The effect of interval training on clinical and physiological outcomes in patients with inclusion body myositis and mitochondrial disorders

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Abstract

Aim: To assess the effect of high-intensity interval training on clinical and physiological outcomes in adults with inclusion body myositis and mitochondrial disorders, and sedentary adults with no myopathy.

Methods: Subjects completed high-intensity interval training three times per week for 16 weeks on a bicycle ergometer. Training involved short bursts of cycling at a rate of perceived exertion of 16-18/20 on the Borg Scale, interspersed with active recovery intervals. Clinical and physiological outcomes included (i) peak work and aerobic exercise capacity (ii) resting heart rate variability (iii) lower limb strength performance (iv) whole body composition (v) fasted blood profiles (vi) fatigue impact and symptoms of anxiety and depression (vii) overall mental well-being and health-related quality of life.

Results: Subjects with inclusion body myositis and mitochondrial disorders completed ≥ 70% of perceptually regulated high-intensity interval training, showing improvement in mental well-being and peak work capacity. Results also demonstrated the importance of modifiable co-morbidities, such as weight, that may contribute to individual exercise responses and general health status.

Conclusion: Adults with inclusion body myositis and mitochondrial disease were able to safely perform high-intensity interval training with access to clinical support. Improvement in psychological and physiological outcome measures suggests that high-intensity interval training has therapeutic potential as an alternative to moderate-intensity continuous aerobic exercise.
Acknowledgements

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Finally, I would like to thank all of the volunteers who took part in this research study. Their contribution is invaluable to the ongoing research into neuromuscular disorders and exercise therapy.
Author Contribution

Katherine Jones: PhD student; exercise outcome assessor, study recruiter, coordinator and provider of exercise training support.

Dr Grainne Gorman: principal investigator, clinical lead and muscle biopsy specialist.

Dr Roger Whittaker: macro-electromyography specialist.

Dr James Miller: patient recruitment support.

Prof Michael Trenell: study implementation support.

Dr Djordje Jakovljevic: PhD supervisor and physiology support in the exercise laboratory.

Prof Douglass Turnbull: PhD supervisor and principal investigator.

Clinical Research Facility team: Dual energy x-ray absorptiometry technicians, John Wilson, Jan Gebby and Celia Miller; nursing team assistance with electrocardiography, blood tests and muscle biopsy procedures; administrative support for assessment bookings.

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Conferences

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- The UK Neuromuscular Translational Research Conference, Newcastle upon Tyne (2012).

Meetings and seminars

- The MRC Adult Neuromuscular Physiotherapy Meeting (2013).
# Abbreviations

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<td>ACSM</td>
<td>American College of Sports Medicine</td>
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<tr>
<td>ADP</td>
<td>Adenosine diphosphate</td>
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<tr>
<td>AG ratio</td>
<td>Android: Gynoid ratio</td>
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<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>a-v O\textsubscript{2}</td>
<td>Arterio-venous oxygen difference</td>
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<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BP</td>
<td>Blood pressure/Bodily pain</td>
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<td>CK</td>
<td>Creatine Kinase</td>
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<td>CO</td>
<td>Cardiac Output</td>
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<tr>
<td>COX</td>
<td>Cytochrome c oxidase</td>
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<tr>
<td>CPEO</td>
<td>Chronic progressive external ophthalmoplegia</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DEXA</td>
<td>Dual Energy X-ray Absorptiometry</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>DSM-III- R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders - revised third edition</td>
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<tr>
<td>ECG</td>
<td>Electrocardiography</td>
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<tr>
<td>EF</td>
<td>Ejection Fraction</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>EPOC</td>
<td>Excess Post-Exercise Oxygen Consumption</td>
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<td>FH</td>
<td>Family history</td>
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<tr>
<td>FIS</td>
<td>Fatigue Impact Scale</td>
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<td>FVC</td>
<td>Forced Vital Capacity</td>
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<td>GH</td>
<td>General health</td>
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<td>GHQ-12</td>
<td>General Health Questionnaire</td>
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<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HADS-A</td>
<td>Hospital Anxiety and Depression Scale - Anxiety</td>
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<td>HADS-D</td>
<td>Hospital Anxiety and Depression Scale – Depression</td>
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<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
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<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>HIIT</td>
<td>High-intensity interval training</td>
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<td>HR</td>
<td>Heart Rate</td>
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<tr>
<td>IBM</td>
<td>Inclusion body myositis</td>
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<tr>
<td>ICC</td>
<td>Intra-class Correlation Coefficient</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>IHD</td>
<td>Ischaemic heart disease</td>
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<tr>
<td>IPAQ</td>
<td>International Physical Activity Questionnaire</td>
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<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
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<tr>
<td>MCS</td>
<td>Mental Component Summary</td>
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<tr>
<td>MCID</td>
<td>Minimal clinically important difference</td>
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<tr>
<td>MHC 1</td>
<td>Major histocompatibility complex class I</td>
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<tr>
<td>MH</td>
<td>Mental health</td>
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<td>Mi-CK</td>
<td>Mitochondrial Creatine Kinase</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>mtDNA</td>
<td>Mitochondrial deoxyribonucleic acid</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>NICOM</td>
<td>Non-Invasive Cardiac Output Monitoring</td>
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<td>NMDAS</td>
<td>Newcastle Mitochondrial Disease Adult Scale</td>
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<td>NMQ</td>
<td>Newcastle Mitochondrial Quality of life</td>
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<td>OA</td>
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<td>PAC-CCO</td>
<td>Pulmonary Artery Catheter - Continuous Cardiac Output</td>
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<td>Physical Activity Readiness Questionnaire</td>
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<td>PCr</td>
<td>Phosphocreatine</td>
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<td>Physical Component Summary</td>
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<td>PEO</td>
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<td>PF</td>
<td>Physical functioning</td>
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<tr>
<td>P-MRS</td>
<td>Phosphorus magnetic resonance spectroscopy</td>
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<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<td>RE</td>
<td>Role-emotional</td>
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<td>RP</td>
<td>Role-physical</td>
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<td>Abbreviation</td>
<td>Description</td>
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</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>RPE</td>
<td>Rate of perceived exertion</td>
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<tr>
<td>RRI</td>
<td>RR interval</td>
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<td>RVI</td>
<td>Royal Victoria Infirmary</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<td>SEM</td>
<td>Standard error of the mean</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SF</td>
<td>Social functioning</td>
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<td>8-Item Short Form Health Survey</td>
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<td>SF-36</td>
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<tr>
<td>SV</td>
<td>Stroke volume</td>
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<td>TG</td>
<td>Triglyceride</td>
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<tr>
<td>VO₂</td>
<td>Oxygen consumption</td>
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<tr>
<td>VT</td>
<td>Vitality</td>
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<tr>
<td>WEMWBS</td>
<td>Warwick-Edinburgh Mental Well-being Scale</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Chapter 1. Introduction

Background and rationale
‘High-intensity interval training’ (HIIT) is a form of exercise that involves intermittent bursts of vigorous exertion separated by resting or active recovery intervals. This form of training includes both ‘all-out’ sprint interval exercise and near-maximal exercise performed over longer interval periods (Gibala and McGee 2008). Cycling and treadmill-running are popular modes of training but the premise of HIIT applies to a range of sports involving bursts of vigorous activity. In addition to the potential for enhancing exercise performance, HIIT may also provide important health benefits. More than 30 years ago, an influential study by Morris et al. (1980) showed that men who engaged in vigorous sport and physical activity had approximately half the incidence of non-fatal manifestations of coronary heart disease and a 40% lower risk of fatal heart attack in the following 8-9 years when compared with colleagues who reported doing no vigorous activities (Morris, Pollard et al. 1980).

Weston, Wisloff et al. (2013) suggest classifying the intensity of sprint interval training as ≥ 100% of the maximal oxygen consumption (VO$_{2\text{max}}$) and high-intensity interval training as 80-90% of the peak heart rate. However, exercise intensity is not only defined by variable cardiopulmonary parameters but also by muscular power and perceived exertion (Wisløff, Støylen et al. 2007; Perry, Heigenhauser et al. 2008; Guiraud, Juneau et al. 2010; Little, Safdar et al. 2010 and Metcalfe, Babraj et al. 2012). Borg’s 6-to-20 scale provides a gauge of exercise intensity whereby the feeling of exertion is graded from ‘none’ to ‘very, very hard’. Rate of perceived exertion corresponds with exercise workload and approximates the change of a normal heart rate response (Borg 1982 and Gearhart, Becque et al. 2005). This simple monitoring approach is regarded as a valid measure of intensity and as an aid for exercise training progression (Astorino, Allen et al. 2012).
Previous studies demonstrate that high-intensity interval training is a time-efficient method for increasing aerobic exercise capacity in clinical and non-clinical populations (Little, Safdar et al. 2010 and Gibala, Little et al. 2012). In healthy adults, Little, Safdar et al. (2010) have shown that exercise performance can improve after six sessions, involving up to 12 minutes of vigorous exercise in a 20-30 minute period. This training time commitment is at least one hour per week less than public health recommendations for moderate-intensity, continuous aerobic exercise and less than half the recommended vigorous-intensity exercise per week in apparently healthy adults (Garber, Blissmer et al. 2011). Whyte, Gill et al. (2010) also found that cardiopulmonary fitness improved in overweight, sedentary adults, after six low-volume sprint interval sessions. As a time-efficient training approach with potential for functional improvement in other physical activities, sprint or high-intensity interval training could appeal to adults who have difficulty sustaining conventional exercise regimes, as well as to competitive athletes.

Further benefits associated with sprint/high-intensity interval training include increased muscular power, mitochondrial oxidative capacity and subcutaneous fat loss (Linossier, Denis et al. 1993; Weber and Schneider 2002; Burgomaster, Hughes et al. 2005; Duffield, Edge et al. 2006; Burgomaster, Howarth et al. 2008; Perry, Heigenhauser et al. 2008; Trapp, Chisholm et al. 2008; McKay, Paterson et al. 2009; Little, Safdar et al. 2010; Talanian, Holloway et al. 2010; Whyte, Gill et al. 2010; Fisher, Schwartz et al. 2011; Hood, Little et al. 2011; Little, Gillen et al. 2011 and Heydari, Freund et al. 2012). Several studies have demonstrated enhanced sensitivity to insulin following intervention, helping to regulate glucose in the body (Perry, Heigenhauser et al. 2008; Trapp, Chisholm et al. 2008; Babraj, Volgaard et al. 2009; Richards, Johnson et al. 2010 and Hood, Little et al. 2011). There is also evidence to suggest that training can safely improve myocardial function in adults with cardiovascular disease and hyperglycaemia in adults with type II diabetes (Wisløff, Støylen et al. 2007; Gibala, Little et al. 2012 and Shiraev and Barclay 2012).

It is anticipated that exercise benefits assessed with high-intensity interval training could offer therapeutic potential to adults with limited exercise capacity due to muscle weakness and mitochondrial dysfunction, as well as for general physical deconditioning and cardio-metabolic comorbidity. Modest improvement in cardiopulmonary fitness has been reported in a study of community-based HIIT (walking/jogging) for overweight and inactive adults (Lunt, Draper et al. 2014).
However, the existing literature has largely focussed on acute, laboratory-based exercise responses, mixed training modes and assessment of a training effect after less than three months. Subsequently, further research is needed to evaluate the longer-term implications of high-intensity interval training as an alternative to moderate-intensity, continuous exercise programmes.

To date, high-intensity interval training has not been widely studied across patient populations. The dominance of moderate-intensity training programmes perhaps reflects a more conservative approach to managing exercise risk, including musculoskeletal injury and cardiovascular events. Studies have highlighted that vigorous physical activity can acutely and transiently increase the risk of myocardial infarction and sudden cardiac arrest, primarily in persons with structural cardiac disease (Haskell, Lee et al. 2007 and Thompson, Franklin et al. 2007). Yet, arguably, this exercise risk is established through individual assessment. Both authors advocate screening of symptomatic or high-risk patients, as well as the need for appropriate monitoring strategies (Haskell, Lee et al. 2007 and Thompson, Franklin et al. 2007).

In terms of exercise tolerance, it is important to recognise interval training as a distinct alternative to continuous exercise. As such, adults affected by fatigue might be able to tolerate perceptually-regulated high-intensity interval training better than conventional, moderate-intensity, continuous exercise. The experience of fatigue is prevalent and has a profound functional impact on many adults living with neuromuscular disease (Feasson, Camdessanche et al. 2006; Kalkman, Schillings et al. 2007 and Ramdharry, Thornhill et al. 2012), and so its management is integral to exercise prescription. Furthermore, mood and illness perceptions are shown to have a major influence on quality of life in adults with muscle disease, emphasising the therapeutic potential of addressing psychosocial aspects of disease management (Sadjadi, Rose et al. 2010 and Rose, Sadjadi et al. 2012).
Clinical investigations and group discussions in Newcastle have also highlighted some of the difficulties patients with mitochondrial disorders experience with fatigue in relation to managing conventional aerobic exercise. Yet, there is evidence to support improved fatigue symptoms in patients with Charcot-Marie-Tooth disease following an aerobic interval training programme (El Mhandi, Millet et al. 2008). While existing physical activity recommendations acknowledge the different needs of people with chronic health conditions, there are still patients who lack the practical support and, or confidence to become more physically active.

The impact of high-intensity interval training on mental well-being has not as yet been established in adults with neuromuscular disease. However, moderately intense, continuous aerobic exercise has previously been associated with improvement in health-related quality of life (Taivassalo, Gardner et al. 2006) and may alleviate symptoms of psychological distress. Assessing the mental aspects of health status could be critical to understanding the motivation and exercise adherence that contribute to individuals’ performance and functional outcomes. It is postulated that perceptually-regulated high-intensity interval training, combined with assessment of psychological well-being and maximal functional capacity, could support a more individualised approach to exercise therapy in both clinical and non-clinical populations.

**Statement of problem**
Cardiopulmonary benefits of unsupervised, conventional aerobic training may be limited by an inability to sustain continuous exercise at a moderate-intensity in apparently healthy adults and patients with neuromuscular disease.

**Statement of purpose**
To optimise the therapeutic potential of aerobic exercise using perceptually-regulated high-intensity interval training in patients with neuromuscular disease and in sedentary adults with no myopathy.
Overall aim and objectives
This thesis aims to assess the impact of perceptually-regulated high-intensity interval training on different aspects of functional capacity, cardiovascular disease risk and mental well-being in (i) sedentary adults (ii) adults with sporadic inclusion body myositis, and (iii) adults with mitochondrial disease.

The overall aim of the thesis is supported by the following objectives:

- To review existing literature on the safety and efficacy of aerobic exercise training in neuromuscular disease and other clinical and non-clinical populations.
- To investigate the effect of perceptually-regulated high-intensity interval training on a battery of clinical and physiological outcome measures, including: peak work and aerobic exercise capacity; resting heart rate variability; lower limb strength performance; whole body composition; fasted blood profiles; fatigue impact and symptoms of anxiety and depression; overall mental well-being and health-related quality of life.

Hypothesis
Exercise tolerance and cardiopulmonary fitness improve in patients with neuromuscular disease and sedentary adults following 16 weeks of perceptually-regulated high-intensity interval training.
Thesis outline

**Chapters 1 and 2:** introduce the concept and aim of ‘high-intensity interval training’ (HIIT) with reference to existing exercise trials and the current understanding of exercise physiology in health and disease.

**Chapter 3:** describes the HIIT methodology and assessment procedures plus health screening, recruitment and selection of outcome measures.

**Chapter 4:** examines individual responses to HIIT in sedentary adults with no myopathy.

**Chapter 5:** examines individual responses to HIIT in adults with sporadic inclusion body myositis.

**Chapter 6:** examines individual responses to HIIT in adults with mitochondrial disorders.

**Chapter 7:** compares and analyses group responses to HIIT intervention.

**Chapter 8:** evaluates the study findings in relation to existing exercise trials, contributing to the understanding of exercise physiology in neuromuscular disease and identifying implications for future exercise research.
Chapter 2. Literature Review

Background physiology:
Aerobic exercise is physical activity that consists of rhythmical movement with large muscle group involvement (e.g. running, cycling and swimming) (ACSM 1998). During aerobic exercise there is an increased demand on the respiratory system to deliver oxygen to the rest of the body, to remove carbon dioxide produced by metabolically active tissue and to maintain pH homeostasis. Oxygen enters the respiratory system through the mouth and nose and reaches gaseous exchange surfaces in the lungs via the trachea, bronchi and bronchioles. Each terminal bronchiole has an alveolus (air sac) which is highly vascularised, and serves as the site for gaseous exchange. Simple diffusion between the alveoli and capillaries is highly efficient for increasing oxygen uptake during exercise, moving the gas along a partial pressure gradient (Katch 2011).

Bassett and Howley (2000) define the maximal oxygen uptake as the highest rate at which oxygen can be taken up and utilised by the body during severe exercise. This concept of maximal oxygen uptake has framed the limits of cardiopulmonary capacity for oxygen transport since its introduction by eminent physiologists, Hill and Lupton (Hawkins, Raven et al. 2007). More than ninety years later, oxygen uptake measurements continue to serve as a primary outcome for assessing aerobic exercise training effect. Potential adaptations in the pulmonary circulation are not yet fully understood but the breathing responses during exercise may reflect neural modulation with training intervention (Babb, Wood et al. 2010 and Babb 2013). In acutely hypoxic conditions, neural responses are stimulated that redress homeostasis, such as hyperventilation. Glomus cells located in the carotid bodies are thought to contain specific K+ -channel proteins or heme proteins that may be mitochondrial in origin, and which function as oxygen sensors (Prabhakar and Peng 2004). The airways themselves are thought to remain largely resistant to an exercise training effect despite potential for alteration in lung structure with chronic hypoxia (Dempsey 2006). However, there is evidence of a correlation between maximal oxygen consumption and a training-induced increase in muscle capillary density that can enhance the arterio-venous oxygen difference (Bassett and Howley 2000).
Choi, Prasad et al. (2013) have found that vascular walls of patients with coronary artery disease and endothelial dysfunction have higher lipid content than in patients with normal endothelial function. These findings support the contribution of regional dysfunction in cells lining the capillary lumen during atherosclerotic plaque formation. While no association was identified between endothelial function and the microcirculation, therapeutic interventions that alter the blood lipid content could be critical for maintaining the integrity of the vascular bed. In particular, high-density lipoprotein is understood to have a cardio-protective effect through the removal of cholesterol from atherosclerotic lesions (De Nardo, Labzin et al. 2014). In vivo and in vitro studies of skeletal muscle cells have indicated that increased high-density lipoprotein is associated with enhanced mitochondrial ATP synthesis and glucose uptake, implicating its role in muscle mitochondrial metabolism and glucose homeostasis (Lehti, Donelan et al. 2013).

As a potential therapy for dyslipidaemia and hyperglycaemia, there is some evidence to support the effectiveness of aerobic exercise in raising the circulating levels of high-density lipoprotein cholesterol and lowering cardiovascular disease risk factors, including triglyceride, low-density lipoprotein cholesterol and glucose (Kelley, Kelley et al. 2004; Kelley and Kelley 2006 and Little, Gillen et al. 2011). However, authors emphasise that additional dietary intervention and, or pharmacological therapy may be necessary to modify the lipid content to within recommended levels (Kelley, Kelley et al. 2004 and Kelley and Kelley 2006).

Following diffusion into the lung capillaries, oxygen is moved through the vascular system by associating with haemoglobin. Changes in temperature and pH facilitate both association and dissociation of oxyhaemoglobin, which allows the oxygen to be transported and used by the rest of the body. The difference in blood oxygen leaving and returning to the heart is referred to as the arterio-venous oxygen difference (a-v O₂). Aerobic exercise increases the a-v O₂, enhancing oxyhaemoglobin dissociation and facilitating greater oxygen delivery to tissue (Detry, Rousseau et al. 1971; Blomqvist and Saltin 1983; De Cort, Innes et al. 1991 and Katch 2011). Within skeletal muscle, the oxygen saturates myoglobin molecules, which in turn release oxygen to mitochondria, where it functions as an electron acceptor in oxidative metabolism (Katch 2011).
Continual contraction (systole) and relaxation (diastole) of cardiac muscle allows the heart to expel oxygenated blood and refill with deoxygenated blood through a separate systemic and pulmonary circulation. During physical activity, skeletal muscle vasculature becomes dilated and the heart (myocardium) delivers more blood under a higher systolic pressure. The high pressure pumping action of the myocardium is facilitated by inherent electrical stimulation. In addition, myocardial stimulation is also under autonomic control through sympathetic (vagal) and parasympathetic (β adrenergic) innervation. These antagonistic influences from the brain stimulate hormone release that can alter heart rate, myocardial contractility, vasodilation and vasoconstriction. Specifically, the sympathetic innervation is associated with increased myocardial activity, while parasympathetic stimulation operates a cardio-inhibitory response. Endurance training is understood to enhance resting parasympathetic activity and heart rate variability, which may be crucial for training-induced autonomic regulation and lowering of the cardiovascular disease risk (Carter, Banister et al. 2003 and Katch 2011).

