help us to develop exercise programs for those patients undergoing major surgery. This in turn may improve patient outcomes following major surgery.

What happens when the research study stops?

Once the total number of participants have been recruited and complete the study we will enter a phase of data analysis and writing up. This is when we will fully analyse the data and write scientific reports about our findings.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Service (PALS) within the hospital. (PALS contact details: Telephone: 01332785156, Freephone: 08007837691, Email: dhft.contactpals@nhs.net.

Will my taking part in the study be kept confidential?

Your data will be used for the purpose of this study only. If you provide consent then it may be used for future studies only if directly relevant. For example should this initial study lead to future studies your data may be analysed again in the future against a new group of volunteers. Only members of the research team will have access to view identifiable data. We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people

to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database. Any information about you which leaves the institution will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for 1 year after the end of the study so that we are able to contact you about the findings of the study and with your consent for possible follow-up studies (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far will not be erased and this information will still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

We will write to your GP and tell them that you are taking part in the study. We will also inform them of any abnormal findings that we might make as a result of the investigations which are part of the study or which could have an impact upon your planned care for your cancer. If we make a finding which we feel could impact upon your upcoming treatment for cancer we will contact your specialist team directly.

What will happen to any samples I give?

Any samples that you give (blood, saliva, muscle) will be labelled with your unique identity number and then stored within our -80 degrees refrigerators in our laboratory. Blood samples will be hand delivered to the pathology lab at Royal Derby Hospital for analysis.

We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate you agree to this on the consent form). The samples will be stored with a code unique to you and securely at the University of Nottingham under the universities Human Tissue Research Licence (no 12265).

Some of these future studies may be carried out by researchers other than current team of Dr Williams who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authorities codes of practice.

Will any genetic tests be done?

We will, with your consent, take one blood sample in a gene PAX tube for possible future genetic analysis. This is specifically mentioned on the consent

form. The results from these tests will not be routinely fed back to participants.

What will happen to the results of the research study?

We aim to publish our findings widely in scientific and health literature. This may involve presenting it at conferences in the UK and abroad. You will be able to obtain a copy of the final results upon completion of the study.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the University. Personal research funds of Dr John Williams, Mr Jon Lund and Dr Bethan Phillips. This study will also form part of a PhD project for Dr James Blackwell at the University of Nottingham and as such will be included in this thesis.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by a NHS Research Ethics Committee.

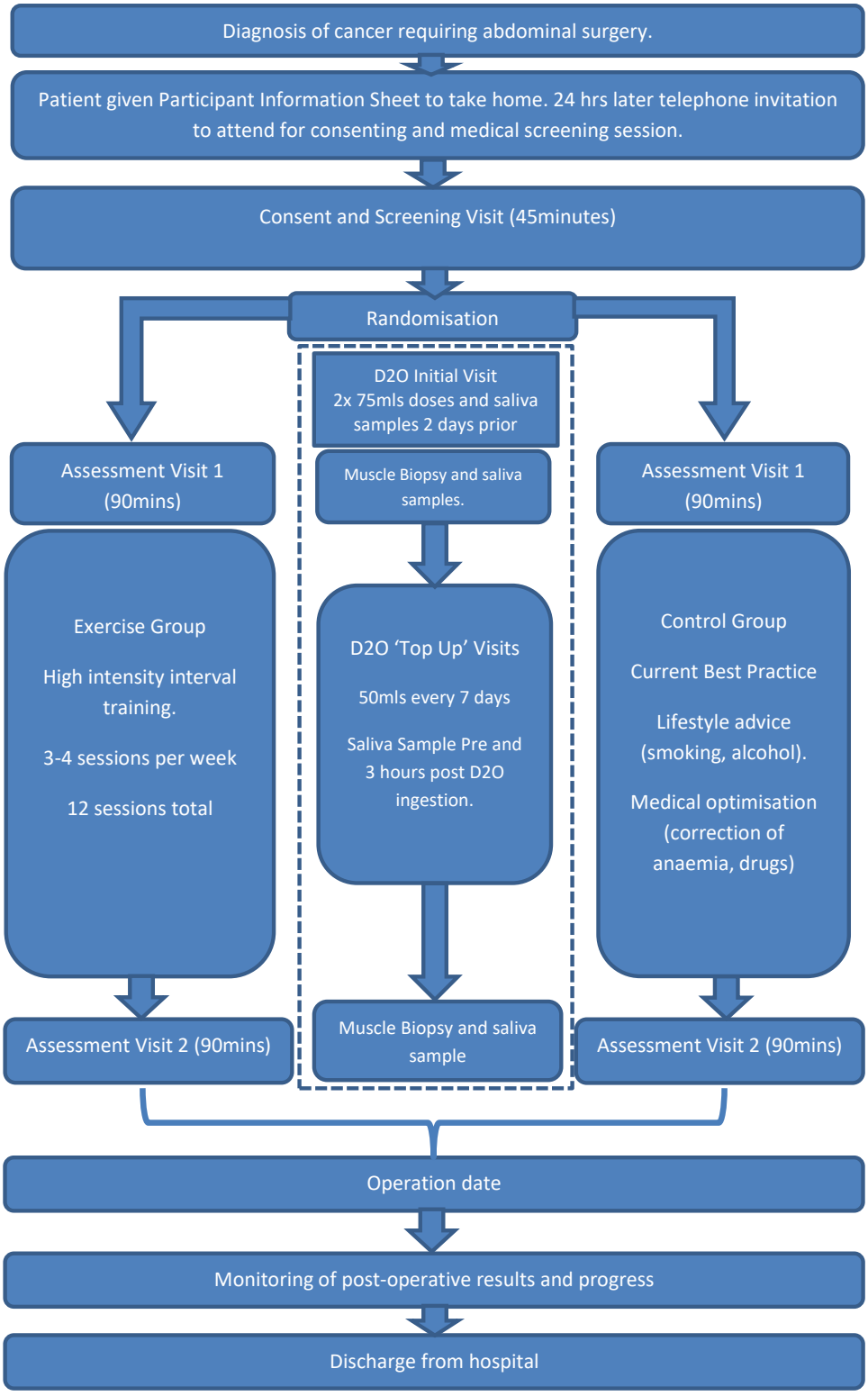
Further information and contact details

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Phone: 01332 724641 Email: john.williams7@nottingham.ac.uk