Together, the neural pathways help to regulate responses to various stressors, such as exercise. In addition to training bradycardia, reduced submaximal heart rate and enhanced stroke volume provide further evidence of cardiovascular training adaptations (Blomqvist and Saltin 1983; Bassett and Howley 2000 and Carter, Banister et al. 2003). As a measure of cardiopulmonary fitness, the maximal oxygen consumption may also be affected by pulmonary diffusing capacity, blood-oxygen carrying capacity and skeletal muscle properties (Blomqvist and Saltin 1983 and Bassett and Howley 2000). Despite a large genetic component in cardiopulmonary fitness (Wei, Kampert et al. 1999), it has been shown that men who have maintained or increased their fitness levels exhibit a lower risk of cardiovascular disease and all-cause mortality at follow-up approximately five years later, when compared with chronically unfit men (Blair, Kohl et al. 1995).
The neurones innervating skeletal muscle (motor units) facilitate voluntary muscle contraction for movement. This action is initiated through electrical impulses travelling from the brain via the spinal cord into the peripheral nervous system. The electrical impulses, or action potentials, synapse at a neuromuscular junction before entering the musculoskeletal system (Enoka and Stuart 1992; Enoka and Duchateau 2008; Enoka, Baudry et al. 2011 and Katch 2011). Motor control varies across different effector muscle groups in relation to the ratio of muscle fibres to each neurone. As such, the extra-ocular muscles exhibit fine motor control with a much lower ratio of muscle fibres per neurone compared with the large limb muscle groups (Yu Wai Man, Chinnery et al. 2005).

The effector muscles themselves consist of bundles of uniform fibres, surrounded by mitochondria and glycogen granules. These features support the energetic demands of muscle contraction, ultimately driven by the hydrolysis of high-energy phosphate bonds in molecules of adenosine triphosphate (ATP). Phosphagens including ATP and phosphocreatine (PCr) provide an immediate energy source in short bursts of intense physical activity. However, over several minutes of intense exercise, the energy is derived more from the glycogen stored in the muscle. Oxidative metabolism, involving the mitochondria surrounding muscle fibres is understood to be the main source of ATP during prolonged, light to moderate-intensity continuous exercise (Katch 2011). Fatty acids and carbohydrates in food serve as the primary energy substrates for mitochondria (Nardin and Johns 2001).

As loci for the essential biochemical pathways involved in oxidative metabolism, mitochondria are ubiquitous subcellular organelles throughout the human body (Greaves, Reeve et al. 2012). Formation of ATP occurs along an electron transport chain through a series of oxidation (loss of electrons) and reduction reactions. This transfer of electrons involves five complexes in the inner membrane of each mitochondrion plus electron shuttles (Coenzyme Q and Cytochrome c), producing an electrochemical gradient (Leonard and Schapira 2000; Nardin and Johns 2001; Schoser and Pongratz 2006). The transfer of electrons is coupled with transfer of potential energy to form ATP from ADP in a process of oxidative phosphorylation. Oxygen is the final electron acceptor in the electron transport chain. The majority of ATP is understood to be reformed in this way, as part of a respiratory chain (Greaves, Reeve et al. 2012).
Formation of the mitochondrial respiratory chain is under the control of nuclear and mitochondrial genomes with the exception of complex II, which is nuclear-encoded only (Schon 2000; McKenzie, Liolitsa et al. 2004 and Schoser and Pongratz 2006), as represented in Figure 2-1. Located in the inner mitochondrial matrix, the mitochondrial genome has 13 genes that encode protein subunits in the electron transport chain and 37 genes involved in ATP production (Schon 2000; Schaefer, Taylor et al. 2001; McKenzie, Liolitsa et al. 2004; Chinnery, Majamaa et al. 2006 and Copeland 2012). There are multiple copies of the mitochondrial genome per mitochondrion and hundreds to thousands of copies in each cell (Greaves, Reeve et al. 2012). It is anticipated that endurance performance may be enhanced by increasing the mitochondrial oxidative enzyme content in muscle. Both mitochondrial volume and mitochondrial enzyme content have been shown to increase following endurance training intervention (Blomqvist and Saltin 1983; Holloszy and Coyle 1984 and Bassett and Howley 2000).

While mitochondrial oxidative capacity may not necessarily correspond with increments in the maximal oxygen consumption (Bassett and Howley 2000), the occurrence of Excess Post-Exercise Oxygen Consumption (EPOC) above resting values could provide further insight into muscle metabolism. EPOC has previously been associated with an accumulation of lactate, providing a carbon reservoir for oxidative metabolism and a possible substrate for glycogen repletion (Gaesser and Brooks 1984; Brooks 2002 and Brooks 2009). Meanwhile the exponential decline in oxygen consumption that is observed following intense exercise has been referred to as a ‘thermic effect of activity’ (LaForgia, Withers et al. 2006) and associated with rapid phosphagen replacement in muscle. A number of other factors may also contribute to EPOC during exercise recovery, including the rate of ADP formation from ATP in creatine kinase reactions (Gaesser and Brooks 1984).
Differences in composition of muscle fibres can affect how ATP is generated by cells. The two main fibre types are slow and fast twitch fibres but there are also intermediate fibres that share properties of both fibre types. The distribution and function of these fibres are genetically-determined in part, varying across muscles and between individuals. Specific features of slow twitch fibres include increased number and size of mitochondria and increased oxidative enzymes, which support aerobic exercise performance. These muscle fibres are smaller than fast twitch fibres, which preferentially use anaerobic energy pathways. Typically, the slow oxidative twitch fibres (type 1) are innervated by small motor neurones that are fatigue-resistant, whereas the fast glycolytic twitch fibres (type 2) are innervated by medium to large motor neurones and fatigue more readily (Yu Wai Man, Chinnery et al. 2005 and Katch 2011).

During muscular fatigue there is a reduction over time in the force-generating capacity of the neuromuscular system (Bigland-Ritchie, Johansson et al. 1983). This decline in force generation can be measured through strength assessment and electromyography. However, it is proposed that the study of muscle fatigue must consider the processes contributing to acute, overall performance impairment, which also includes effort perception (Enoka and Stuart 1992).

The development and widespread application of Borg’s scale of perceived exertion demonstrates the relevance of subjective symptoms in exercise performance (Borg 1982). In parallel with this exploration into exercise perception, the Canadian psychologist, Bandura, formulated the concept of ‘self-efficacy’ as a component of social cognitive theory. This concept represented the persistence in, and mastery of activities that could be perceived as threatening in some way (Bandura 1977). Irrespective of the roots of self-efficacy, meta-analyses of various lifestyle risk factors for mortality clearly demonstrate the value of social relationships beyond self-reported quality of life; over 7-8 years, the increased likelihood of survival associated with having so-called ‘adequate’ social relationships is reported to be comparable with smoking cessation in coronary heart disease (Holt-Lunstad, Smith et al. 2010).
In addition to health perceptions, exercise performance is also affected by energy intake and nutrition. Low energy intake can increase the risk of fatigue, injury and illness (Rodriguez, Di Marco et al. 2009). However, regular exercise can also help to improve the energy balance for intake and expenditure (Jakicic and Otto 2005), supporting weight control and maintenance of muscle mass and bone mineral density (Jakicic and Otto 2005 and Rodriguez, Di Marco et al. 2009).

**Background pathophysiology:**
Neuromuscular disease encompasses a broad spectrum of pathology that is not yet fully understood. This thesis specifically focuses on patients with myopathy associated with primary and secondary mitochondrial dysfunction, in the form of mitochondrial disease and sporadic inclusion body myositis. There is currently no cure for either of these neuromuscular conditions and clinical management is largely supportive intervention (Chinnery, Majamaa et al. 2006; Engel and Askanas 2006; Askanas and Engel 2008; Askanas, Engel et al. 2009; Benveniste, Guiguet et al. 2011 and Pfeffer, Majamaa et al. 2012).

Mitochondrial disorders are reported to affect at least 1 in 8000 of the general population (Chinnery, Majamaa et al. 2006). These disorders arise from genetic mutations encoding proteins within the mitochondria (Copeland 2012). It is thought that the mitochondrial DNA (mtDNA) may also be particularly susceptible to further mutations or clonal expansion of existing mutations in response to a leakage of reactive oxygen species from the respiratory chain or to DNA polymerase γ errors (Greaves, 2012). Clinical signs of mitochondrial disorders manifest where the proportion of mutant to wild-type (normal) mitochondrial DNA per cell (heteroplasmy) is above a critical threshold that varies across different tissues (DiMauro 2001; DiMauro and Schon 2001; Schaefer, Taylor et al. 2001; McKenzie, Liolitsa et al. 2004 and Greaves, Reeve et al. 2012). Subsequently, mitochondrial disease presents with a highly varied clinical phenotype.
In addition to genetic mutations, evidence of mitochondrial abnormalities may include: low activities of oxidative enzymes; abnormal proliferation of mitochondria (ragged red fibres), as shown in Figure 2-2 A; the presence of cytochrome c oxidase deficient fibres, as shown in Figure 2-2 B and C, and crystalline inclusions containing mitochondrial creatine kinase (Mi-CK) (Stadhouders, Jap et al. 1994; Lee and Brazis 2002; Schoser and Pongratz 2006 and Diaz and Moraes 2008). Highly ordered Mi-CK inclusions have also been observed in cultured rat cardiomyocytes that are depleted of creatine; supplementation with creatine is reported to reverse the emergence of these inclusions (Wyss and Wallimann 1994). However, serum creatine kinase levels are expected to remain normal or only mildly elevated in mitochondrial myopathies, as an indicator of cell necrosis (Nardin and Johns 2001).

Possible mtDNA protection of muscle creatine may indicate creatine supplementation for age-related mutagenesis and improving muscle strength (Tarnopolsky and Martin 1999 and Berneburg, Gremmel et al. 2005). But aside from the evidence for improving performance, exercise as therapy is also supported by the stimulation of increased mitochondrial volume, enhancing oxidative capacity (Holloszy and Coyle 1984 and (Katch 2011).
While the manifestations of mitochondrial dysfunction may be systemic, extra-ocular neurological signs are reported to be the most common clinical presentation (Leonard and Schapira 2000 and Schoser and Pongratz 2006). Chronic progressive external ophthalmoplegia and ptosis are typical neuromuscular features, reflecting the particularly high energetic demands of extra-ocular muscles (Bau and Zierz 2005 and Yu Wai Man, Chinnery et al. 2005). Patients’ functional status may also be compromised in relation to neuromuscular manifestations of mitochondrial disease, such as myopathy, ataxia and muscle-related or generalised fatigue.

Sporadic inclusion body myositis (IBM) and, to a lesser degree the ageing process, appear to be marked by secondary mitochondrial dysfunction (Argov, Taivassalo et al. 1998; Needham and Mastaglia 2007; Boengler, Schulz et al. 2009 and Schon, DiMauro et al. 2012). Characteristic mitochondrial abnormalities include the presence of ragged red fibres, cytochrome c oxidase deficient fibres, as shown in Figure 2-3, and hyaline eosinophilic inclusions (Oldfors, Larsson et al. 1993; Oldfors, Moslemi et al. 1995 and Askanas and Engel 2008). Oldfors, Larsson et al. (1993) found that the cytochrome c oxidase deficient fibres were associated with multiple deletions in mitochondrial DNA. These multiple deletions can also be observed in aged muscle and tissue affected by mitochondrial disorders, such as autosomal dominant progressive external ophthalmoplegia (adPEO) (Oldfors, Moslemi et al. 2006 and Chinnery, Majamaa et al. 2006). However, no nuclear mutations were identified in a small number of IBM patients who were assessed for specific gene mutations associated with impaired mitochondrial maintenance and multiple DNA deletions (POLG, ANT1 and C10orf2) (Oldfors, Moslemi et al. 2006).

Figure 2-3. Evidence of mitochondrial dysfunction in inclusion body myositis: sequential cytochrome c oxidase and succinate dehydrogenase (COX/SDH) histochemistry demonstrating occasional COX-deficient fibres (blue) in the quadriceps muscle of a patient with inclusion body myositis. This image was included with permission from Dr K. Rygiel and Prof D.M. Turnbull.
IBM also differs from a primary mitochondrial myopathy in the findings from phosphorus magnetic resonance spectroscopy. Results from IBM patients with variable mitochondrial dysfunction have indicated normal recovery rates of ADP following exercise compared with controls; in contrast, patients with primary mitochondrial myopathies are reported to have elevated ADP during recovery compared with controls (Argov, Taivassalo et al. 1998; Lodi, Taylor et al. 1998 and Trenell, Sue et al. 2006). Yet, it is also postulated that ATP and the ATP/ADP ratio may not reliably measure cellular energy levels due to homeostatic regulation (Berneburg, Gremmel et al. 2005).

IBM is reported to be the most common idiopathic inflammatory myopathy in adults over 50 years old (Amato and Barohn 2009) and more frequently reported in men (Dimachkie and Barohn 2012). The condition has been estimated to affect between three and five people per million in the Netherlands and Sweden (Amato and Barohn 2009) and three to four adults per 100,000 aged over 50 years in Western Australia (Phillips, Zilko et al. 2000); evidence for increasing IBM prevalence has primarily been associated with improved case ascertainment (Needham, Corbett et al. 2008).

The pathogenesis of IBM is not yet fully understood, featuring inflammatory changes alongside autoimmune and degenerative features (Dalakas 2010 and Greenberg 2010). IBM is an acquired inflammatory myopathy, associated with selective and progressive weakness and atrophy (Phillips, Cala et al. 2001 and Amato and Barohn 2009). Oldfors, Moslemi et al. (2006) suggest that the secondary mitochondrial dysfunction is likely to contribute to muscle weakness and atrophy in those patients with a high number of cytochrome c oxidase-deficient fibres. Meanwhile, an end-stage study of patients with IBM found that most deaths were attributed to respiratory problems (Cox, Titulaer et al. 2011).

Internationally proposed criteria for potential IBM diagnosis include: disease duration over 12 months; age at disease onset ≥ 45 years; serum creatine kinase levels no greater than 15-fold above the upper limit of normal; knee extension weakness ≥ hip flexion weakness and, or finger flexion weakness ≥ shoulder abduction weakness. In addition, pathological features of IBM include: endomysial inflammatory infiltrate; upregulation of MHC class I; rimmed vacuoles and protein accumulation or 15-18 nm filaments (Rose 2013). Earlier criteria proposed for IBM diagnosis omit an elevated serum creatine kinase level, however (Benveniste and Hilton-Jones 2010 and Hilton-Jones, Miller et al. 2010).
As evidence for degenerative change in IBM, the rimmed vacuoles in muscle are found to contain a number of proteins that are also found in cerebral plaques in Alzheimer’s disease, such as prions, hyperphosphorylated tau and apolipoprotein e (Garlepp and Mastaglia 1996). Dalakas (2010) proposed that effective therapy must suppress both the degenerative processes and immunopathogenesis, irrespective of the initiating conditions. Since then, blood diagnostic investigations have identified a potential biomarker for IBM in the form of an autoantibody against cytosolic 5’-nucleotidase 1A; this enzyme, also a phosphotransferase, is thought to be involved in DNA repair metabolism (Larman, Salajegheh et al. 2013) and could perhaps provide further insight into the role of mitochondria in the disease process.

In a study of 32 IBM cases, muscle weakness, disease duration and level of serum creatine kinase all correlated with the number of fatty infiltrated muscles although not with inflamed muscles. Patterns of muscle weakness and atrophy showed some asymmetry and marked involvement of muscles in the upper anterior leg (Cox, Reijnierse et al. 2011). This knee extensor weakness can particularly affect mobility and functional status, contributing to increased dependence on assistive technology and eventual wheelchair dependence for many patients (Cox, Titulaer et al. 2011). In addition, the effects of obesity and physical inactivity on musculoskeletal and cardiopulmonary function could compound health problems in progressive myopathies, such as IBM. Exercise has been advocated for improving function and health-related quality of life in patients with idiopathic inflammatory myopathies but there is currently a lack of consensus guidelines on supportive management in IBM (Alexanderson 2012 and Rose 2013).
Moderate-intensity continuous cycling in non-clinical populations

Many studies have shown an improvement in aerobic exercise tolerance and capacity following conventional, moderate-intensity aerobic cycling intervention (Crouse, O'Brien et al. 1997; Hepple, Mackinnon et al. 1997; Short, Vittone et al. 2005; Zarins, Wallis et al. 2009; Harber, Konopka et al. 2009; Finucane, Sharp et al. 2010; Hiruntrakul, Nanagara et al. 2010; Konopka, Douglass et al. 2010; Lovell, Cuneo et al. 2010; Stasiulis, Mockiene et al. 2010; Murias, Kowalchuk et al. 2011 and Harber, Konopka et al. 2012). However, there is a lack of randomised controlled trials that address effective exercise ‘dose’ (i.e. duration, intensity and frequency of exercise) on physiological and psychological outcomes. In part, this limitation may be due to study logistical constraints. The following critique refers to specific studies that have contributed to the evidence base for moderate-intensity continuous cycling in non-clinical populations.

More than twenty years ago, Blumenthal et al. (1989) investigated the cardiovascular and behavioural effects of different types of exercise in healthy older males and females. Subjects aged between 60 and 83 years old were randomly allocated to 16 weeks of aerobic exercise training (cycle ergometry and walking/jogging), a yoga/flexibility class or a control group (usual activity but no aerobic exercise). Twelve of the 113 subjects were excluded for cardiorespiratory conditions (ECG changes during exercise testing; evidence of coronary artery disease; asthma; uncontrolled hypertension; beta-blocker medications and a lung operation) or due to difficulties attending training and assessment. Another four participants were unable to attend review tests for reasons unrelated to training intervention (Blumenthal, Emery et al. 1989).

Both aerobic and yoga/flexibility exercise programmes involved taking part in supervised training for one hour sessions but the frequency of these sessions was three times per week for aerobic exercise and at least twice per week for yoga/flexibility. No progression in either training group was indicated although rate of perceived exertion and heart rate were monitored to maintain aerobic exercise intensity at 70% of the maximum heart rate reserve. It is unclear what the intensity of the yoga/flexibility exercise was in comparison. Thus, the effects of both exercise intensity and frequency may have confounded this study’s comparison of exercise type effectiveness. The apparent lack of progression in training might also limit participants’ motivation to
exercise. While yoga/flexibility exercise was delivered in a class, it is not stated whether the aerobic exercise was one-to-one or also delivered in a class; this factor could influence study outcomes and exercise adherence. Nevertheless, 96% of subjects were reported to have adhered across the interventions in this study. Blumenthal et al. (1989) found a significant mean increase in peak absolute aerobic capacity (11.6%) in the aerobic exercise group only. It remains unclear how this improvement in aerobic capacity translated into a functionally significant effect as there were no functional outcome measurements included in the study (Blumenthal, Emery et al. 1989).

The exercise groups and a non-training group all experienced a small significant weight loss, while only the aerobic exercise group demonstrated a significant reduction in cholesterol. In addition, there was also a significant reduction in symptoms of depression for male subjects following aerobic exercise intervention according to the Center for Epidemiologic Studies Depression Scale. Study authors do not indicate whether the improvement in psychological symptoms correlated primarily with weight loss or improved aerobic fitness (Blumenthal, Emery et al. 1989).

In summary, this study identified cardiopulmonary benefits and some improvement in depressive mood following aerobic training in otherwise healthy older adults (Blumenthal, Emery et al. 1989). However, the quality of the evidence was limited by a lack of accounting for differences in exercise intensity and frequency between training groups.

Other exercise studies have often focussed on the physiological impact of aerobic exercise intervention. Finucane et al. (2010) investigated the impact of 12 weeks of supervised cycling training in older adults (36 x one hour sessions at 50-70% maximal work) and found a significant improvement in subjects’ maximal work capacity compared with a non-trained, control group (Finucane, Sharp et al. 2010). Results also showed significant reductions in the trained adults’ body weight and waist circumference. However, there were no significant differences found in average lean mass, fat mass, lipid profiles, fasting glucose or HbA1c levels. There were also no significant changes in health-related quality of life following exercise intervention according to mental and physical component summaries of the SF-8 questionnaire. However, further analyses indicated improvement in the social functioning domain of health-related quality of life following aerobic exercise intervention. These findings were based on 50 exercising adults and 50 non-exercising adults who were screened at
baseline for diabetes, untreated or unknown ischaemic heart disease and any medical condition that would prevent them from cycling unaided for 30 minutes. Four hundred and ninety one others were approached but declined, did not respond or were excluded from the study (Finucane, Sharp et al. 2010).

Finucane et al. (2010) suggest that body scans and muscle biopsy procedures may have been major factors in the low recruitment rate. But it is also important to highlight that only 20% of exercisers attended all of the training sessions. Five subjects attended less than 32% of the training programme, including three subjects who failed to start the programme (Finucane, Sharp et al. 2010). This level of adherence is expected to influence study outcomes and could have negative implications for adherence to unsupervised exercise in older adult populations. Qualitative studies of exercise participation in older adults have highlighted a number of potential barriers to exercise, including health issues and environmental and social factors, such as access to classes and peer support (Guerin, Mackintosh et al. 2008).

Harber, Konopka et al. (2009 and 2012) undertook much smaller studies of older adults and reported 100% exercise compliance. Significant improvements were found in the peak absolute and relative oxygen consumption and peak work capacity, as well as knee extensor power and quadriceps muscle volume. In addition, quadriceps biopsy showed significantly increased MHC I (slow twitch) myofibre size. However, participation was subject to extensive exclusion criteria. At baseline all subjects were screened for (1) BMI ≥ 28 kg/m² (but not obesity, classified as a BMI of ≥ 30 kg/m²) (2) diabetes (3) uncontrolled hypertension (4) cancer or treatment for cancer in the past five years (5) coronary artery disease (6) cardiovascular disease (7) abnormal thyroid function (8) resistance or aerobic training more than once per week for at least 20 minutes over the previous year (9) regular or chronic use of non-steroidal anti-inflammatory medication (10) any condition that presents a limitation to exercise training: severe arthritis, chronic obstructive pulmonary disorder, neuromuscular disorder, moderate or severe cognitive impairment, Alzheimer’s disease, vertigo or dizziness (Harber, Konopka et al. 2009 and Harber, Konopka et al. 2012). This breadth of study exclusion criteria could exclude a substantial proportion of today’s older adult population, limiting the application of study findings.
In a study of healthy older males (aged 70-80 yrs), Lovell et al. (2010) reported significant improvements in maximal relative oxygen consumption, leg strength and power following 16 weeks of supervised cycling intervention (three x 30-45 minutes per week at 50-70% maximal oxygen consumption) (Lovell, Cuneo et al. 2010). Average body mass and proportion of body fat were also significantly lower post-intervention. At baseline, these healthy older adults were free from known cardiovascular and respiratory disease and used no medications at the time of the study. Aerobic fitness improvements occurred with approximately 98% attendance of exercise sessions (Lovell, Cuneo et al. 2010).

In another study of healthy older males (aged 65-74 yrs), there were similar improvements in the peak oxygen consumption recorded following resistance and aerobic exercise programmes. However, leg muscle biopsies showed a significant increase in capillary density following aerobic training only (Hepple, Mackinnon et al. 1997). Such exercise-induced capillarisation is found to occur on the same time-scale for older and younger men (aged 69 ± 7 yrs vs. 22 ± 1 yr) (Murias, Kowalchuk et al. 2011).

In postmenopausal females (aged 50 ± 1 yrs), Zarins, Wallis et al. (2009) reported significant improvements in peak work capacity and peak relative and absolute oxygen consumption following 12 weeks of cycling intervention (5 x one hour sessions per week at 65% peak oxygen consumption). Exercising blood lactate levels and resting heart rate were also significantly lower post-intervention, supporting an aerobic training effect (Zarins, Wallis et al. 2009).

Kelley, Kelley et al. (2004) performed a meta-analysis of randomised controlled trials between 1955 and 2003 to assess for change in the lipid profile following aerobic exercise intervention. These trials involved at least eight weeks of aerobic dance, walking, jogging, cycling and, or stair-climbing by adult females. A random effects model showed significant improvements across the trials in triglyceride (-5%), high-density lipoprotein (+3%), low-density lipoprotein (-3%) and total cholesterol (-2%). Similarly, increased high-density lipoprotein and reductions in triglyceride and total cholesterol were also later reported in a meta-analysis of randomised controlled aerobic exercise trials involving men (Kelley and Kelley 2006). The clinical significance of such changes is not yet known except for an association between low-density lipoprotein and major cardiac events. Based on short-term trials, it has been reported
that for every 1% decrease in low density lipoprotein there is 1% reduction in the risk of myocardial infarction and coronary heart disease death (NCEP 2002).

In a study by Short, Vittone et al. (2005), ‘healthy’ adults were represented by adults who performed less than 30 minutes of exercise on two or fewer occasions per week over nine months. Selected subjects (aged 21-87 yrs) completed 16 weeks of progressive cycling training (20-40 minute sessions x 3-4 per week at 70-80% peak heart rate) and reported more than 90% adherence. In addition to significant improvements in absolute aerobic capacity and knee extensor force, there was a small reduction in weight despite instruction to maintain body weight at the beginning of the study. Nevertheless, the proportion of fat and fat-free mass did not change significantly following exercise intervention. There were also no significant physiological changes found in a usual activity plus flexibility exercise control group. While the findings are consistent with other studies, the rationale for selecting low active adults and excluding adults with a BMI of more than 32 kg/m² was not clear; obesity is typically classified as a BMI of ≥ 30 kg/m² (WHO 2004).

Hiruntrakul, Nanagara et al. (2010) defined ‘sedentary’ as performing less than one hour per week of exercise over the previous 12 months. Nineteen young, sedentary males (aged 18-25 years) completed 12 weeks of cycling exercise intervention. The training programme consisted of one hour per week of cycling at 60% maximal oxygen consumption, including warm-up and warm-down. As found in previous studies, maximal relative aerobic capacity increased and resting heart rate decreased significantly post-intervention compared with a non-exercising control group. Upper and lower limb strength measurements also supported improved fitness performance. Meanwhile, body weight and proportion of body fat remained unchanged, contrasting with findings from the study of low active adults by Short, Vittone et al. (2005) (Hiruntrakul, Nanagara et al. 2010).

Despite evidence presented in the meta-analysis by Kelley, Kelley et al. (2004), Crouse, O'Brien et al. (1997) reported no significant changes in the lipid profile of males with hypercholesterolaemia following aerobic exercise intervention. However, transient changes in lipid content were recorded during the study. Absolute aerobic exercise capacity improved significantly and the subjects’ experienced weight loss even though they were instructed to maintain usual dietary habits (Crouse, O'Brien et al. 1997).
In summary, cycling exercise interventions consistently appear to improve peak work capacity and oxygen consumption as measures of exercise tolerance and aerobic fitness. These exercise benefits are gained across different study populations and with different training regimes. Diet and weight change are fundamental factors that have been difficult to control in exercise studies. There are also differences in study exclusion criteria across non-clinical populations, which may be expected to affect exercise outcomes. At present, the benefits of aerobic exercise are gauged primarily on physiological change. Assessing the outcomes in relation to functional and self-reported outcomes may help to determine the health value of aerobic exercise programmes.
**High-intensity interval cycling in non-clinical populations**

Similarly to conventional cycling training, high-intensity interval (HIIT) programmes have been associated with significant increments in peak workload and oxygen consumption, as measures of improved aerobic exercise capacity (Weber and Schneider 2002; Duffield, Edge et al. 2006; Edge, Bishop et al. 2006; McKay, Paterson et al. 2009; Perry, Heigenhauser et al. 2008; Little, Safdar et al. 2010; Talanian, Holloway et al. 2010; Leggate, Carter et al. 2012 and Jacobs, Flück et al. 2013). To date, these HIIT programmes have mostly involved less than eight weeks of supervised exercise in physically active and healthy adults.

An eight-week study by Duffield, Edge et al. (2006) investigated the effects of three times per week of supervised HIIT in ten young and physically active females (aged 20 ± 4 yrs). The results demonstrated increased absolute maximal oxygen consumption with no significant change in body mass. This programme consisted of two minute intervals cycling at 130-180% of the baseline power at lactate threshold, which were repeated 4-12 times with one minute rest intervals.

McKay, Paterson et al. (2009) investigated high-intensity interval training at 120% of the baseline maximal work rate, indicating supramaximal exertion The training was completed over 19 days and involved one minute of supramaximal cycling, which was repeated 8-12 times with one minute active recovery intervals. This programme was compared with 90-120 minutes of continuous cycling at 65% of the baseline maximal oxygen consumption. Twelve recreationally active males (aged 25 ± 4 yrs) completed the supervised programmes and results showed no significant change in the absolute maximal oxygen consumption but significant weight loss for both groups. Yet, the peak work capacity and weight-adjusted, relative maximal oxygen consumption did improve significantly following training intervention. These findings suggest that weight loss contributed to improvement in the peak relative aerobic capacity although there was no dietary intervention included in the study. None of the aerobic parameters showed a statistically significant difference between training programmes despite the total exercise time being more than ten times longer for continuous training intervention (McKay, Paterson et al. 2009).
In another comparative study of aerobic exercise, Edge, Bishop et al. (2006) reported no significant changes in body mass following intervention. Eight recreationally active females (aged 20 ± 1 yrs) completed high-intensity interval exercise, involving two minute intervals at 120-140% of the baseline peak power at lactate threshold, which were repeated up to ten times with one minute rest intervals. Supervised training was completed three times per week over five weeks and compared with a moderately intense, continuous exercise programme (80-95% of the baseline peak power at lactate threshold). The total work was equivalent between training groups but resting blood lactate was more than three times higher in the HIIT group than the moderately intense exercise group following intervention. During exercise testing, both groups showed significantly increased time to exhaustion and relative peak oxygen consumption. There was no significant difference between training programmes for the change in exercise tolerance or peak aerobic capacity (Edge, Bishop et al. 2006).

Several studies have investigated the impact of HIIT on mitochondrial oxidative capacity in skeletal muscle (Perry, Heigenhauser et al. 2008; Talanian, Holloway et al. 2010; Little, Safdar et al. 2010 and Jacobs, Flück et al. 2013). After only two weeks of training, leg muscle biopsies have shown increased protein content and maximal activity of citrate synthase and cytochrome c oxidase (Little, Safdar et al. 2010). Similarly, increases in cytochrome c oxidase content and maximal citrate synthase activity are identified after six weeks of longer interval duration HIIT intervention (Perry, Heigenhauser et al. 2008). Little, Safdar et al. (2010) also demonstrated an increase in SIRT1 and nuclear but not total PGC-1α content, involved in mitochondrial biogenesis. In addition, Talanian, Holloway et al. (2010) report a significant change in the citrate synthase content when expressed per wet weight of muscle but not when expressed in isolated mitochondria. These findings highlight the impact of methodological approach on the measurement of change in oxidative capacity.
Hood, Little et al. (2011) proposed interval training to be a time-efficient form of aerobic exercise in sedentary adults (aged 45 ± 5 yrs). In this study, ‘sedentary’ was defined as not having participated in a regular exercise programme, involving two or fewer sessions of ≤ 30 minutes per week over the previous year. The authors found no significant reduction in fasted glucose following two weeks training intervention (10 x one minute intervals at 60% of the baseline peak power, interspersed with one minute recovery intervals). However, training was associated with significantly enhanced oxidative capacity, based on increased mitochondrial protein content post-intervention (Hood, Little et al. 2011).

The effects of HIIT have also been studied in overweight and obese men (aged 23.7 ± 5.2 yrs) with a mean BMI of 29.1 ± 3.1 (Leggate, Carter et al. 2012). Six supervised training sessions were completed, which involved 10 x 4-minute cycling intervals (approximately 85% of the baseline peak oxygen consumption) with an undefined rest interval. There were no significant changes in fasted glucose, weight or BMI although waist circumference was significantly lower post-intervention. As a cardiovascular risk factor, this waist measurement remained above 90 cm following HIIT intervention. However, as an indicator of fitness improvement, the relative and absolute peak oxygen consumption both improved significantly.

Collectively, these studies involved mostly young adults who were physically active prior to HIIT intervention. Few contraindications were specified although several studies excluded subjects taking medication. Subsequently, it is not yet clear whether exercise benefits might also apply to older adults living with chronic health conditions, such as neuromuscular disease.
Sprint interval cycling in non-clinical populations

As a variation of high-intensity interval exercise, sprint interval training typically involves repetition of ‘all-out’ sprints for less than one minute, interspersed with recovery intervals. In healthy adults, this type of training has been associated with performance enhancement and metabolic adaptations within two weeks (Burgomaster, Hughes et al. 2005; Whyte, Gill et al. 2010 and Little, Safdar et al. 2010). After only six sessions of sprint interval training, recreationally active adults doubled their exercise time to volitional fatigue and cycled for significantly longer than a non-exercising control group (Burgomaster, Hughes et al. 2005). As a marker for oxidative capacity, citrate synthase activity also increased by 38% following intervention (Burgomaster, Hughes et al. 2005). Similarly, Linossier, Denis et al. (1993) demonstrated a significant improvement in peak work performance after six sessions of sprint interval exercise. However, the investigators found no significant change in peak oxygen consumption, as a marker for cardiopulmonary fitness (Linossier, Denis et al. 1993). Combined, these outcomes support association between enhanced oxidative metabolism and exercise tolerance rather than maximal aerobic exercise capacity.

Despite a large difference in training volume, similar adaptations have been identified in a comparison of sprint interval training with moderately intense, continuous cycling intervention. Following six weeks of training, both groups showed enhanced peak power and mitochondrial enzyme activity, as well as increased PGC-1α protein content, associated with mitochondrial biogenesis (Burgomaster, Howarth et al. 2008). In contrast, Gibala, McGee et al. (2009) found no significant change in the expression of PGC-1α after a single bout of sprint interval training although protein expression was significantly higher after three hours in another study using a similar protocol (Little, Safdar et al. 2010). These results suggest a time-dependent component to the measurement of exercise effect on muscle oxidative capacity.
Several studies have reported enhanced insulin sensitivity following sprint interval exercise (Babraj, Vollaard et al. 2009; Richards, Johnson et al. 2010 and Whyte, Gill et al. 2010). However, only Richards, Johnson et al. (2010) applied the hyperinsulinaemic euglycaemic clamp technique, described as the gold-standard measurement for insulin sensitivity. Furthermore, Whyte, Gill et al. (2010) also found that six training sessions precipitated weight loss and a significant reduction in waist circumference in sedentary overweight and obese men. As cardiovascular disease risk factors, these outcomes have important health implications. Yet, vigorous, ‘all-out’ sprint training can also have negative side effects, such as light-headedness and nausea, which may affect exercise enjoyment and adherence in the longer term (Richards, Johnson et al. 2010).
Moderate-intensity continuous cycling in neuromuscular disease

Benefits of conventional, moderate-intensity aerobic exercise have been demonstrated in adults with neuromuscular disease as well as non-clinical populations. In adults with mitochondrial and inflammatory myopathies, there is evidence to suggest that aerobic exercise training can safely improve work capacity and cardiopulmonary fitness (Wiesinger, Quittan et al. 1998¹; Wiesinger, Quittan et al. 1998²; Taivassalo, Shoubridge et al. 2001; Jeppesen, Schwartz et al. 2006; Taivassalo, Gardner et al. 2006; Trenell, Sue et al. 2006; Jeppesen, Duno et al. 2009; Habers and Takken 2011; Voet, van der Kooi et al. 2010; Bates, Newman et al. 2013 and Voet, van der Kooi et al. 2013).

In a systematic review of adults with idiopathic inflammatory myopathies (polymyositis, dermatomyositis and inclusion body myositis), Habers and Takken (2011) identified four studies that assessed aerobic exercise capacity. Based on these findings, it was concluded that aerobic training supported fitness benefits for physically active and inactive adults with stable inflammatory myopathies. It was also concluded that exercise was safe based upon the absence of significant worsening of disease activity and pain. However, functional gains and improvement in health status were less clear because different outcome measures were applied and the results did not consistently show significant improvement. Furthermore, the review authors highlight potential study selection and allocation bias for more physically active and motivated individuals (Habers and Takken 2011). This concern is also raised in a review of treatments in mitochondrial disease. Potential exercise performance and outcome detection biases are emphasised where studies have failed to blind the assessors (Pfeffer, Majamaa et al. 2012).

Voet, van der Kooi et al. (2010 and 2013) completed systematic reviews of randomised controlled trials and quasi-randomised trials relating to exercise training in muscle disease. The updated review included only two trials with a minimum of six weeks cycling-based intervention (Wiesinger, Quittan et al. 1998¹; Wiesinger, Quittan et al. 1998² and Cejudo, Bautista et al. 2005). Overall, authors concluded that aerobic exercise was not harmful in polymyositis or dermatomyositis but lacked clear evidence of benefit. Meanwhile, aerobic exercise appeared to safely improve submaximal endurance in adults with mitochondrial myopathies, as concluded previously. Both studies
exhibited potential bias in blinding and incomplete reporting of outcome measurements (Voet, van der Kooi et al. 2013).

In the study by Cejudo et al. (2005), effects of a mixed cycling and upper body strength training programme were investigated in adults with mitochondrial myopathies (Cejudo, Bautista et al. 2005). Twenty subjects were randomly allocated to training and non-training groups (aged 44 ± 11 yrs) and there was one drop-out from each group during the study. Training was supervised for 12 weeks and involved training three times per week. Each session consisted of 30 minutes of cycling at 70% of the baseline peak work rate. The authors reported 95% session completion and significant improvements in peak absolute oxygen consumption, minute ventilation and upper body strength in the training group only (Cejudo, Bautista et al. 2005).

In adults with mitochondrial disease, submaximal cycling distance and duration also improved significantly following training compared to the non-training control group. In addition, elevated resting venous lactate declined markedly for two individuals following training although the average lactate levels did not change significantly. Meanwhile perceived health status (symptom severity and the Nottingham Health Profile) showed some improvement. All exercising subjects presented with exercise intolerance, moderate to severe myalgia and fatigue at baseline, reaching less than 83% of predicted maximal oxygen consumption. Subsequently, the completion of three months of exercise training is expected to have required a high level of motivation, which may contribute to exercise outcomes. As well as evidence of exercise intolerance, participation criteria included absence of bone or joint deformities, evidence of cardiac or respiratory disease and uncontrolled epilepsy (Cejudo, Bautista et al. 2005).

After six month of aerobic training, Wiesinger et al. (1998)² found that adults with idiopathic inflammatory myopathy significantly improved peak relative oxygen consumption, minute ventilation and isometric strength in the lower extremities (n = 8). These changes were not replicated in a non-training control group (n = 5). Aerobic exercise consisted of six months of supervised cycling and step exercise, which was completed by adults with polymyositis and dermatomyositis (aged 25-64 yrs). Cycling duration was not specified but training intensity peaked at 60% of the baseline peak heart rate. Subjects were also encouraged to undertake three hours of additional aerobic physical activity (walking or cycling), which was not monitored or quantified as part of the study. It is unclear why investigators encouraged a volume of aerobic exercise that
is potentially in excess of existing recommendations for apparently healthy adults (Garber, 2011). However, no adverse responses were reported and blood creatine kinase levels did not change significantly following intervention (Wiesinger, Quittan et al. 1998).

To date, one trial is known to have assessed the effects of cycling exercise in adults with sporadic inclusion body myositis (IBM) (Johnson, Collier et al. 2009). This trial combined aerobic and strength training over 12 weeks. The cycling exercise was performed three times per week at 80% of the baseline maximal heart rate and at a cycling cadence of 40-50 revolutions per minute. Although heart rate may be a poor gauge of exercise intensity in adults limited by severe leg muscle weakness, the results showed significantly increased peak absolute and relative oxygen consumption. This study also showed some improvement in lower limb muscle strength in the absence of any significant change in walking speed, stair climbing ability or serum creatine kinase levels. It was concluded that aerobic exercise intervention safely improved cardiopulmonary fitness (Johnson, Collier et al. 2009).

Several studies have investigated the impact of aerobic training on muscle mitochondrial function in adults with mitochondrial disease (Taivassalo, Shoubridge et al. 2001; Jeppesen, Schwartz et al. 2006; Taivassalo, Gardner et al. 2006; Trenell, Sue et al. 2006 and Adhihetty, Taivassalo et al. 2007). In a study of eight adults with mixed mtDNA defects (n = 8) and seven healthy controls (n = 7), the mitochondrial content and PGC-1α expression were higher in those with myopathy. However, only mitochondrial content and not PGC-1 α expression increased significantly following cycling intervention lasting 14 weeks. This result perhaps reflect a greater mitochondrial volume in adults with myopathies due to abnormal mitochondrial proliferation rather than exercise-induced biogenesis (Adhihetty, Taivassalo et al. 2007).

Nevertheless, Jeppesen, Schwartz et al. (2006) reported improved oxidative capacity and unchanged muscle morphology in adults with mitochondrial myopathy following cycling intervention. This three-month study found evidence of increased mitochondrial citrate synthase content and relative maximal oxygen consumption in adults with single large-scale deletions, a microdeletion and point mutations in mtDNA (Jeppesen, Schwartz et al. 2006). There was also a decline in capillary density that was not replicated in a healthy control group following exercise intervention. It is postulated that an angiopathy associated with mitochondrial disease could account for these
differences. However, further investigations showed evidence of angiogenesis after 12 months of exercise in a sub-group of adults with mitochondrial myopathies (Jeppesen, Duno et al. 2009).

When Taivassalo, Shoubridge et al. (2001) and Taivassalo, Gardner et al. (2006) assessed adults with mitochondrial myopathies they also found some evidence for increased citrate synthase activity after aerobic training programmes. In terms of mutational load, the authors initially reported an increase in the proportion of mutant mitochondrial DNA. However, subsequent investigations applied the same training protocol and found no significant change in the percentage of mutant mtDNA or copy number following exercise intervention (Taivassalo, Shoubridge et al. 2001 and Taivassalo, Gardner et al. 2006).