Diagnosis of cancer requiring abdominal surgery.
Patient given Participant Information Sheet to take home. 24 hrs later telephone invitation to attend for consenting and medical screening session.
Consent and Screening Visit (45minutes)
Randomisation
D2O Initial Visit
2x 75mls doses and saliva samples 2 days prior
Muscle Biopsy and saliva samples.
Assessment Visit 1 (90mins)
Assessment Visit 1 (90mins)
Exercise Group
High intensity interval training.
3-4 sessions per week
12 sessions total
D2O 'Top Up' Visits
50mls every 7 days
Saliva Sample Pre and 3 hours post D2O ingestion.
Control Group
Current Best Practice
Lifestyle advice (smoking, alcohol).
Medical optimisation (correction of anaemia, drugs)
Assessment Visit 2 (90mins)
Muscle Biopsy and saliva sample
Assessment Visit 2 (90mins)
Operation date
Monitoring of post-operative results and progress
Discharge from hospital

8.5 Quality of Life Questionnaires

8.5.1 EuroQoL 5 dimension



Health Questionnaire

English version for the UK

Sample

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Sample

8.5.2 International Physical Activity Questionnaire

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

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

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**
   _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

   _____ **days per week**

   ☐ No moderate job-related physical activity → ***Skip to question 6***

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

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

_____ **hours per day**
_____ **minutes per day**

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

LONG LAST 7 DAYS SELF-ADMINISTERED version of the IPAQ. Revised October 2002.

8.5.3 Dukes activity status index

Duke Activity Status Index

Overview:

The Duke Activity Status Index is a self-administered questionnaire that measures a patient's functional capacity. It can be used to get a rough estimate of a patient's peak oxygen uptake.

Item	Activity	Yes	No
1	Can you take care of yourself (eating dressing bathing or using the toilet)?	2.75	0
2	Can you walk indoors such as around your house?	1.75	0
3	Can you walk a block or two on level ground?	2.75	0
4	Can you climb a flight of stairs or walk up a hill?	5.50	0
5	Can you run a short distance?	8.00	0
6	Can you do light work around the house like dusting or washing dishes?	2.70	0
7	Can you do moderate work around the house like vacuuming sweeping floors or carrying in groceries?	3.50	0
8	Can you do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?	8.00	0
9	Can you do yardwork like raking leaves weeding or pushing a power mower?	4.50	0
10	Can you have sexual relations?	5.25	0
11	Can you participate in moderate recreational activities like golf bowling dancing doubles tennis or throwing a baseball or football?	6.00	0
12	Can you participate in strenuous sports like swimming singles tennis football basketball or skiing?	7.50	0

Duke activity status index =

= SUM(values for all 12 questions)

Interpretation:

• maximum value 58.2

• minimum value 0

estimated peak oxygen uptake in mL/min =

= (0.43 * (duke activity status index)) + 9.6

8.5.4 The Warwick Edinburgh Mental Well-being scale

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS)[1]

Below are some statements about feelings and thoughts.

Please tick the box that best describes your experience of each over the last 2 weeks

STATEMENTS	None of the time	Rarely	Some of the time	Often	All of the time
I've been feeling optimistic about the future	1	2	3	4	5
I've been feeling useful	1	2	3	4	5
I've been feeling relaxed	1	2	3	4	5
I've been feeling interested in other people	1	2	3	4	5
I've had energy to spare	1	2	3	4	5
I've been dealing with problems well	1	2	3	4	5
I've been thinking clearly	1	2	3	4	5
I've been feeling good about myself	1	2	3	4	5
I've been feeling close to other people	1	2	3	4	5
I've been feeling confident	1	2	3	4	5
I've been able to make up my own mind about things	1	2	3	4	5
I've been feeling loved	1	2	3	4	5
I've been interested in new things	1	2	3	4	5
I've been feeling cheerful	1	2	3	4	5

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8.5.5 HIIT Acceptability questionnaire

This questionnaire was designed and developed within this research department. It has previously been used in studies using our HIIT protocol (Boereboom *et al.*, 2016).



HIT Acceptability Questionnaire

Please rate how strongly you agree with the following statements regarding HIT exercise training.

1 – Strongly disagree
2 – Disagree
3 – Neither
4 - Agree
5 – Strongly agree

	Disagree				Agree
The HIT study was adequately explained	1	2	3	4	5
HIT has been an enjoyable experience	1	2	3	4	5
HIT has been a significant time burden	1	2	3	4	5
I would recommend HIT to friends	1	2	3	4	5
HIT has been physically more demanding than I expected	1	2	3	4	5
I would perform the same HIT regime again	1	2	3	4	5
This study has interfered with other aspects of my life due to					
a) the time commitment	1	2	3	4	5
b) the travelling involved	1	2	3	4	5
c) the physical strain	1	2	3	4	5
I believe HIT has improved my fitness	1	2	3	4	5
I have am pleased to have done something to improve my fitness	1	2	3	4	5
I would have preferred to exercise in a group setting	1	2	3	4	5
I would have preferred to exercise at home	1	2	3	4	5

What has been the most challenging part of the HIT training?

What has been the best part of the HIT training?

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