For adults with mitochondrial myopathy, Taivassalo, Gardner et al. (2006) proposed that improved exercise performance was driven primarily by enhanced peripheral oxidative capacity rather than increased cardiac output. In addition to significantly increased peak work capacity and oxygen consumption the authors reported significant increase in the arterio-venous oxygen difference (Taivassalo, Gardner et al. 2006). Importantly, however, cardiac output was estimated non-invasively by acetylene rebreathing methods and the arterio-venous difference was calculated as a function of peak oxygen consumption, using Fick’s equation. In terms of health status, subjects reported significantly improved quality of life in the SF-36 questionnaire following exercise training intervention. The perceived improvement in physical health was also reflected in a lower rate of perceived exertion during submaximal exercise (Taivassalo, Gardner et al. 2006).

In summary, moderate intensity, continuous aerobic training has shown therapeutic potential for improving exercise tolerance in neuromuscular disease. However, there are also important study limitations affecting the significance of group-level clinical outcomes, such as small sample size and disease heterogeneity.
High-intensity interval cycling in clinical populations

One of the major concerns associated with prescribing aerobic exercise in clinical populations relates to the risk of cardiovascular events. These adverse responses to exercise are often not reported fully in clinical trials (Weston, Wisloff et al. 2013). Rognmo et al. (2012) investigated the incidence of cardiac arrest and acute myocardial infarction during supervised high-intensity interval training and moderate-intensity continuous exercise in adults with coronary heart disease (n = 4,846) (Rognmo, Moholdt et al. 2012). This HIIT programme involved exercising at 85-95% of the peak heart rate, while moderate-intensity exercise was performed at approximately 60-70% of the peak heart rate. Borg’s 6-to-20 scale for rate of perceived exertion was also used as a method of monitoring intensity, whereby moderate-intensity exercise corresponded to a score of approximately 12-14/20 and high-intensity exercise was equivalent to > 15/20 to 17/20. Results identified one fatal cardiac arrest in 129,456 hours of moderate-exercise and two non-fatal cardiac arrests in 46,364 hours of HIIT intervention. No myocardial infarction was reported in either exercise programme. The authors concluded that both forms of clinically-supported exercise showed a low risk of cardiovascular events in coronary heart disease (Rognmo, Moholdt et al. 2012). This overview is important for safety awareness in exercise prescription although individual assessment of the cardiovascular risk remains essential.

In a systematic review of lifestyle-induced cardio-metabolic disease, Weston et al (2013) reported greater improvement in peak relative oxygen consumption following HIIT than moderate-intensity, continuous exercise intervention. Ten randomised controlled studies were included in this review, involving subjects with coronary heart disease, heart failure, hypertension, metabolic syndrome and obesity. Adherence to supervised exercise was at least 70% across the studies and no adverse events were recorded in any study. The authors also report some evidence for improved quality of life and symptoms of anxiety and depression with HIIT intervention. However, training-induced lowering of the cardio-metabolic risk appeared less consistent across different studies (Weston, Wisloff et al. 2013).
To date, only one study is known to have investigated interval training in adults with neuromuscular disease. El Mhandi, Millet et al. (2008) studied the benefits of interval cycling on functional capacity and fatigue in adults with Charcot-Marie-Tooth disease (n = 8). Subjects completed three supervised sessions per week in a hospital setting for 12 weeks, followed by 12 weeks of unsupervised training at home. Each session lasted approximately 45 minutes and involved 4-minute intervals of low-intensity cycling at 40% of the baseline peak power and one-minute intervals of higher intensity cycling at 80% of the peak power. Training adherence was reported as 85 ± 10% when supervised and 84 ± 13% at home. There were no exercise-related complications highlighted during the study and creatine kinase levels did not change significantly, as a biomarker for muscle damage. Exercise benefits included significant improvements in peak relative oxygen consumption and isokinetic knee flexion and extension strength after 12 weeks; these benefits were maintained after 24 weeks. In addition, symptoms of fatigue improved on a visual analogue scale and time-scored functional activities showed significant improvement (ascending/descending stairs, 6 m and 50 m walk and rising from supine). However, the time to rise from sitting and peak isometric knee flexion and extension strength did not show significant improvement following exercise intervention (El Mhandi, Millet et al. 2008).

Critically, aerobic cycling may not be expected to improve the performance of functional tasks that have low aerobic demands. In terms of muscle strength, it is possible that power-regulated training could contribute to enhanced exercise and functional capacity. Results from this study suggest that cycling may have a greater effect on dynamic rather than isometric leg strength (El Mhandi, Millet et al. 2008). However, the relative strength test-retest reliability is not known for this population, affected often by distal myopathy.

Little, Gillen et al. (2011) investigated the impact of high-intensity interval training on hyperglycaemia and mitochondrial oxidative capacity in adults with type II diabetes (aged 63 ± 8 yrs). As a condition that can be lifestyle-induced, the therapeutic potential of HIIT for reducing hyperglycaemia is particularly relevant to the disease management. In this study, eight subjects completed six sessions of HIIT over two weeks. Training involved 10 x one minute intervals cycling at approximately 90% of the baseline maximal heart rate, interspersed with one minute rest or active recovery intervals. In total, the programme required 75 minutes of weekly exercise and was completed...
without any reported complications or drop-outs. The authors found a significant reduction in the 24-hour average blood glucose following HIIT intervention. Peak work capacity, rate of perceived exertion and resting heart rate improved significantly and there was also evidence of enhanced oxidative capacity, based on increased citrate synthase activity and protein content of complex subunits in the mitochondrial respiratory chain (Little, Gillen et al. 2011).

In summary, there is evidence to suggest that high-intensity interval training can be performed safely in clinical populations and improve exercise tolerance with a lower volume of training than conventional aerobic exercise programmes. Further studies are needed to assess the wider safety implications and therapeutic potential of HIIT across different clinical populations.
Key findings

- Measures of exercise tolerance and aerobic fitness appear to improve with different aerobic training programmes and across different clinical and non-clinical populations.

- High-intensity interval training is shown to be a more time-efficient approach to aerobic training than conventional, moderate-intensity continuous exercise programmes.

- There is a low incidence of reported complications and adverse events following high intensity interval training programmes.

- Few trials have assessed the impact of high-intensity interval training on mental well-being and quality of life.

- To date, no known studies have investigated the therapeutic potential of high-intensity interval training in adults with mitochondrial and inflammatory myopathies.
Chapter 3. Methods

Recruitment
Patients with sporadic inclusion body myositis (IBM) and mitochondrial disorders were recruited to this study from across the country through specialist outpatient clinics at the Royal Victoria Infirmary (RVI) Hospital in Newcastle upon Tyne. Recruitment targeted men and women who were ambulant and able to commit to a 16-week exercise programme. Those patients recruited from the mitochondrial clinic exhibited milder phenotypes within the disease spectrum although no specific genotype was excluded from the study.

A group of ‘sedentary’ adults with no known neuromuscular disease was also recruited locally through adverts posted at the hospital and Newcastle University sites, including a research volunteer network.

Preliminary screening
Initial screening for participation in the study was performed either in person or by telephone following provision and discussion of the study information. Subjects included were adults (aged over 18 years) who were able to walk with or without a walking aid. Self-ascribed ‘sedentary’ adults did not take part in regular endurance exercise training (e.g. running, cycling, swimming), defined as ≥ 30 min of such activity ≥ 3 times every week. The adults with IBM or mitochondrial disorders reported being either recreationally active or did not take part in regular endurance exercise training each week.

In addition to the presence of known ischaemic heart disease (IHD), other exclusion criteria were signs and symptoms of IHD during health examination due to the greater risk of cardiac events with unsupervised high-intensity interval exercise. Pregnancy was also an exclusion criterion for assessment and exercise intervention due to the health risk. In terms of medications, warfarin and beta-blocker medication were absolute contraindications. Subjects were not allowed to take warfarin medication due to the risk of bleeding associated with invasive assessment procedures. Based on previous exercise investigations in mitochondrial disease, beta-blocker medication was specifically contra-indicated for its effect on the interpretation of exercise training responses.
**Health examination**

Subjects were assessed by a medical practitioner and a physiotherapist/ACSM-certified exercise specialist. This health screen involved completion of (1) the Physical Activity Readiness Questionnaire (2) medical examination including history-taking and physical examination, and (3) ECG-monitoring at rest and during an incremental cardiopulmonary exercise test.

Evidence of ischaemic heart disease on the ECG was a contraindication to entering the study. Subjects were also excluded if the medical practitioner identified a significant individual risk, which included life-threatening illness, potentially life-threatening hypoglycaemia with unsupervised high-intensity interval exercise, and muscle biopsy risk associated with skin conditions or previous minor surgery complications.

**Study site**

Exercise outcome measures were assessed at a clinical research facility at the RVI Hospital in Newcastle upon Tyne. Blood samples and muscle tissue collected at the research facility were transported to hospital biochemistry laboratories for analysis. Macro-electromyography (macro-EMG) was conducted at the hospital’s neurophysiology department.

**Assessment schedule**

The exercise assessment schedule was carried out prior to training intervention and repeated within the following two weeks after intervention completion. The same order of assessments was maintained throughout the study:

- medical history and examination
- fasted blood sample collection
  - light breakfast
- resting cardiopulmonary and autonomic cardiovascular assessment
- incremental cardiopulmonary exercise test
- dual energy x-ray absorptiometry (DEXA) scan
- isometric muscular strength assessment
- 30 second sit-to-stand test
  - lunch
- questionnaire provision
Baseline physical activity monitoring was completed prior to the initial exercise assessment. Additional muscle biopsy and macro-EMG procedures were also arranged in the days following exercise assessment or as soon after as logistically feasible.

**Fasted blood test**

Fasted venous blood tests were performed before and after exercise intervention. The fasting preparation involved avoiding food and drink except for water between midnight and assessment the next morning. A minimum 8-hour fast was indicated for interpreting fasted glucose and lipid profiles.

Blood samples were collected from the upper limb via a butterfly needle and tested for laboratory-referenced components including: serum creatine kinase; urea and electrolytes; HbA1c; fasted glucose and lipid profiles. The normality of blood measures was interpreted according to the laboratory reference range values. Although monitored, change in serum lactate was not supported by laboratory reference values. Collectively, the blood measurements helped to identify potential markers for impaired muscle function and exercise tolerance, as well as cardiovascular disease risk factors including impaired fasting glucose and dyslipidaemia.

**Incremental cardiopulmonary exercise testing**

An incremental cardiopulmonary exercise test to volitional fatigue was performed before and after exercise intervention. The test was completed using an electromagnetically controlled bicycle ergometer (Lode, Corivel, Groningen, Netherlands) with a gas exchange measurement system (Metalyzer 3B, Cortex, Leipzig, Germany) and a 12-lead ECG (custo diagnostic, Ottobrunn, Germany). Simultaneous non-invasive cardiac output monitoring was undertaken at rest and during exercise (NICOM, Cheetah Medical, Delaware, USA). These procedures were completed under the supervision of the study researcher and a second ACSM-certified exercise specialist experienced in cardiopulmonary assessment.
All exercise tests were scheduled for the morning through to lunchtime. Following venepuncture, subjects were provided with a light breakfast of cereal and juice or water at least one hour prior to further examinations. They were asked to avoid caffeine on the morning of assessment, and to refrain from exercise and drinking alcohol 24 hours prior. Subjects received standard instruction for performing the incremental exercise test, including use of the Borg Scale for monitoring rate of perceived exertion. Height and weight measurements were taken and entered into the system software prior to exercise performance.

Incremental exercise was performed on a semi-recumbent bicycle with a display for cycling wattage and revolutions per minute (rpm). Cycling workload was standardised through an interface between the bicycle and a computer that controlled the wattage increments according to a pre-defined protocol. The workload protocol involved five minutes of resting measurements followed by 10 Watt-per-minute increments in workload from an initial 20 Watt workload. Cycling speed was maintained at 60-70 revolutions per minute and subjects’ monitored their rate of perceived exertion by pointing to a score on Borg’s 6-to-20 scale. The subjects were asked to cycle for as long as possible and to terminate the test voluntarily at near maximal to maximal rate of perceived exertion (18-20/20) provided no signs or symptoms demanded earlier termination by assessors (Borg 1982). Verbal encouragement was given during the test and subjects had visual feedback on their performance through the cardiopulmonary exercise system. On completion of the test, subjects were encouraged to continue low-intensity cycling for active recovery and were monitored for five minutes.

Heart rate and electrical activity were displayed in real-time before, during and after the incremental exercise test using 12-lead electrocardiography (ECG). These ECG recordings were interpreted for normality of cardiac function at rest and during exercise stress. Exercise laboratory and American College of Sports Medicine (ACSM) criteria for ECG were used to define test termination, which included: evidence of second or third degree atrioventricular block; atrial fibrillation with fast ventricular response; increasing premature ventricular contractions; sustained ventricular tachycardia and technical inability to interpret ECG. Relative contraindications included exercise-induced bundle branch block, pronounced ST changes (i.e. ST segment depression and/or elevation) and less serious arrhythmias (ACSM 2010).
The cardiopulmonary exercise system also involved breath-by-breath respiratory and gas exchange measurement. Subjects were fitted with a face mask (Hans Rudolf, Inc., Kansas City, USA) connected to the Metalyzer 3B for continuous monitoring of oxygen and carbon dioxide content, and ventilatory volumes. The face mask attachment housed a non-rebreathing valve to separate the inspired and expired airflow during ventilation. Calibration of the cardiopulmonary system was performed for ambient air conditions, system pressure, gas and volume prior to each exercise test.

Subjective laboratory criteria for test termination included the subject’s request to stop, as well as signs and symptoms of an adverse reaction (chest pain; skin pallor; cyanosis; unusual shortness of breath; skin coldness; clamminess and central nervous system symptoms). Relative contraindications included leg cramps and intermittent claudication (grade 3-4), wheezing, shortness of breath and severe fatigue.

A blood pressure device (SunTech Tango, Morrisville, USA) interfaced with the gas exchange and ventilatory system to provide automated blood pressure recordings every three minutes at rest, during and after the incremental exercise test. The blood pressure cuff was attached around the left upper arm and measurements checked pre-exercise against another cuff attached to the right upper arm. The exercise test was terminated if systolic blood pressure dropped with increasing workload and adverse signs and symptoms. A hypertensive response (SBP > 250 mm Hg; DBP >115 mm Hg) was considered a relative contraindication for continuing the exercise test.

As a gold standard measurement for cardiopulmonary fitness, peak exercise oxygen consumption was determined as the highest value attained within the last 60 seconds of maximal work. The peak oxygen consumption was expressed in absolute terms (i.e. litres per minute) and in units adjusted by total body mass, which was measured in the body composition assessment (i.e. millilitres per kilogram per minute).
Heart rate, stroke volume and cardiac output were continuously monitored at rest and during exercise using the bioreactance method (NICOM, Cheetah Medical, Delaware, USA). The device connected to four sensors positioned on the upper and lower back while the subject sat at rest and then cycled on a bicycle ergometer. As an alternative to invasive thermodilution methods for measuring cardiac output, the NICOM estimates cardiac output using changes in an alternating current applied across the thorax in response to pulsatile blood flow, based on a time delay (phase shift) between the applied current and voltage measurement. Changes in the time delay between the applied current and voltage measurement (phase shifts) provide an estimate of the cardiac stroke volume (Jakovljevic, Moore et al. 2012). As shown in the equation on page 80, cardiac output is calculated as the product of heart rate and stroke volume. Peak exercise stroke volume was identified at the peak heart rate within the final minute of cardiopulmonary exercise tests. The NICOM device was adjusted for subjects’ age, height and clothed body weight.

**Resting cardiopulmonary and autonomic cardiovascular control**

Resting ventilation and gas exchange were monitored in the supine position for thirty minutes prior to incremental exercise testing using the cardiopulmonary exercise system described previously. This steady state monitoring ensured a standard rest period for all subjects prior to exercise testing and facilitated subject familiarisation with wearing the face mask and other monitor attachments. Resting autonomic cardiovascular control parameters were also monitored using the Task Force Monitor (CNS Systems, Graz, Austria). Designed primarily for syncope assessment, the Task Force Monitor displayed real-time data for resting heart rate variability via a 3-channel ECG. In addition to the resting heart rate, these data are expected to provide a measure of cardiovascular fitness that is independent of exertion (Carter, Banister et al. 2003). For the purpose of this study, time-domain heart rate variability was assessed, based upon the standard deviation of the RR interval (SDRRI).

During assessment, subjects lay in the supine position and were covered with a blanket for 30 minutes of quiet resting measurements under dimmed laboratory lighting, as per laboratory standard operating procedures. The steady state assessments were typically completed by mid to late morning. Light breakfast was consumed at least 30 minutes before proceeding to the exercise laboratory for steady state assessment, and caffeine was avoided prior to cardiopulmonary and autonomic assessment.
**Dual energy x-ray absorptiometry**

Dual energy x-ray absorptiometry (Lunar iDXA, GE Healthcare, UK) involved the posterior to anterior passage of an x-ray beam through the body to a detector. The filtered x-ray beam had two different x-ray energies that were attenuated differently by fat, lean mass and bone mineral. The ratio of low to high x-ray energy attenuation was used to distinguish between the three types of body tissue, creating high resolution images and quantification of the whole body composition (Wagner and Heyward 1999 and Plank 2005).

These data were interpreted in relation to age- and gender-matched reference populations. Specific measurements included: total lean and fat mass; percentage of total body fat; android fat mass and an indicator of abdominal obesity based on the android: gynoid ratio (AG ratio) in relation to normal waist-to-hip ratios (female: < 0.78; male < 0.89 (ACSM 2010). Body mass, body mass index (BMI) and skeletal bone mineral density were also recorded. As a risk factor for cardiovascular disease, obesity was classified as a BMI of $\geq 30$ kg/m$^2$ (normal range = 18.5 to 24.9 kg/m$^2$; overweight = $\geq 25.0$ kg/m$^2$) (WHO 2004). To interpret the bone mineral density data, t-scores and z-scores provided young and age-matched standard deviations respectively for identifying osteoporosis (-2.5 standard deviations or lower).

As a precaution, subjects were screened for pregnancy prior to the DEXA scan due to the low-dose of radiation exposure associated with this procedure (Wagner, 1991). Recent radiation exposure and any past history of surgery involving metal implants were also considered as relative contraindications. To minimise x-ray interference, metal jewellery was removed prior to the DEXA scan. The subjects also removed outer clothing prior to weighing and positioning themselves in supine on the scanner. A DEXA technician assisted subjects to align themselves correctly and instructed the subjects to lie as still as possible for the duration of the scan to optimise image quality.
**Isometric strength assessment**

Isometric knee extensor/flexor strength was assessed before and after exercise intervention using an isokinetic dynamometer (HUMAC NORM, CSMI, Boston, USA). This controlled method of measuring peak torque (the moment of force) minimised the risk of musculoskeletal injury as compared with the use of free weights. The protocol was designed to test for any change in leg strength in relation to maximal cycling performance and isometric quadriceps electromyography. As a measure of functional capacity, weight-adjusted strength ratios below 3.5 also previously corresponded with impaired transfer skill in the 30-second sit-to-stand test (Ploutz-Snyder, Manini et al. 2002). Strength was assessed in mid-range muscle length and the dynamometer was calibrated prior to each test using free weights.

Standard test instructions were given to all subjects before assessment. Having removed footwear, the subjects positioned themselves in sitting on the dynamometer chair. Position settings on the dynamometer were adjusted individually (position of range of movement stops; chair rotation scale, fore/aft position, back angle, back translation and seat position; dynamometer tilt, rotation scale and height; monorail position; knee/hip adapter length). A safety belt and test leg strap were fitted for stabilisation, and settings adjusted for the active knee range of movement following gravity correction.

During testing, subjects were instructed to lightly hold handle bars on either side of the dynamometer and to position their non-tested leg behind a leg rest for stabilisation. Display screens were turned away from the subjects’ view, removing the visual feedback. Three practice tests were performed, which each involved a five-second submaximal exertion with five seconds of relaxation in between. After 30 seconds recovery, ten maximal effort contractions were performed with a five second “push” against the dynamometer and a five second “relax”. For consistency, the right leg was always tested before the left leg.
The 30-second chair-stand test

Designed primarily to assess lower body strength in community-dwelling older adults, the 30-second chair-stand test provided an indicator of what authors term ‘functional fitness’ and ‘at-risk’ subjects, as defined by a score of less than eight unassisted stands in the allotted time (Jones and Rikli 2002). Subjects were asked to perform as many repetitions as possible in 30 seconds, moving from sitting on a chair to standing upright and sitting back down again without using their arms. During testing, subjects were asked to cross their arms across their chest. All tests were performed using an armless chair with a seat height of 45 cm, which was positioned against a wall. The number of sit-to-stand repetitions was counted aloud by the assessor in this study, providing subjects with performance feedback.

Health-related questionnaires

A series of questionnaires on health and well-being were completed before and after exercise intervention, which included (i) the Fatigue Impact Scale, rated by increasing impact from 0-160. This scale contains cognitive (memory, thinking and organisation of thoughts), physical (motivation, effort, stamina and coordination) and psychosocial (isolation, emotions, workload and coping) functioning dimensions although a four-factor model may have greater validity (behavioural, cognitive, emotional and physical dimensions) (Fisk, Ritvo et al. 1994, Theander, Cliffordson et al. 2007, Frith and Newton 2010) (ii) the Hospital Anxiety and Depression Scale, rated by increasing severity of psychological distress from 0-42 (Zigmond and Snaith 1983) and with subscale cut-off scores of 8/21 for detecting caseness in a study by (Bjelland, Dahl et al. 2002) (iii) the Warwick-Edinburgh Mental Well-being Scale, rated on an increasing scale from 14-70 with a median reference population score of 51/70 in a study by (Tennant, Hiller et al. 2007), and (iv) the 36-Item Short Form Health Survey on health-related quality of life (version 2), which is rated on a norm-based, transformed scale of 0-100; mean reference population score = 50 and standard deviation = 10 (QualityMetric 2014).

Subjects were given these questionnaires to complete independently and in no set order. Qualitative feedback was also provided in response to the subject being asked to describe their current level of fitness and any specific issue preventing them from exercising or doing more exercise. Missing questionnaire responses were identified by the study researcher and reviewed by the subject for completion.
Additional clinical investigations

Macro-electromyography (EMG) of the non-biopsied, left vastus lateralis was performed by a neurophysiology specialist. Warfarin medication was a contraindication for this procedure due to the risk of bleeding. The macro-EMG needle (Kallista Medical Limited, Surrey, UK) had a dual function of measuring focal action potentials from 1-2 muscle fibres and whole motor unit activity triggered by the individual fibre activity. This dual function has the precision of single fibre EMG and provides a measure of electrical activity across the motor unit, accounting for fibre variation. Recordings were made using a needle with global (5-10 mm) and focal (25 µm) electrode recording surfaces (Stålberg 1980).

A sterilised macro EMG needle was inserted into different sites in the belly of the vastus lateralis prior to voluntary contraction. Subjects then performed a series of isometric quadriceps contractions in a long-sitting position. Twenty recordings of sustained contractions were attempted over a period of approximately 45 minutes. The contractions involved pushing the knee down onto the plinth or elevating the heel several inches off the plinth.

For the purposes of this study, muscle biopsy provided confirmation of mitochondrial diagnoses and histochemical biomarkers for the severity of mitochondrial dysfunction in skeletal muscle. The subjects were provided with pre- and post-biopsy information and discussed the procedure and associated risk with a biopsy specialist. Subjects were required to stop taking anti-inflammatory medication (e.g. indomethacin, ibuprofen or voltarol), anti-platelet drugs (e.g. aspirin, dipyridamole or clopidogrel) or anti-thrombotic drugs (e.g. heparin or warfarin) up to two weeks prior to the procedure and with confirmation from the biopsy specialist. Routine observations, skin condition, allergies, Creutzfeldt-Jakob disease risk and any previous biopsy results were also considered before proceeding to biopsy.

The biopsy site was marked in the middle region of the vastus lateralis of the leg not tested for macro-EMG. Local anaesthetic was injected into the skin and tactile sensation tested once the local anaesthetic took effect. A needle biopsy was used to pass through a small cut in the skin and remove a piece of muscle (approximately 1 cm³). Adhesive strips sealed the wound and a dressing was affixed around the leg. The subjects’ recovery was monitored in hospital and further self-care discussed and monitored after
discharge home. Subjects were advised to avoid heavy physical activity for at least two weeks following the biopsy procedure.

Tissue preparation was completed at a mitochondrial diagnostics laboratory. The muscle tissue was divided for histochemical, biochemical and molecular biological investigations using a forceps and disposable scalpel. For histochemical preparation, approximately 50 mg of tissue was frozen in an isopentane freezing bath to prevent ice crystal artefact, and stored at -80°C, according to laboratory protocol. Cryostat sections (10 μg) were cut from the muscle and reacted for cytochrome c oxidase (COX) and succinate dehydrogenase (SDH). The percentage of COX-deficient fibres was estimated as a marker of oxidative defect in skeletal muscle mitochondria.

For subjects with mitochondrial disorders, completion of the Newcastle Mitochondrial Disease Adult Scale (NMDAS) and the Newcastle Mitochondrial Quality of Life (NMQ) provided additional case information on disease-specific features, severity and impact. The NMDAS was completed jointly with a medical physician and examiner, while the NMQ was completed independently by subjects. Self-reported Neuromuscular Symptom Scores also contributed supplementary clinical information on disease impact in IBM and mitochondrial disease although lacking validation as an outcome measure.

As an indicator of sedentary activity, estimates of daily sitting time were recorded using the International Physical Activity Questionnaire and a 7-day physical activity diary was also provided at baseline for subjects to record their everyday activities prior to exercise intervention.

**Health review**

As part of the study subjects were required to attend a health review in Weeks 6 and 12 of their exercise programme, which involved review of overall health and medications, discussion of exercise progress and any concerns. A non-fasted blood sample was collected to test for creatine kinase as a marker for muscle damage. Blood pressure, heart rate and ECG-monitoring were performed at rest and during incremental exercise to assess cardiovascular health. A 30-second chair-stand test was also repeated to review functional independence. If the health visit was completed with no adverse responses, the subject continued with their exercise programme. However, if any adverse responses were identified, these were followed up by the study’s principal investigators for further clinical investigation.
Training schedule and support
Subjects attended a local gym to complete three alternate day sessions per week of high intensity interval training (HIIT) for 16 weeks. Training was performed on modern, recumbent bicycles with a display for pedal resistance and speed. Most cycle ergometers also had integrated heart rate sensors.

The majority of the exercise training programme was completed unsupervised, however, a familiarisation session (Week 0) and three progress visits (Weeks 3, 9 and 15) were completed with the study physiotherapist. In addition, an interim contact was made between visits to support exercise adherence. Subjects were instructed not to undertake any additional structured exercise during the study.

Exercise familiarisation
The high-intensity interval training programme (HIIT) was individually tailored to manage variation in the subjects’ baseline exercise tolerance and work capacity. Subjects were provided with an exercise diary to record their training and an interval timer (Gymboss, St Clair, USA), pre-set for HIIT sessions by the study researcher/physiotherapist. A copy of the Borg 6-to-20 scale for rate of perceived exertion (RPE) was used to identify different intensities of exercise, whereby change in an individual’s RPE was expected to correspond with change in workload, heart rate and oxygen consumption. A heart rate monitor (Polar, Kempele, Finland) was fitted during the familiarisation session to assist tailoring of the programme intensity at approximately 85-95% of the peak heart rate achieved in the pre-training incremental exercise test.

The training programme consisted of five minutes warm-up, cycling at ≤ 60 rpm and with minimal pedal resistance, followed by 15 minutes of HIIT and 5 minutes warm-down at ≤ 60 rpm and with minimal pedal resistance again. The HIIT component of the session consisted of alternating low and high-intensity cycling bouts where low-intensity intervals (RPE 10-12/20) were performed for one minute and 40 seconds at a comfortable speed, ≤ 70 rpm, and with minimal resistance; high-intensity intervals (RPE 16-18/20) were performed for one minute and 20 seconds and required an increase in both cycling speed and resistance to elicit an elevated heart and work rate. Quadriceps, hamstring and calf stretches were performed at the end of the session (three x 20 seconds hold for each leg).
**Exercise progression**
All subjects’ training began with five sets of high intensity cycling bouts, and their progress was reviewed in the third week. If any subjects experienced setbacks, such as missed sessions, illness or any difficulty performing the programme, they were given the support to continue if they were able and willing to do so. Subjects who were independent with the programme progressed training to six sets of high-intensity cycling bouts in Week Three. A further interval was added in Weeks 9 and 15 as able, totalling a maximum of eight high-intensity cycling bouts over the course of 16 weeks.

**Selection of exercise outcome measures**
Exercise outcome measures were selected to assess for change in aerobic exercise tolerance and capacity, as well as to monitor the safety aspects of training and exercise impact on cardiovascular disease risk and mental well-being. In order to select appropriate outcome measures it was important to examine their validity and reliability, as well as the clinical meaningfulness of any change following intervention. While methodological assessment within the study population was beyond the scope of the selection process, previous studies provided evidence for criterion-related validity of the selected outcome measures as a form of external validation. Similarly, the reliability of outcome measurement was established in relation to existing evidence for the precision and sensitivity of assessment tools, and test-retest performance. A clinically meaningful change in outcome measurement was established from evidence for intervention responsiveness; the detection of a minimal clinically important difference (MCID) typically involves distribution-based methods in relation to an average response. For the purposes of this study, qualitative evidence that referred to a change in fitness following HIIT intervention also provided a form of anchor-based MCID in relation to the primary outcome measure of fitness, peak oxygen consumption.

Valid representation of variables and their constructs in outcome measurement can be assessed through the measurement of content and construct validity. Establishing the dimensionality of outcome measures and the relative importance of items for a given population are key considerations in understanding the internal validity. These aspects of validation are reflected upon following the practical application of outcome measures in the study population, and in the absence of prior evidence in the patient population. The practical considerations for outcome measure validity and their cross-study application are identified and evaluated in the Results and Discussion Chapters.
Pages 70-79 tabulate the supporting evidence for ten selected outcome measures in this study. The specific contribution of each outcome measure is stated in relation to the overall aim and objectives of this study. Unless otherwise stated, a p-value of < 0.05 is the assumed significance level for rejecting the null hypothesis. Blood testing for fasted glucose and lipid profiles is not included in the evaluation due to a lack of comparable measures to assess the cardiovascular disease risk that is associated with blood component concentrations; internationally agreed risk factors including serum glucose, low density lipoprotein, high density lipoprotein and triglyceride are described as outcome measures in Chapter Two. Rejected study outcome measures included the Beck’s Anxiety and Depression Inventories, which served as diagnostic screens for specific psychological disorders not investigated as part of the study. The Autonomic Symptom Profile was also deselected as an outcome measure due to language and comprehension difficulties limiting the completion and scoring of questionnaires.

**Discussion of exercise outcome measures**

As a measure or aerobic exercise capacity, peak cycling oxygen consumption measurements (page 70) are shown to be similar on repetition and correspond with peak non-invasive measurements for cardiac output. As an indicator of exercise intensity, submaximal oxygen consumption is also found to correspond with measurements of both cardiac output and perceived exertion. These results support the widespread use of peak oxygen consumption as an outcome measure for cycling training, as well as the relevance of subjective exercise intensity for monitoring training workload. However, there is a lack of evidence to detect quantitative MCID in aerobic exercise capacity using incremental exercise tests.

Evidence for the Bioreactance method of measuring cardiac output (page 71) is supported by a high correlation with invasive, resting measurements. Cardiac output measurements also demonstrate sensitivity to detect increments and decrements, which was an important factor in selecting the Bioreactance method as an aerobic exercise outcome measure. The Bioimpedance method (page 72) lacks comparable evidence for sensitivity to change and provides significantly lower peak exercise values for cardiac output. However, as a resting measure of cardiovascular health, the Bioimpedance method is found to be reliable in determining time-domain heart rate variability. Similarity in the heart rate variability values obtained using different monitoring systems also provides validation for its measurement. Furthermore, resting heart rate
variability offers a potential alternative to incremental exercise testing for measuring cardiovascular health and fitness in patients limited functionally by muscle weakness.

As a measure of body composition, dual energy x-ray absorptiometry (page 73) is supported by precision error measurements for bone, fat and lean tissue mass. Equipment manufacturers (Lunar iDXA, GE Healthcare, UK) also state that 68% of repeat scans fall within one standard deviation (± 0.0010 g/cm² for total bone mineral density; ± 280 g total fat mass and ± 310 g total lean mass). Any changes in excess of these measurement errors could potentially support a change in body composition following HIIT intervention, such as muscle hypertrophy or fat loss.

While the evidence for isokinetic dynamometry relates mainly to dynamic muscle strength, isometric contractions were expected to correspond better with the macro-emg test procedures involved in this study. Practice trials of isometric protocols were also found to produce less compensatory movement than dynamic test protocols. Assessment mid joint range testing (60° knee flexion) was selected for the purposes of this cycling exercise study, which is reported to correlate better with functional performance than higher and lower angles of knee flexion.

The measurement of weight-adjusted isometric leg extension (page 74) has provided sensitive cut-off thresholds for chair-rise performance as an indicator of functional impairment. There is also evidence to support consistency in isometric quadriceps strength and performance of the 30-second chair-stand test on repetition (pages 74-75). Subsequently, it may be possible to establish the impact of any strength gains following HIIT in relation to functional capacity. As a simple functional task, the chair-rise is identified as particularly relevant to neuromuscular patient populations affected by leg extensor weakness, which is a common feature of inclusion body myositis.

For assessing health perceptions in relation to everyday activities, the Fatigue Impact Scale (FIS) (page 76) has demonstrated test-retest reliability in neurological disease associated with fatigue, as well as being validated against the mental health scale within a quality of life questionnaire. The low correlation found between the Fatigue Impact Scale and the Fatigue Severity Scale could emphasise a distinction between subjects’ perceptions of symptom severity and symptom impact. It is not yet clear how responsive the Fatigue Impact Scale is to either change in symptoms or everyday activities. The Hospital Anxiety and Depression Scale (HADS) (page 77) has undergone
more extensive validation across different study populations although primarily applied as a case finder rather than an intervention measure.

Evidence suggests the HADS has a high degree of sensitivity and specificity with a cut-off score of 8 in each subscale. Yet, as a global measure of psychological distress in patients undergoing musculoskeletal rehabilitation (Pallant and Tennant 2007), there is some evidence to support modification of the questionnaire construct in certain neurological populations (Forjaz, Rodriguez-Blazquez et al. 2009 and Gibbons, Mills et al. 2011); the value of performing ‘goodness of fit’ validation in the study population, such as Rasch analysis, is considered further in the Discussion Chapter.

Of all the study questionnaires, the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) (page 78) is the only questionnaire developed as an intervention outcome measure; it is supported by evidence of individual and group-level responsiveness, as well as test-retest reliability and external validation in apparently healthy populations. This questionnaire is found to be unidimensional in cross-cultural evaluation (Taggart, Friede et al. 2013) but has showed some item redundancy using Cronbach’s alpha (Tennant, Hiller et al. 2007). Modification of the WEMWBS has been performed following Rasch analysis, suggesting the potential value of a similar validation in the study population, as considered in Chapter Eight (Stewart-Brown, Tennant et al. 2009).

As a surrogate measure for health-related quality of life, the 36-Item Short Form Health Survey (SF-36v2) (page 79) is found to correlate moderately with another general health questionnaire in a patient population; mental subscales of the SF-36v2 also correlate moderately with the HADS, suggesting content overlap for measuring psychological distress and health-related quality of life. Despite evidence for moderate overall test-retest reliability, the mental health summary scores are found to be less reliable than physical health summary scores. These differences in SF-36v2 subscale stability could affect the responsiveness to intervention and require further consideration in outcome measure validation.
Primary outcome measurement: Incremental cardiopulmonary exercise testing for peak oxygen consumption

<table>
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<tr>
<th>Criterion-related validity:</th>
<th>Test-retest reliability:</th>
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<tr>
<td>▪ Comparison of oxygen consumption with cardiac output measurement by pulsed Doppler ultrasound (n = 6) suggested early increments in oxygen consumption during cycling were mostly due to increased cardiac output (De Cort, Innes et al. 1991).</td>
<td>▪ Repetition of a symptom-limited, incremental work rate cycle test after one week (n = 12) showed no significant difference in gas exchange variables including: peak oxygen consumption; minute ventilation; heart rate; power output and rate of perceived exertion (p &gt; 0.05) (Jakovljevic, Moore et al. 2012).</td>
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<td>▪ Comparison of oxygen uptake with cardiac output measurement by the chest bioreactance method (n = 12) identified a high correlation (r = 0.84, p &lt; 0.01) at peak cycling (Jakovljevic, Moore et al. 2012).</td>
<td></td>
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<td>▪ Comparison of oxygen uptake with Borg’s rate of perceived exertion at 9-15/20 (n = 18) showed a high correlation (r ≥ 0.78, assumed p-value &lt; 0.05) (Morris, Lamb et al. 2010).</td>
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Study contribution:
As a function of cardiac output and perceived exertion, the oxygen consumption during incremental cycling provides a gold standard measure of aerobic exercise capacity and tolerance before and after cycling intervention.
Secondary outcome measurement: Bioreactance method for measuring peak stroke volume and cardiac output

<table>
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<tr>
<th>Criterion-related validity:</th>
<th>Sensitivity:</th>
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<tr>
<td>▪ Comparison of the chest bioreactance method with thermodilution (n = 110) identified a high correlation ( r = 0.82, p &lt; 0.05 ) for averaged resting measurements of cardiac output in intensive care (Squara, Denjean et al. 2007).</td>
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<td>▪ Comparison of chest bioreactance with the bioimpedance method (n = 12) identified a significantly higher peak cycling cardiac output using bioreactance ( p &lt; 0.05 ) (Jakovljevic, Moore et al. 2012).</td>
<td>▪ The bioreactance method has demonstrated 93% sensitivity for detecting significant directional changes in resting cardiac output ( n = 110 ) (Squara, Denjean et al. 2007).</td>
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**Study contribution:**

Bioreactance methods provide a non-invasive estimate of cardiac output that is sensitive to change and can help to assess the cardiovascular benefits of aerobic exercise intervention.
### Secondary outcome measurement: Bioimpedance method measuring for resting heart rate variability

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<th>Criterion-related validity:</th>
<th>Test-retest reliability:</th>
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<tr>
<td>▪ Comparison of five-minute recordings from the Polar S810 heart rate monitor and software with the CardioPerfect 12-lead ECG module (n = 33) identified a high correlation ($r = 0.85-0.99$, assumed p-value &lt; 0.05) for heart rate variability parameters (Nunan, Donovan et al. 2009).</td>
<td>▪ Repeated recordings after one-week (n = 33) demonstrated a good intra-class correlation coefficient (assumed p-value &lt; 0.05) for the raw mean RR interval (0.80-0.92) and the log transformed standard deviation of normal RR intervals (0.76-0.77) using the CardioPerfect 12-lead ECG module; raw frequency parameters for normalised units of heart rate variability were less reliable measures (0.40-0.65) (Nunan, Donovan et al. 2009).</td>
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**Study contribution:**

Time-domain measurements of resting heart rate variability may provide a useful, non-exertional indicator of cardiovascular health and fitness.
Secondary outcome measurement: Dual energy x-ray absorptiometry for whole body composition

<table>
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<tr>
<th>Criterion-related validity:</th>
<th>Precision:</th>
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<tr>
<td>• Comparison of mean percentage body fat measured by dual energy x-ray absorptiometry (DEXA) and a four-component model involving hydrostatic weighing, deuterium dilution and DEXA (n = 172) showed a high correlation ($r = 0.94$, $\alpha &lt; 0.05$) (Prior, Cureton et al. 1997). But, comparison of mean percentage body fat measured by dual energy x-ray absorptiometry (DEXA) and the four-component model (n = 152) also showed a significant difference ($p &lt; 0.001$) (Van Der Ploeg, Withers et al. 2003).</td>
<td>• Ten DEXA scans performed over 5-7 days (n = 12) demonstrated a precision error of &lt; 0.01 g/cm$^2$ for bone mineral density, 1.4% for percentage body fat, 1.0 kg for fat mass and 0.8 kg for lean mass (Mazess, Barden et al. 1990).</td>
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Study contribution:
DEXA has demonstrable precision in assessing whole body composition, which can help to determine soft tissue changes in relation to muscle strength and cardiovascular disease risk following HIIT intervention. In addition, the DEXA scan is a gold standard measure for the diagnosis of osteoporosis, which may also affect functional capacity.
**Secondary outcome measurement: Isokinetic dynamometry for isometric muscle strength**

<table>
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<tr>
<th>Criterion-related validity:</th>
<th>Test-retest reliability and sensitivity:</th>
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<tr>
<td>▪ Comparison of maximum static knee extension measurements using an isokinetic dynamometer and a hand-held dynamometer (n = 20) demonstrated a moderate intra-class correlation coefficient (0.797) (Bohannon 1990).</td>
<td>▪ Repetition of maximum isometric quadriceps force after up to one week (n = 26) identified no significant difference in force at 25° and 50° knee flexion (assumed p-value &gt; 0.05) (Robertson, Frost et al. 1998).</td>
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<td>▪ Comparison of weight-adjusted peak isometric leg extension torque (STR/WT) at 24°, 42°, 60°, 78° and 96° knee flexion with various functional task performance showed the greatest correlation at 60° (r = 0.38-0.50, p &lt; 0.001) (Ploutz-Snyder, Manini et al. 2002).</td>
<td>▪ The STR/WT ratio of 3.5 identified 81% of older adults who had some difficulty performing a chair rise (n = 20). STR/WT &lt; 3.0 represented a substantial risk for impaired chair rise (Ploutz-Snyder, Manini et al. 2002).</td>
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</table>

**Study contribution:**
Isometric quadriceps force in mid-range knee flexion provides a measure of muscular strength, which may affect cycling performance and the risk of functional impairment.
**Secondary outcome measurement: The 30-second chair-stand test**

<table>
<thead>
<tr>
<th>Criterion-related validity:</th>
<th>Test-retest reliability:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Comparison of the 30-second chair-stand test with weight-adjusted leg press performance (n = 76) demonstrated a moderate correlation (r = 0.77, assumed p-value &lt; 0.05) (Jones, Rikli et al. 1999).</td>
<td>▪ Same day repetition of the 30-second chair-stand test (n = 47) demonstrated a high correlation (r = 0.93, p = 0.001) (McCarthy, Horvat et al. 2004).</td>
</tr>
<tr>
<td>▪ Comparison of the 30-second chair-stand test with the five times sit-to-stand test (n = 47) demonstrated a high correlation (r = -0.83, p ≤ 0.01) (McCarthy, Horvat et al. 2004).</td>
<td>▪ Repetition of the 30-second chair-stand test after 2.5 days (n = 76) demonstrated good intra-class correlation coefficient in men (0.84) and women (0.92) (Jones, Rikli et al. 1999).</td>
</tr>
</tbody>
</table>

**Study contribution:**

The 30-second chair-stand test provides a functional index for lower limb strength. Test reliability and performance differences in relation to physical activity levels (Jones, Rikli et al. 1999) suggest this measure can help to assess the functional impact of HIIT intervention.
## Secondary outcome measurement: The Fatigue Impact Scale (FIS)

<table>
<thead>
<tr>
<th><strong>Criterion-related validity:</strong></th>
<th><strong>Test-retest reliability:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Comparison of the FIS and the Fatigue Severity Scale in multiple sclerosis (n = 54) demonstrated low correlation ($r = 0.44$, assumed p-value &lt; 0.05) (Mathiowetz 2003).</td>
<td>▪ Repeated completion of the FIS after six weeks (n = 54) demonstrated a moderate intra-class correlation coefficient in adults with multiple sclerosis (0.76-0.81) (Mathiowetz 2003).</td>
</tr>
<tr>
<td>▪ Comparison of ratings on the FIS with the mental health scale of the 36-Item Short Form Health Survey in multiple sclerosis (n = 54) demonstrated moderate correlation ($r = -0.62$, $p &lt; 0.01$) but poor correlation with the physical functioning scale (-0.28, $p &lt; 0.05$) (Mathiowetz 2003).</td>
<td></td>
</tr>
</tbody>
</table>

### Study contribution:

As a perceived rating, the Fatigue Impact Scale can help to assess change in health perceptions following HIIT intervention through the impact of fatigue on everyday activities.
Secondary outcome measurement: The Hospital Anxiety and Depression Scale (HADS)

<table>
<thead>
<tr>
<th>Criterion-related validity:</th>
<th>Sensitivity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Systematic comparison of the HADS and the Beck Depression Inventory (747 publications) has shown moderate correlation ($r = 0.73$, assumed p-value &lt; 0.05). The Beck Depression Inventory also correlated moderately with the anxiety subscale of HADS ($r = 0.61-0.83$) and the depression subscale ($r = 0.62-0.73$) (Bjelland, Dahl et al. 2002).</td>
<td>• Optimal sensitivity and specificity of the HADS (approximately 80%) defined caseness by a cut-off score of 8 for each subscale in clinical and non-clinical populations (Bjelland, Dahl et al. 2002).</td>
</tr>
</tbody>
</table>

**Study contribution:**
As a measure of psychological distress, HADS can help to assess the impact of HIIT intervention on health perceptions in clinical and non-clinical populations. HADS can also be used as a case finder for anxiety disorders and depression.
Secondary outcome measurement: The Warwick-Edinburgh Mental Well-being Scale (WEMWBS)

<table>
<thead>
<tr>
<th>Criterion-related validity</th>
<th>Test-retest reliability and responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Comparison of the WEMWBS with the General Health Questionnaire-12 (n = 1233) showed moderate correlation (-0.53, p &lt; 0.01) (Tennant, Hiller et al. 2007); there was also moderate correlation across a larger population (n = 3355) (r = -0.62, p &lt; 0.01) (Lloyd and Devine 2012).</td>
<td>▪ Repetition of the WEMWBS after 7 days demonstrated moderate correlation (r = 0.83, p &lt; 0.01) in a university student population (n = 124) (Tennant, Hiller et al. 2007).</td>
</tr>
<tr>
<td>▪ Secondary analysis of mean change in WEMWBS scores following mental health intervention showed the probability of change statistic was &gt; 0.7 for most studies and an individual change score of 3 (1 SEM) was greater than the measurement error in most studies (Maheswaran, Weich et al. 2012).</td>
<td></td>
</tr>
</tbody>
</table>

**Study contribution:**
The WEMWBS can help to assess change in mental well-being with HIIT intervention in relation to general health.
### Secondary outcome measurement: The 36-Item Short Form Health Survey (SF-36v2)

<table>
<thead>
<tr>
<th>Criterion-related validity:</th>
<th>Test-retest reliability:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Comparison of the physical function domain of the SF-36 with the Modified Health Assessment Questionnaire in rheumatoid arthritis (n = 233) demonstrated a moderate Spearman rank correlation (-0.89, p = 0.0001) (Ruta, Hurst et al. 1998).</td>
<td>• Repetition of the SF-36 after two weeks by adults with rheumatoid arthritis (n = 31) showed a good intra-class correlation coefficient (ICC) for the physical component summary score (0.80) and a moderate ICC for the mental component summary score (0.58) (Ruta, Hurst et al. 1998).</td>
</tr>
<tr>
<td>• The HADS showed a moderate Spearman rank correlation (p &lt; 0.0001) with the mental health scale of the SF-36 (-0.80) and the mental component summary score (-0.81) in rheumatoid arthritis (n = 233) (Ruta, Hurst et al. 1998).</td>
<td></td>
</tr>
</tbody>
</table>

**Study contribution:**
The SF-36 can help to assess change in health-related quality of life in relation to exercise capacity and mental well-being following HIIT intervention.
Exercise-related equations and statistical analysis

Cardiac output (CO) was determined from non-invasive measurements of cardiac stroke volume (SV) and heart rate (HR), according to the following equation:

\[
\text{CO (l/min)} = \text{SV} \times \text{HR}
\]

As an indicator of oxygen extraction by muscles during peak exercise, the arteriovenous oxygen difference was then calculated using Fick’s equation:

\[
\text{a-v difference (ml/100ml blood)} = \frac{(100 \times \text{VO_{2peak}})}{\text{CO}}
\]

Statistical analysis of the data was completed using SPSS version 21.0 (SPSS Inc., IL USA) with values expressed as mean and standard deviation except for average isometric strength measurements, expressed by median and interquartile ranges with outliers identified. Large heart rate variability datasets were screened for outliers prior to linear time-domain analysis, using a z-score cut-off of +3.29 and -3.29. For the grouped data analysis, Shapiro-Wilk tests for normality were applied; the Wilcoxon Signed-Rank Test was then applied to non-normally distributed data, while normally distributed data were compared using paired t-tests presented with a 95% confidence interval. Intervention effect size was calculated using the Eta squared statistic \(\frac{t^2}{t^2 + (N - 1)}\), whereby 0.01 = small effect, 0.06 = moderate effect, and 0.14 = large effect.
Key methodological considerations

- A multi-disciplinary approach is integral to the health assessment and review of all subjects involved in this study.

- Standardisation of assessment procedures is emphasised throughout the study in order to minimise methodological error in the evaluation of study outcomes.

- One-to-one exercise support is provided from the same physiotherapist/ACSM-certified exercise specialist throughout training intervention and with ready access to multi-disciplinary health care.

- The flexibility of perceptually-regulated high intensity interval training facilitates participation of individuals with different levels of disability and fitness.

- Validity and reliability are considered in the selection of exercise outcome measures to address the study objectives.
Chapter 4. Results from Sedentary Adults

Recruitment and health screening
Fifty people responded to recruitment advertising for sedentary, low active adults to participate in this exercise study. Only eleven adults proceeded into the study following further discussion of study information and requirements. Based on study exclusion criteria, one potential recruit was excluded for using beta-blocker medication. On medical consultation, three more people were excluded who were using high-dose anti-rheumatic medication or who had potentially life-threatening unstable epilepsy or metastatic cancer. The reasons given for others declining to proceed in the study included:

(i) being too active or having other exercise commitments  
(ii) time commitment/other commitments  
(iii) muscle biopsy/intrusive procedures involved  
(iv) current medical concerns  
(v) current family concerns  
(vi) participating in another research study  
(vii) unknown

Of the eleven adults (10 female, 1 male) successfully recruited into the study, a further four adults did not proceed beyond baseline assessment. These drop-outs included two females who withdrew from the study on re-consideration of invasive assessment procedures. One female was excluded on medical assessment due to increased muscle biopsy risk associated with previous complications following minor surgery. A second female was also excluded on medical assessment of muscle biopsy risk associated with skin allergies.

Seven adults (6 females, 1 male) completed baseline assessments and proceeded to exercise intervention. A 45-year-old female withdrew from the study prior to her week 6 health review, indicating a change in work commitments. A 47-year-old female was withdrawn from the study following medical review in week 12 due to acute abdominal symptoms that worsened on exercise. Also, a 61-year-old male withdrew from the study prior to his week 12 health review, indicating that the nature of the exercise programme was too restrictive for him. All three of these exercise drop-outs previously reported missing multiple training sessions, which could suggest a need for greater support and more individualised intervention.
Four females completed the study in total, representing less than 10% of the initial contacts made, as summarised in the flow diagram in Figure 4-1. Extensive and invasive assessment procedures involved in this study are expected to have contributed to a low recruitment rate.

**Figure 4-1. A flow diagram of the recruitment of sedentary adults into interval training intervention.**
Baseline characteristics
The baseline characteristics of subjects recruited into HIIT (six females, one male) are summarised in Table 4-1 and Table 4-2. These subjects were aged 53 ± 18 years (range 22-74 yrs), Caucasian and living in the Tyne and Wear region of the UK. All bar one of the subjects reported a known history of either heart disease or stroke in parents or grandparents. Six of the seven subjects were obese and all subjects had an above average body mass index.

The subjects each underwent muscle biopsy and macro-EMG procedures at baseline. These investigations confirmed the absence of a mitochondrial genetic disorder and skeletal muscle disease. However, the male subject was known to have an autosomal chromosome defect, neurofibromatosis type 1 (NF1), producing non-cancerous tumours in the body. Secondary conditions associated with NF1 may have contributed to this subject’s cardiovascular disease risk.

At baseline, three subjects were taking anti-hypertensive medication, including the subject with NF1, and two other subjects were taking medication for clinical depression. The subject with NF1 also had sleep apnoea, associated with obesity, for which continuous positive airway pressure treatment had not been effective. Only one of the seven subjects reported doing once weekly exercise prior to commencing HIIT intervention. In-depth analysis of individual responses to exercise is presented in the following case studies.
Table 4-1. Baseline characteristics of sedentary adults who completed high-intensity interval training intervention (FH = parent/grandparent family history).

<table>
<thead>
<tr>
<th>Subject</th>
<th>001</th>
<th>006</th>
<th>016</th>
<th>021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Age</td>
<td>55</td>
<td>22</td>
<td>74</td>
<td>70</td>
</tr>
<tr>
<td>BMI</td>
<td>31.6</td>
<td>27.2</td>
<td>36.5</td>
<td>33.5</td>
</tr>
<tr>
<td>Occupation</td>
<td>IT</td>
<td>Student</td>
<td>Retired</td>
<td>Retired</td>
</tr>
<tr>
<td>Habitual exercise</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Over-50s class x 1pwk</td>
</tr>
<tr>
<td>Lung disease/breathing problems</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hypertension</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>TIA/stroke</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Clinical anxiety/depression</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>FH heart disease</td>
<td>Unknown</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>FH lung disease</td>
<td>Unknown</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>FH diabetes</td>
<td>Unknown</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>FH stroke</td>
<td>Unknown</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>
Table 4-2. Baseline characteristics of sedentary adults who did not complete high-intensity interval training intervention (FH = parent/grandparent family history).

<table>
<thead>
<tr>
<th>Subject</th>
<th>009</th>
<th>017</th>
<th>019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Age</td>
<td>47</td>
<td>61</td>
<td>45</td>
</tr>
<tr>
<td>BMI</td>
<td>42.29</td>
<td>41.94</td>
<td>33.57</td>
</tr>
<tr>
<td>Occupation</td>
<td>Unemployed</td>
<td>Retired</td>
<td>Solicitor</td>
</tr>
<tr>
<td>Habitual exercise</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Lung disease/breathing problems</td>
<td>N</td>
<td>Sleep apnoea</td>
<td>N</td>
</tr>
<tr>
<td>Hypertension</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>TIA/Stroke</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Clinical anxiety/depression</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>FH heart disease</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>FH lung disease</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>FH diabetes</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>FH stroke</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
</tbody>
</table>
Case One.

Abstract

*Rationale:* To assess how high-intensity interval training (HIIT) affects the health of a non-exercising, 55-year-old female.

*Presenting condition:* This subject presented with no known cardiovascular, respiratory or neurological disease but had a high BMI (31.6 kg/m^2_), engaged in no regular physical activity and reported an unknown family history of chronic disease.

*Intervention:* Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

*Outcomes:* This subject reported 96% attendance of gym sessions and demonstrated an improvement in mental well-being, muscle strength performance and aerobic exercise capacity following HIIT intervention.

*Implications:* HIIT intervention was completed without complication and was beneficial for improving functional capacity and aspects of quality of life in a case presenting with an elevated risk of cardiovascular disease.
Background

This subject was a 55-year-old female, employed in a desk-based occupation. Her presenting condition was a lack of regular physical activity and above average BMI. She suffered from heart burn, for which she took a proton pump inhibitor (30 mg lansoprazole daily), and sometimes experienced migraines. This subject did not know her family history of cardiovascular disease risk.

Auscultation of the heart was performed by a medical physician as part of the standard physical screening procedures prior to exercise intervention. This assessment, combined with a resting ECG, identified a heart murmur that was found to be benign in subsequent cardiac investigations. Biopsy of the right vastus lateralis confirmed the absence of a genetic mitochondrial disorder. Approximately 1-2% of muscle fibres were cytochrome c oxidase deficient, consistent with age-related changes.

HIIT intervention and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 97-101% (133-138 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject managed to progress from five to seven sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 21 minutes. According to the exercise diary, this subject completed 96% of the training programme (45/47 sessions). Reasons given for missed sessions were due to a severe migraine. However, interim health review visits in weeks 6 and 12 were completed without complication, and the subject was able to resume exercise without indication for an onward medical referral.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 29% (126-163 W) following HIIT intervention. While trends in minute ventilation with increasing exercise intensity remained similar between tests (Figure 4-2), the exercising heart rate was consistently lower and oxygen consumption higher post-intervention (Figure 4-3 and Figure 4-4). There was a 52% increase in peak oxygen consumption (1.335-2.035 l/min) following HIIT. When adjusted by weight, these results again supported greater exercise capacity following HIIT intervention (13-21 ml/kg/min).

Cardiac output and stroke volume

NICOM showed a 14% decrease in stroke volume (162 to 149.4 ml) and 19% improvement in cardiac output (12.0-14.3 l/min) with 5% difference in peak heart rate (146-154 bpm) following HIIT intervention. In addition, the arterio-venous oxygen difference increased from by 3 ml/100ml blood post-intervention.

Resting heart rate variability

Resting heart rate data showed a large reduction in the mean resting heart rate post-HIIT intervention (PRE: 83 ± 3 bpm vs. POST: 66 ± 2 bpm). In conjunction with this lowering of heart rate, there was an increase in the RR interval duration (RRI) (PRE: 727 ± 26 ms vs. POST: 906 ± 32 ms) following training intervention. As a measure of heart rate variability, the RRI standard deviation increased by 6 ms.
Figure 4.2. Case One: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 4.3. Case One: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Figure 4-4. Case One: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.

Lower limb strength performance

There were statistically significant improvements in right and left leg torque when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test with interquartile range (Figure 4-5 and Figure 4-6). Peak knee extensor/flexor torque also increased in both legs following intervention and these changes were supported by weight-adjusted strength ratios (right PRE: 2.0 vs. POST: 2.1; left PRE: 1.5 vs. POST: 1.8). In addition, functional lower limb strength performance showed improvement in the 30-second chair-stand test following training (PRE: 10 stands vs. POST: 13 stands).
Figure 4.5. Case One: isometric right knee extensor/flexor torque PRE and POST interval training intervention (p = 0.007).

Figure 4.6. Case One: isometric left knee extensor/flexor torque PRE and POST interval training intervention (p = 0.011).
**Body composition and blood profile**

The subject was on the 95th centile for whole body fat when compared with an age- and gender-matched population. Although fat mass increased marginally above the Lunar iDXA precision error (343 g), total body mass changed by less than 0.5 kg following HIIT intervention. Regional analysis showed that abdominal fat constituted over half of the tissue mass (android % PRE: 56.6 vs. POST: 60.4), contributing to an AG ratio > 0.89.

As a biomarker for muscle damage, serum creatine kinase remained within normal laboratory ranges pre- and post-HIIT intervention. Fasted glucose and glycated haemoglobin (HbA1c) concentrations remained similar following training and were within normal laboratory ranges, supporting the absence of diabetes. The fasted lipid profiles also showed normal laboratory values for cardiovascular disease risk before and after HIIT intervention. However, there was a marked reduction in low-density lipoprotein following intervention (PRE: 4.2 vs. POST: 3.5 mmol/l).

**Mental well-being and health-related quality of life**

Fatigue Impact scores increased marginally post-intervention (PRE: 45/160 vs. POST: 48/160) despite a decrease in reported symptoms of psychological distress according to the Hospital Anxiety and Depression Scale (HADS). The subject consistently demonstrated an above threshold subscale score for depressive mood (≥ 8/22) before and after HIIT intervention, while anxiousness decreased below threshold following intervention (Figure 4-7).
When asked to describe her fitness prior to exercise intervention, the subject reported “struggling” on stairs. Specific limitations to exercise included motivation and also concerns about her appearance. As an indicator of perceived sedentary behaviour, she reported an average weekday sitting time of eleven hours. Following HIIT intervention, the subject described feeling fitter, being able to “do more without getting out of breath” and being able to see a change in her body shape. Reported weekday sitting time decreased by 5.5 hours post-intervention.

Total scores on the Warwick-Edinburgh Mental Well-being Scale remained below average before and after HIIT intervention despite an improvement in scores (PRE: 32/70 vs. POST: 38/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) suggest the subject perceived having better physical than mental components of quality of life. Both physical and mental component summary scores reflected an improvement in quality of life post-intervention, however. In particular, health-related vitality increased markedly (Table 4-3).
Table 4-3. Case One: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

<table>
<thead>
<tr>
<th></th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
<th>VT</th>
<th>SF</th>
<th>RE</th>
<th>MH</th>
<th>MCS</th>
<th>PCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>46.5</td>
<td>49.5</td>
<td>50.3</td>
<td>26.7</td>
<td>27.1</td>
<td>40.5</td>
<td>44.2</td>
<td>30.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POST</td>
<td>54.9</td>
<td>52</td>
<td>62.1</td>
<td>31.5</td>
<td>52.1</td>
<td>29.6</td>
<td>48.1</td>
<td>41.6</td>
<td>37.8</td>
<td>54.4</td>
</tr>
</tbody>
</table>

**Summary of findings**

This 16-week high-intensity interval training programme was well tolerated by the subject and completed safely. Key findings from the case study are that the subject showed improved functional capacity and mental well-being following exercise intervention. As an obese adult (> 30 kg/m²) (WHO 2004), negligible changes were found in body mass following training but the subject described seeing a change in her body shape. Change in mental well-being following intervention represented a statistically important improvement based on established individual responsiveness to change (≥ 3 change score) (Maheswaran, Weich et al. 2012).

This subject showed marked improvement in cardiopulmonary fitness following HIIT intervention, which was supported by increased peak cardiac output but not stroke volume. A cardiovascular training effect was also indicated by the reduction in resting heart rate and an increase in heart rate variability. Improved lower limb strength performance provided further evidence of enhanced functional capacity following HIIT intervention.
Case Six.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a non-exercising, 22-year-old female.

Presenting condition: This subject was previously diagnosed with depression, had an elevated BMI (27.2 kg/m²) and engaged in no regular physical activity.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 81% attendance of gym sessions and experienced less fatigue impact following intervention although symptoms of psychological distress worsened and cardiopulmonary exercise tolerance remained similar.

Implications: HIIT intervention was completed without complication in a subject presenting with severe depression. Due to the cessation of anti-depressant medication it was not possible to attribute changes in mental well-being to exercise intervention, or the reverse. Change in psychological symptoms may have contributed to discrepancies in measures of exercise tolerance and capacity.
Background

This subject was a 22-year-old female student. Her presenting condition was a lack of regular exercise and above average body weight. She was receiving medical treatment for clinical depression (300 mg trazadone daily), and reported a family history of stroke. Biopsy of the right vastus lateralis confirmed the absence of a genetic mitochondrial disorder and showed no evidence of cytochrome c oxidase deficient muscle fibres.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 84% (150 bpm) of the peak heart rate attained in the baseline incremental cardiopulmonary exercise test. At nine weeks, peak heart rate was recorded as 93% of the baseline peak heart rate. The subject progressed from five to eight sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 24 minutes. According to the exercise diary, she completed 81% of the training programme (38/47 training sessions). While interim health review visits in weeks 6 and 12 were completed without complication, the subject was advised to visit her GP upon stopping anti-depressant medication.

Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity increased by 7% (154-165 W) following HIIT intervention. Although exercising heart rate was consistently lower post-intervention (Figure 4-8), the trends in minute ventilation and oxygen consumption remained similar during incremental exercise tests (Figure 4-9 and Figure 4-10). There was a 4% increase in peak oxygen consumption (1.932-2.006 l/min) following HIIT intervention. When adjusted by weight, these results supported negligible change in exercise capacity post-intervention (28-27 ml/kg/min).
Cardiac output and stroke volume

NICOM showed a 32% increase in stroke volume (95-125.7 ml) and 40% improvement in cardiac output (15.1-21.1 l/min) with 6% difference in peak heart rate (159-168 bpm) following HIIT intervention.

Resting heart rate variability

There was a reduction in mean resting heart rate (PRE: 63 ± 6 bpm vs. POST: 53 ± 7 bpm) and an increase in the RR interval duration (RRI) (PRE: 960 ± 98 ms vs. POST: 1147 ± 136 ms) post-HIIT intervention. As a measure of heart rate variability, the RRI standard deviation increased by 38 ms.

Figure 4-8. Case Six: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Figure 4-9. Case Six: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 4-10. Case Six: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.
Blood profile and body composition

As a measure of the blood oxygen-carrying capacity, haemoglobin levels were 11 g/l lower (127-116 g/l) following HIIT intervention, which contributed to borderline anaemia and potentially impaired exercise tolerance. While the blood profile showed no abnormalities indicative of an elevated risk of cardiovascular disease or diabetes, this subject was on the 97th centile for whole body fat when compared with an age- and gender-matched population. Following HIIT intervention, she increased total body mass by 3.6 kg, gaining fat (28568 - 31737 g) and lean mass (37632 - 38037 g); these changes were in excess of the Lunar iDXA precision error. Abdominal fat constituted approximately half of the regional tissue mass (android % PRE: 50.5 vs. POST: 54.0), contributing to an AG ratio ≥ 0.89.

Lower limb strength performance

There were statistically significant improvements in right and left leg torque when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test with interquartile range (Figure 4-11 and Figure 4-12). Peak knee extensor/flexor torque also increased in both legs following intervention and these changes were supported by weight-adjusted strength ratios for the right leg (PRE: 1.9 vs. POST: 2.1) but not the left leg (PRE: 1.7 vs. POST: 1.6). Also, functional lower limb strength performance showed improvement in the 30-second chair-stand test following HIIT intervention (PRE: 17 stands vs. POST: 19 stands).
Figure 4-11. Case Six: isometric right knee extensor/flexor torque PRE and POST interval training intervention ($p = 0.005$).

Figure 4-12. Case Six: isometric left knee extensor/flexor torque PRE and POST interval training intervention ($p = 0.017$).
Mental well-being and health-related quality of life

Prior to HIIT intervention, this subject described her fitness as “poor” and reported “get[ting] tired fairly quickly” on stairs. Motivation was identified by the subject as a factor limiting exercise. Following HIIT intervention, the subject described her fitness as “very low”, which she attributed, in part, to diet. Additional limiting factors included tiredness, lack of energy and workload. However, the subject suggested there may have been some improvement in her fitness compared with four months earlier. As an indicator of perceived sedentary behaviour, she reported an average weekday sitting time of ten hours, which increased by one hour post-intervention.

Fatigue Impact scores were high compared with other subjects at baseline (75/160) and showed considerable improvement following training intervention (53/160). In contrast, post-intervention levels of psychological distress in the Hospital Anxiety and Depression Scale (HADS) were severe and declined following intervention. This subject consistently demonstrated above threshold subscale scores for depressive mood (≥ 8/22) and anxiousness (≥ 8/22) before and after HIIT intervention (Figure 4-13).

*Figure 4-13. Case Six: Hospital Anxiety and Depression Scale scores for Depression (HADS-D) and Anxiety (HADS-A) PRE and POST interval training intervention.*
Total scores on the Warwick-Edinburgh Mental Well-being Scale were below average and declined following HIIT intervention (PRE: 31/70 vs. POST 21/70). In the 36-Item Short Form Health Survey (SF-36v2), mental component summary scores were also below the norm and declined post-intervention (Figure 4-14). Emotional role and vitality were aspects of quality of life that consistently scored below average, while scores for social functioning declined below average only after intervention. Overall responses in the SF-36v2 showed the subject perceived having better physical than mental health-related quality of life. The scores for physical aspects of quality of life remained similar following HIIT intervention (Table 4-4).

Figure 4-14. Case Six: The 36-Item Short Form Health Survey (SF-36v2) mental component summary scores PRE and POST interval training intervention.

Table 4-4. Case Six: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; PCS = physical component summary score).

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Summary of findings

Key findings from this case study are that the subject was able to adhere to the 16 week HIIT programme safely despite initial anxiety associated with exercise and cessation of anti-depressant medication during the programme. However, symptoms of anxiety and depression were severe at baseline and worsened on review post-intervention. This psychological distress was reflected in aspects of the subject’s quality of life. Perceptions of physical functioning scored better and remained a stable component of the participant’s quality of life. Meanwhile, the impact of fatigue on activities of daily living was high at baseline and improved following training even though reported vitality declined post-intervention and haematological markers indicated borderline anaemia.

Together, these outcomes could suggest that psychological symptoms were not perceived as having a detrimental effect on physical activities of daily living. Meanwhile, questions on vitality were related to perceptions that may be regarded as more existential in origin. The decline in mental well-being following intervention, and cessation of medication, represented a statistically important change based on established individual responsiveness to change (≥ 3 change score) (Maheswaran, Weich et al. 2012).

Total body fat and lean mass were found to increase above the Lunar iDXA precision error following HIIT intervention although lean mass increased by less than 0.8 kg as an alternative estimate of precision error (Mazess, Barden et al. 1990). While the subject showed negligible change in peak oxygen consumption, her exercise performance in terms of work capacity and strength did show some improvement following intervention. In addition, measurements of cardiac function at rest and during incremental exercise also supported a cardiovascular training effect. Following training, average heart rate variability increased with a reduction in resting and exercising heart rates. These changes could reflect reduced levels of anxiety during testing, and or a fitness training effect.
Case Sixteen.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a non-exercising, retired 74-year-old female.

Presenting condition: This subject had a high BMI (36.5 kg/m²), hypertension and knee osteoarthritis.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a gym bicycle for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 69% attendance of gym sessions and improved general health. Peak cardiopulmonary fitness and perceived physical function did not improve following HIIT intervention. However, body composition analysis identified a reduction in total fat mass and an increase in lean mass post-intervention.

Implications: HIIT intervention was well-tolerated but a combined exercise and dietary intervention may be preferable for improving physical aspects of quality of life and lowering cardiovascular disease risk.
Background

This subject was a retired 74-year-old female and former model. Her presenting concerns were a lack of regular exercise combined with knee osteoarthritis, hypertension and an above average BMI. She reported a family history of heart disease and took anti-hypertensive medications daily (4 mg perindropril and 2.5 mg bendrofluomithazide). She was also diagnosed with osteoarthritis and had undergone a left knee joint replacement two years prior to the study. She participated in sport as a younger adult but no longer engaged in regular exercise.

This subject described long-standing symptoms of impaired sensation in her lower limbs, including cold feet and numbness, and had experienced slow leg wound-healing in the past. On examination, she demonstrated reduced tactile sensation in the lower limbs. Macro-EMG of the left vastus lateralis newly identified a moderately severe, length dependent axonal neuropathy affecting lower limb motor and sensory fibres. Meanwhile, biopsy of the right vastus lateralis confirmed the absence of a genetic mitochondrial disorder and showed that approximately 1-2% of muscle fibres were cytochrome c oxidase deficient, consistent with age-related changes.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 90% (130 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject managed to progress from five to six sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 18 minutes. According to the exercise diary, this subject completed 69% of the training programme (33/47 sessions), with missed sessions mainly due to holiday and poor weather. Interim health review visits in weeks 6 and 12 were completed without complication but the subject was advised to visit her GP following the second visit due to high exercising blood pressure and delayed recovery following maximal exertion. Resting blood pressure was understood to have improved on medical review but the subject’s perindropril dose was increased to 6 mg daily and she was allowed to resume exercise.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity remained unchanged at 116 W following HIIT intervention. Exercising heart rate, minute ventilation and oxygen consumption were all consistently lower post-intervention (Figure 4-15, Figure 4-16 and Figure 4-17). There was a 6% decline in peak oxygen consumption (1.729-1.631 l/min) following HIIT intervention. When adjusted by weight, these results supported no change in exercise capacity (16 ml/kg/min).

Cardiac output and stroke volume

NICOM showed an 8% decrease in stroke volume (64.6-59.2 ml) and 9% reduction in cardiac output (10.9-9.9 l/min) with no change in peak heart rate (168 bpm) following HIIT intervention.

Figure 4-15. Case Sixteen: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Figure 4-16. Case Sixteen: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 4-17. Case Sixteen: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.
Resting heart rate variability

There was a reduction in mean resting heart rate (PRE: 65 ± 4 bpm vs. POST: 60 ± 2 bpm) and an increased RR interval length (RRI) (PRE: 931 ± 50 ms vs. POST: 1007 ± 41 ms) post-HIIT intervention. As a measure of heart rate variability, the RRI standard deviation decreased by 9 ms.

Blood profile and body composition

This subject’s fasted glucose concentration remained within a normal laboratory range, supporting the absence of diabetes as a risk factor for cardiovascular disease, and a leading cause of peripheral neuropathy. However, fasting lipid profiles indicated elevated triglyceride (TG) and low density lipoprotein (LDL) concentrations, increasing the cardiovascular disease risk. There was a reduction in these lipid concentrations and glucose in the blood following HIIT intervention (Table 4-5).

At baseline, this subject was 93rd on the centile for proportion of whole body fat when compared with an age- and gender-matched population. Total body mass decreased by approximately 1 kg with a loss of fat (50229 - 48284 g) and a gain in lean tissue mass (51150 - 52190 g) following HIIT intervention; these changes were in excess of the Lunar iDXA precision error. The proportion of abdominal fat also declined post-intervention but still constituted more than half of the regional tissue mass (android % PRE: 59.7 vs. POST: 56.6), contributing to an AG ratio > 0.89.

Table 4-5. Case Sixteen: fasted blood measures for cardiovascular disease risk PRE and POST interval training intervention (* = above normal).

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<td>LDL</td>
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Lower limb strength performance

There was no significant change in the subject’s right knee extensor/flexor torque when maximal isometric contractions were performed following training and the changes assessed using Wilcoxon’s Signed Rank-Test with interquartile range (right PRE: 129.64 Nm (15.09) vs. POST: 128.96 Nm (11.63), p = 0.241). The weaker left leg with a knee joint replacement showed statistically significant improvement but test performances included multiple outliers (left PRE: 107.74 Nm (10.27) vs. POST: 123.67 Nm (6.78), p = 0.009). There was no change in the peak force for either leg when adjusted by weight (right: 1.4, left: 1.2). Meanwhile, there was an improvement in functional lower limb performance of the 30-second chair-stand test (PRE: 16 stands vs. POST: 19 stands).

Mental well-being and health-related quality of life

This subject was minimally affected by fatigue prior to, and after HIIT intervention according to the Fatigue Impact Scale (PRE: 1/160 vs. POST: 0/160). She reported no symptoms of psychological distress in the Hospital Anxiety and Depression Scale. Prior to exercise intervention, the subject described herself as “pretty fit for [her] age compared with many friends of a similar age.” She identified having “a positive attitude to life”. In terms of limitations, she explained “arthritic knees prevent me from doing long walks (8-9 miles) which I did regularly up to 4 years ago”. Following HIIT intervention, the subject described feeling “healthy, fit and active” and said she enjoyed the cycling exercise. She “did a three mile walk...which caused no problems” and reflected that “since having a knee replacement...[she] found [her] previous distances of 9 mile walks – a bit too long – causing back pains. 3-5 are manageable.” As an indicator of perceived sedentary activity, she reported an average weekday sitting time of five hours, which increased by one hour post-intervention.

Total scores on the Warwick-Edinburgh Mental Well-being Scale were stable and above average before and after HIIT intervention (PRE: 69/70 vs. POST: 70/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) also showed the subject’s mental but not physical component summary scores were above average when compared to a reference population. Perceived general health was the aspect of quality of life that
improved most following training, while the subject’s sense of vitality remained extremely high before and after HIIT intervention (Table 4-6).

Table 4-6. Case Sixteen: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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Summary of findings

This case study shows that perceptually-regulated high-intensity cycling was achieved safely by an older adult with chronic hypertension and knee osteoarthritis. She demonstrated exceptionally high vitality and reasonable gym attendance. Perceptions of general health improved markedly following HIIT intervention, while perceived physical functioning remained the same and there was no change in peak cycling capacity. This subject attained the same peak workload with a lower minute ventilation and heart rate, which may suggest improved cycling efficiency. Regular exercise training could account for these changes but the subject’s increased dose of anti-hypertensive medication may also have influenced test performance. Both exercise training and perindropil medication are associated with enhanced pumping action of the heart although this cardiac response was not reflected in the peak stroke volume, cardiac output or change in resting heart rate variability.

Incidentally, this case study provided diagnostic evidence of a moderately severe peripheral neuropathy. The cause of the subject’s neuropathy was not known but fasted blood tests excluded diabetes as a possible cause. Reduction in the subject’s lower limb pain sensation combined with obesity (> 30 kg/m$^2$) (WHO 2004) and regular long-distance walking perhaps exacerbated degenerative changes in the knee joints, leading to a reduction in physical activity levels as an older adult.
There is limited existing evidence to determine the impact of exercise on functional capacity in peripheral neuropathy, partly due to the heterogeneity of this condition (White, Pritchard et al. 2004). No clear functional gains were identified in this case study following high-intensity interval training but there was a reduction in total body fat mass and increased lean mass in excess of the precision error estimates. A combined exercise and dietary intervention could be effective for lowering cardiovascular disease risk.
Case Twenty One.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a retired 70-year-old female with multiple chronic health conditions.

Presenting condition: This subject presented with a high BMI (33.5 kg/m$^2$), hypertension and spinal spondylosis/spondylolisthesis.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 72% attendance of gym sessions and demonstrated an improvement in cardiopulmonary function and perceived general health although back and knee pain appeared to have a more negative impact on quality of life post-intervention.

Implications: HIIT intervention can be completed safely by individuals with multiple chronic health conditions but assessment and review of the associated risks and benefits must be undertaken on an individual basis, and exercise adapted accordingly.
Background

This subject was a retired 70-year-old female and church warden. Her presenting concerns were spinal spondylosis/spondylolisthesis, hypertension and an above average BMI.

History

The subject presented with long-standing back and neck problems associated with degenerative changes of the spine (spondylosis and spondylolisthesis). Biopsy of the right vastus lateralis confirmed the absence of a genetic mitochondrial disorder and showed approximately 1% of muscle fibres were cytochrome c oxidase deficient, consistent with age-related changes. She reported a family history of heart disease, diabetes and stroke, and was treated for chronic hypertension (5 mg amlopidine and 25 mg losartan daily). She was also prescribed cholesterol-lowering medication (40 mg lipitor daily) and omeprazole (20 mg daily). Prior to the study, this subject engaged in once-weekly, gentle exercise at an over-50s class. She had previously been referred onto a gym exercise programme but was unable to continue this due to joint pains.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 94% (142/151 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject managed to complete five sets of intervals throughout the programme, with an interval training time of 15 minutes. According to the exercise diary, this subject completed 72% of the training programme (34/47 sessions). Reasons given for missed sessions were related to poor weather and back and knee pains. However, interim health review visits in weeks 6 and 12 were completed without complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity remained unchanged following HIIT intervention (99 W). Heart rate was markedly lower throughout incremental exercise following HIIT intervention (Figure 4-18). The pre- and post-training volumes for minute ventilation and oxygen consumption diverged only in the final minute of incremental exercise, when post-training volumes increased rapidly (Figure 4-19 and Figure 4-20). There was an 11% increase in peak oxygen consumption (PRE: 1.365 l/min vs. POST: 1.513 l/min) following HIIT intervention. When adjusted by weight, these results again supported greater exercise capacity following training intervention (17-19 ml/kg/min).

Cardiac output and stroke volume

Following HIIT, there was a 41% increase in the NICOM stroke volume (117.9-165.7 ml) and 22% increase in cardiac output (17.4-21.2 l/min) despite a reduction in peak heart rate (148-128 bpm).

Resting heart rate variability

There was a small reduction in mean resting heart rate post-HIIT intervention (PRE: 59 ± 3 bpm vs. POST: 58 ± 3 bpm) and an increase in RR interval duration (RRI) (PRE: 1019 ± 62 ms vs. POST: 1035 ± 53 ms). However, the RRI standard deviation decreased by 9 ms, suggesting a reduction in heart rate variability.
Figure 4-18. Case Twenty One: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 4-19. Case Twenty One: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Body composition and blood profile

At baseline, this subject was on the 96th centile for whole body fat compared with an age- and gender-matched population. Total body mass increased by 1.8 kg following HIIT, with an increase in both fat (39698 - 40077 g) and lean mass (37112 - 38532 g); these changes were in excess of the Lunar iDXA precision error. Abdominal fat constituted just over half of the regional tissue mass (android % PRE: 51.7 vs. POST: 51.0) and contributed to a high AG ratio > 0.89. As a prognostic marker for osteoporosis, the subject’s bone mineral density (BMD) was found to be within a normal age-matched range but a t-score of -1.2 was indicative of age-related osteopenia.

Fasted glucose concentration decreased by 0.7 mmol/l post-intervention and remained within a normal laboratory range, supporting the absence of diabetes. Also, this subject’s cardiovascular disease risk was reduced by the presence of elevated high-density lipoprotein cholesterol in the blood (Table 4-7).
Table 4-7. Case Twenty One: fasted blood measures for cardiovascular disease risk PRE and POST interval training intervention (* = above normal).

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Lower limb strength performance

There was a reduction in the dominant, left leg torque when maximal isometric knee extensor/flexor contractions were performed and changes assessed using Wilcoxon’s Signed Rank Test with interquartile range (left PRE: 105.77 Nm (1.3) vs. POST: 99.26 Nm (1.2), p = 0.214). There was also a statistically significant decrease in the weaker right leg force although multiple outliers were found in these data (right PRE: 87.87 Nm (4.54) vs. right POST: 82.51 Nm (2.98), p = 0.009). Similarly, the peak knee extensor/flexor torque decreased in both legs following intervention and these trends were supported by weight-adjusted strength ratios in the right leg (PRE: 1.2 vs. POST: 1.1) and left leg (PRE: 1.3 vs. POST: 1.2). In contrast, functional lower limb strength showed improvement in the 30-second chair-stand test following HIIT intervention (PRE: 11 stands vs. POST: 14 stands).

Mental well-being and health-related quality of life

This subject was unaffected by fatigue prior to, and after HIIT intervention according to the Fatigue Impact Scale. In terms of psychological distress, she reported minimal symptoms on the Hospital Anxiety and Depression Scale (PRE: 6/42 vs. POST: 5/42). The subject described herself as “pretty fit” prior to HIIT intervention and referred to her “enjoyment of life”. She reported having multiple medical conditions but felt that these were under control. Following training, she described her fitness as “pretty average” and indicated having “a bit of trouble with [her] knees” affecting her enjoyment of cycling exercise. As an indicator of perceived sedentary behaviour, the subject reported an average weekday sitting time of 10-12 hours, which decreased by 4-6 hours post-intervention.
Total scores on the Warwick-Edinburgh Mental Well-being Scale were stable before and after HIIT intervention (53/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) on health-related quality of life suggest the subject perceived having better mental than physical components of quality of life. However, physical and mental component summary scores both declined following HIIT intervention. In particular, the subject’s bodily pain and perceived physical role became prominent factors in the decline in her quality of life. Vitality and social functioning were other aspects of the subject’s quality of life that also declined, while perceived general health improved post-intervention (Table 4-8).

Table 4-8. Case Twenty One: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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Summary of findings

The 16-week high-intensity interval training programme was completed safely but this subject’s adherence was affected by long-standing back and knee pain. Prior to training, she reported a high level of mental well-being but habitual physical activities were limited by spinal spondylosis /spondylolisthesis. She associated her fitness with being able to keep her health conditions under control.

This subject showed no improvement in peak work capacity but oxygen consumption increased rapidly in the final minute of testing post-intervention. The difference in oxygen consumption could infer improvement in test performance rather than a cardiopulmonary training effect. Crucially however, measurements for peak stroke volume were more than 40% higher following training, supporting a cardiovascular training effect. Furthermore, resting heart rate was also lower post-intervention although reduction in the resting heart rate variability did not support improvement in cardiopulmonary fitness. Aside from possible cardiovascular adaptations, total lean body mass increased above precision error estimates; functional lower limb performance improved post-intervention in the 30-second chair-stand test and peak torque declined in isometric knee extensor/flexor tests. These results may reflect the impact of knee pain on the subject’s exercise performance with maximal exertion.

This subject was obese with a BMI in excess of 30 kg/m² (WHO 2004), representing an independent risk factor for cardiovascular disease (ACSM 2010) and potentially exacerbating symptoms of knee pain. Total body fat mass increased above the Lunar iDXA precision error following intervention. However, fasting glucose and lipid profiles did not reflect an elevated cardiovascular disease risk. Regulation of the lipid profile may be attributed, in part, to the use of cholesterol-lowering medication. The subject’s elevated high-density lipoprotein is also thought to have a cardio-protective effect (ACSM 2010).

In conclusion, high-intensity interval training was completed safely by the subject but the impact of joint pain may have inhibited both exercise training and test performance. This subject learnt to adjust her physical activity in order to manage long-term health conditions. Nevertheless, she reported both improved general health and increased bodily pain following HIIT intervention.
Key findings

- Only 4/50 adults entered and completed this exercise study, highlighting a major issue in the recruitment of sedentary adults to exercise intervention. The commitment and assessment procedures, in particular muscle biopsy, were major contributing factors according to those who declined participation.

- The participating four subjects were overweight or obese and prescribed at least one medication at the beginning of the study; three of the four subjects experienced a change in their medication during intervention that could also potentially influence study outcomes.

- Across an age range of 22-74 years, leg muscle biopsies consistently showed only 0-2% COX-deficient fibres as an indicator of mitochondrial dysfunction and age-related change. Other novel findings from the four sedentary case studies included the identification of a heart murmur (Case One), peripheral neuropathy (Case Sixteen), hypercholesterolemia and hypertriglyceridemia (Case Sixteen), borderline anaemia (Case Six) and osteopenia (Case Twenty One).

- Self-reported exercise adherence ranged from 69-96% with variable training progression. The oldest two subjects reported their exercise habits being limited by joint problems, while the younger subjects reported a lack of motivation. Other reasons given for missed gym sessions included holiday and poor weather.

- Levels of psychological distress were elevated in the two younger subjects and were reflected in much lower mental than physical components of health-related quality of life in contrast to the two older subjects.

- All subjects’ showed a lower resting heart rate following HIIT intervention. The subjects also improved functional performance in the 30-second chair-stand test.
In terms of responsiveness to cycling training, only the younger two subjects increased peak cycling work capacity and resting heart rate variability following HIIT intervention. The peak oxygen consumption increased markedly for Case One, decreased for Case Sixteen and increased by 4-11% for Cases Six and Twenty One. Only Case One reported subjective improvement in fitness following training and showed increases in cardiac output and arterio-venous oxygen difference. Also, Case One was the only subject who showed increased weight-adjusted peak torque ratios for both lower limbs during isometric knee extensor/flexor contractions pre- and post-HIIT intervention. However, Cases Six, Sixteen and Twenty One showed increased total lean body mass above the Lunar iDXA precision error. All subjects showed increased total body fat mass above the Lunar iDXA precision error following HIIT intervention.

There are three-fold implications from these case findings: firstly, inherent differences between the subjects’ baseline health status and responsiveness to training were qualified only through extensive diagnostic and exercise assessment. Secondly, inherent and environmental differences were found to have an impact on subject’s exercise adherence and progression, and potentially on their exercise outcomes. Finally, only one of the four subjects showed consistent improvement across the exercise outcomes following HIIT intervention. These findings demonstrate the importance of a battery of clinical exercise assessments to identify therapeutic potential.
Chapter 5. Results from Adults with Inclusion Body Myositis

Recruitment, health screening and baseline characteristics

During the recruitment phase of this study, seventeen adults with IBM declined taking part, primarily due to activity limitations associated with their physical impairments. Of those initially interested in taking part, one person was contraindicated for ischaemic heart disease. Two individuals were excluded for using beta-blocker medication and another person was excluded for using warfarin medication. During baseline assessment, one individual was excluded for breathlessness and heart arrhythmia, requiring onward medical referral.

Only one male and one female with IBM completed baseline assessments and proceeded to HIIT intervention. The very low recruitment rate demonstrates a major limitation for prescribing exercise in this condition. Nevertheless, both subjects were able to complete the HIIT programme (Figure 5-1); their baseline characteristics are summarised in Table 5-1 and responses to exercise investigated in the following case studies.

Figure 5-1. A flow diagram of the recruitment of adults with inclusion body myositis into interval training intervention.
Table 5-1. Baseline characteristics of adults with inclusion body myositis who completed high-intensity interval training intervention (FH = parent/grandparent family history).

<table>
<thead>
<tr>
<th>Subject</th>
<th>008</th>
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<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
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<tr>
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<td>Occupation</td>
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<tr>
<td>Habitual exercise</td>
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<td>Upper limb weights daily</td>
</tr>
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<td>Lung disease/breathing problems</td>
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<td>N</td>
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<tr>
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<tr>
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</tr>
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<tr>
<td>FH stroke</td>
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</tr>
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</table>
Case Eight.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a retired 60-year-old female with sporadic inclusion body myositis.

Presenting condition: This subject presented with muscle weakness associated with sporadic inclusion body myositis. She also had rheumatoid arthritis and hypertension.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 90% attendance of gym sessions and showed improvement in aerobic exercise capacity and peak isometric knee extensor/flexor torque but not cardiac output following HIIT intervention.

Implications: HIIT has therapeutic potential for improving cardiopulmonary fitness in adults with sporadic inclusion body myositis. Further investigations may need to specifically determine the impact of exercise on pulmonary function.
Background

This subject was a 60-year-old female and retired teacher. Her presenting concerns were sporadic inclusion body myositis, rheumatoid arthritis and hypertension. The subject was diagnosed with IBM less than one year prior to the study and reported symptoms for approximately five years before diagnosis. Her rheumatoid arthritis was diagnosed three years before the IBM diagnosis. She was prescribed anti-rheumatic medication (20 mg methotrexate weekly) with a folic acid supplement (5 mg weekly). She was also treated for chronic hypertension (5 mg of amlodipine daily) and had a family history of heart disease and stroke.

This subject did not engage in any structured exercise but she kept physically active through dog-walking and gardening. Specific physical activities affected by her condition included climbing stairs and rising from a chair. She reported sometimes suffering from falls and experienced tiredness with moderate to prolonged exertion. Biopsy of the right vastus lateralis could not determine the level of mitochondrial dysfunction as only fat and connective tissue were identified in the muscle sample.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. Exercise intensity was perceptually-regulated using Borg’s 6-to-20 scale, and adjusted by speed and power (wattage). There was no heart rate monitor integrated into the gym bicycle, however, heart rate was expected to be a less useful indicator of exercise intensity as 90% of the subject’s peak heart during incremental exercise testing was equivalent to 118 bpm only. During programme familiarization, cycling speed responses peaked at 65 revolutions per minute, and cycling power peaked at 85-90 Watts, exceeding the peak work capacity attained in the baseline incremental exercise test. The subject managed to complete five sets of intervals throughout the programme, with an interval training time of 15 minutes. According to the exercise diary, this subject completed 90% of the training programme (43/47 sessions). During week 12, she experienced a fall and dislocated a finger. However, the subject was able to return to training promptly and completed both interim health review visits without complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 22% (76-93 W) following HIIT intervention. While exercising heart rate remained similar (Figure 5-2), the exercising minute ventilation and oxygen consumption increased post-intervention (Figure 5-3 and Figure 5-4). There was a 39% increase in peak oxygen consumption (0.846-1.175 l/min) following HIIT intervention. When adjusted by weight, these results again supported greater exercise capacity following HIIT intervention (16-23 ml/kg/min).

Unexpectedly, the subject’s oxygen consumption continued to rise during the active recovery period following incremental exercise tests pre- and post-intervention (Figure 5-5). In conjunction with this observation, ventilatory volumes continue to increase while the heart rate decreases immediately on lowering the workload. Both tests show a peak oxygen consumption occurring 10 seconds after the peak work performance. Pre-intervention oxygen consumption increased by an additional 0.029 l/min and post-intervention by 0.042 l/min, supporting further increments in peak oxygen consumption.

Cardiac output and stroke volume

Following HIIT, there was a 15% decrease in the NICOM stroke volume (82.6-69.8 ml) and 10% reduction in cardiac output (10.6-9.5 l/min) with 6% increase in peak heart rate (128-136 bpm). According to Fick’s Principle, the arterio-venous oxygen difference at peak exercise increased by 4 ml/100ml blood post-HIIT intervention, suggesting enhanced peripheral oxygen utilisation.
Resting heart rate variability

There was a small increase in the mean resting heart rate post-HIIT intervention (PRE: 63 ± 2 bpm vs. POST: 66 ± 1 bpm) and a reduction in the RR interval duration (RRI) (PRE: 948 ± 32 ms vs. POST: 916 ± 18 ms). As a measure of heart rate variability, the RRI standard deviation decreased by 14 ms (32-18 ms).

Figure 5-2. Case Eight: heart rate responses during incremental exercise tests PRE and POST interval training intervention.

Figure 5-3. Case Eight: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.
Figure 5-4. Case Eight: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.

Figure 5-5. Case Eight: oxygen consumption responses during active recovery (PRE-training: 20 W; POST-training: 0-15 W) following peak exercise workload.
**Body composition and blood profile**

At baseline, this subject had a normal BMI (20 kg/m\(^2\)), AG ratio < 0.78 and was on the 41st centile for whole body fat when compared with an age- and gender-matched population. Total body mass decreased marginally following exercise training, with a loss of fat mass in excess of the Lunar iDXA precision error (17766 - 17168 g) and negligible change in lean mass (31686 - 31751 g). As a prognostic marker for osteoporosis, the bone mineral density (BMD) was found to be within a normal age-matched range with a z-score of 0.5. However, the subject’s t-score of -1.3 was indicative of age-related osteopenia.

Fasted blood glucose and glycated haemoglobin (HbA1c) concentrations increased following training but remained within normal laboratory ranges, supporting the absence of diabetes. Fasted lipid profiles also showed normal laboratory values for cardiovascular disease risk except for post-intervention low-density lipoprotein (LDL), which increased by 1.1 mmol/l (Table 5-2). Serum creatinine, as an indicator of low muscle mass, was consistently below normal (PRE: 53 µmol/l vs. POST: 54 µmol/l). But, as a biomarker for muscle damage, serum creatine kinase levels remained within a normal laboratory range pre- and post-HIIT intervention (PRE: 151 U/L vs. POST: 134 U/L).

Table 5-2. Case Eight: fasted blood measures for cardiovascular disease risk PRE and POST interval training intervention (* = above normal).

<table>
<thead>
<tr>
<th>Blood measures (mmol/l)</th>
<th>PRE</th>
<th>POST</th>
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<tr>
<td>Glucose</td>
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<td>5.4</td>
</tr>
<tr>
<td>TG</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>HDL</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>LDL</td>
<td>3.2</td>
<td>4.3*</td>
</tr>
</tbody>
</table>
**Lower limb strength performance**

There were statistically significant improvements in right and left leg torque generation when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test with interquartile range ((PRE right: 26.98 Nm (0.90) vs. POST right: 41.02 Nm (2.68), p = 0.005; PRE left: 35.46 Nm (2.51) vs. POST left: 42.65 Nm (2.37), p = 0.005). Peak knee extensor/flexor torque also increased in both legs following intervention and these changes were supported by weight-adjusted strength ratios in the right leg (PRE: 0.6 vs. POST: 0.9) and left leg (PRE: 0.8 vs. POST: 0.9). Functionally, however, the subject remained unable to move from sitting to standing without the use of her hands.

**Mental well-being and health-related quality of life**

Fatigue Impact scores (FIS) and levels of psychological distress on the Hospital Anxiety and Depression Scale (HADS) were low and decreased following intervention (FIS: 19/160 to 17/160; HADS 8/42 to 5/42). The subject consistently demonstrated below threshold subscale scores for depressive mood (2/22) and anxiousness (6/22 to 3/22) pre- and post-HIIT intervention.

At baseline, the subject described her fitness level “as such that [she is] able to go for a reasonably long walk (no steep descents) – say six miles without feeling too exhausted.” Specific limitations to exercise related to “weakness in [her] legs which has caused [her] to fall down on several occasions.” She also “shied away from group exercise classes…because of this weakness…” Following HIIT intervention, the subject described herself as “active” and added that she had “a fairly busy social life.” She indicated that she became tired faster: “I used to be able to garden all day now I find a 3 hour stint about long enough.” She thought that “the tiredness is a symptom of rheumatoid arthritis - as well as age!”
Total scores on the Warwick-Edinburgh Mental Well-being Scale increased following HIIT intervention (PRE: 55/70 vs. POST: 59/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) on health-related quality of life suggest this subject perceived having better mental than physical components of quality of life. Both physical and mental aspects of quality of life declined post-intervention. In particular, perceived physical role and mental health scores declined most, while the lowest score for perceived physical functioning remained unchanged (Table 5-3).

Table 5-3. Case Eight: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

<table>
<thead>
<tr>
<th></th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
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<td>POST</td>
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<td>55.9</td>
<td>50.0</td>
<td>54.9</td>
<td>41.6</td>
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</table>

**Summary of findings**

The 16-week high-intensity interval training programme was completed safely and was well tolerated, with 90% gym session attendance. Key findings from this case study were evidence of increased peak work capacity and oxygen consumption following exercise training, supporting an improvement in cardiopulmonary fitness. Yet, cardiac haemodynamics suggest peak stroke volume was lower following training and that exercising heart rate remained similar. Together, these findings may support a pulmonary training effect primarily. While impaired pulmonary function may not be recognised as a key feature of inclusion body myositis (IBM), a 12-year follow-up study found that disorders of the respiratory system were the most common cause of death in IBM (Cox, Titulaer et al. 2011). The unexpected rise in oxygen consumption during active recovery from cardiopulmonary exercise appeared to correspond with a rise in the ventilatory volume. Such discrepancy between oxygen consumption and work load is not known to have been reported in past exercise studies.
In addition to improved peak work capacity, this subject attained markedly increased isometric peak torque for knee extensors/flexors and had a higher proportion of lean body tissue post-intervention. These changes are important because inclusion body myositis is associated with progressive muscle loss, fat infiltration and weakness, particularly affecting the knee extensors (Cox, Reijnierse et al. 2011). The findings reflect possible skeletal muscle conditioning with HIIT although functionally the subject remained unable to move from sitting to standing unaided. Indeed, previous findings suggest that muscle strength can improve in IBM but improves more in the less affected muscles (Spector, Lemmer et al. 1997). Therefore, the subject’s improvement in strength performance could reflect an enhanced ability to compensate for specific muscle weakness. Blood tests showed the subject had consistently low creatinine, a breakdown product of muscle creatine. This test result is anticipated to be a consequence of muscle atrophy in IBM.

Despite having multiple chronic health conditions, the subject attributed post-intervention feelings of tiredness specifically to rheumatoid arthritis and ageing, and not IBM. The Fatigue Impact Scale (FIS) failed to reflect worsening symptoms of tiredness post-intervention. Indeed, total scores for FIS and the Hospital Anxiety and Depression Scale did not suggest symptoms of fatigue or psychological distress were strongly impacting on the subject’s everyday activities. However, improvement in mental well-being following intervention represented a statistically important change based on established individual responsiveness to change ($\geq 3$ change score) (Maheswaran, Weich et al. 2012).
Case Twelve.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a retired 71-year-old male with sporadic inclusion body myositis.

Presenting condition: This subject presented with knee joint instability and muscle weakness associated with sporadic inclusion body myositis. He also had a high BMI (30.7 kg/m$^2$) and hypertension.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: Reported health improvement was not clearly reflected in exercise outcomes despite an increase in peak exercise oxygen consumption and excellent adherence to HIIT intervention.

Implications: Health and exercise outcome measurements may need to be constructed differently to better assess therapeutic potential in complex muscle diseases, such as sporadic inclusion body myositis.
Background

This subject was a 71-year-old male and retired mechanical engineer. His presenting concerns were an above average BMI (30.7 kg/m²), sporadic inclusion body myositis (IBM) and hypertension. The subject was diagnosed with IBM one year prior to the study and he reported the first symptoms of IBM affecting his left knee for approximately one year before diagnosis. He had previously experienced multiple left anterior cruciate ligament tears, and stated that the problem with his knees pre-dated any muscle problems. This subject had no known ischaemic heart disease or family history of heart disease, stroke or diabetes although he was receiving treatment for chronic hypertension at the time of the study (4 mg doxosin daily).

No cardiac or other potential contraindication to HIIT intervention was identified at baseline. The subject undertook daily upper limb exercise at home using dumbbell weights. Specific activities managed with great difficulty included rising from a chair and sitting up from lying. He used an elbow crutch to assist walking due to knee instability.

Previous biopsy of the left vastus lateralis identified the presence of inclusion bodies, inflammatory infiltrate and fat deposition. There were multiple mitochondrial DNA deletions present and approximately 30% of muscle fibres were cytochrome c oxidase deficient, indicative of mitochondrial dysfunction in excess of normal ageing. In addition, macro-EMG of the right vastus lateralis was performed during isometric contraction of the quadriceps. Findings at baseline showed no evidence of impulse block or increased jitter but repeated testing post-intervention showed a marked reduction in signal amplitude with 5% block and 40% jitter, indicating possible denervation.
HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. Exercise intensity was perceptually-regulated using Borg’s 6-to-20 scale, and adjusted primarily by pedal resistance (wattage). Heart rate was not used by the subject to guide exercise intensity due to poor reliability of the heart rate monitor. The subject noted his left foot slipping from the pedal on several occasions, making it particularly difficult for him to adjust cycling speed to elevate his heart rate. He managed to complete five sets of intervals throughout the programme, with an interval training time of 15 minutes. According to the exercise diary, this subject completed 104% of the training programme (49 sessions) despite experiencing some knee pains. However, interim health review identified ECG abnormalities with no accompanying signs or symptoms. Cardiology review of the ECGs indicated there were long-standing ischaemic changes and possibly more recent changes. Following medical review, this subject was allowed to continue his exercise programme to completion.

Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved slightly following HIIT intervention (61-66 W). Exercising minute ventilation, heart rate and oxygen consumption were all lower relative to the workload following training however (Figure 5-6, Figure 5-7 and Figure 5-8). There was an 8% increment in the peak oxygen consumption (1.233-1.337 l/min) following HIIT. When adjusted by weight, these results supported enhanced exercise capacity following HIIT intervention (13-15 ml/kg/min). The subject’s oxygen consumption continued to rise for 30 seconds during post-test active recovery (Figure 5-9). Similarly, ventilatory volumes continued to increase while the heart rate decreased immediately on reducing workload. In total, pre-intervention oxygen consumption increased to 1.368 l/min, surpassing the peak exercise oxygen consumption post-intervention.
Cardiac output and stroke volume

NICOM showed a 12% decline in stroke volume (161-142.4 ml) and 10% reduction in cardiac output (10.6-9.5 l/min) with a 3 bpm difference in peak heart rate (147-150 bpm). According to Fick’s Principle, the arterio-venous oxygen difference at peak increased by 1 ml/100ml blood post-HIIT intervention.

Resting heart rate variability

There was a decrease in the mean resting heart rate (PRE: 71 ± 2 bpm vs. POST: 66 ± 2 bpm) and increased RR interval length (RRI) (PRE: 844 ± 25 ms vs. POST: 916 ± 29 ms) post-HIIT intervention. As a measure of heart rate variability, the RRI standard deviation increased by 4 ms (25-29 ms).

Figure 5-6. Case Twelve: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.
Figure 5.7. Case Twelve: heart rate responses during incremental exercise tests PRE and POST interval training intervention.

Figure 5.8. Case Twelve: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.
Figure 5-9. Case Twelve: oxygen consumption responses during active recovery (PRE and POST-training: 0 W) following peak exercise workload.

Body composition and blood profile

At baseline this subject was on the 100th centile for whole body fat when compared with an age- and gender-matched population. However, total body mass decreased by 3.6 kg following HIIT, with a loss of fat (43296 - 41257 g) and lean mass (44977 - 43612 g) in excess of precision error estimates. Abdominal fat constituted over half of the regional tissue mass (android % PRE: 59.3 vs. POST: 58.4) and contributed to an AG ratio > 0.89. Blood tests showed the subject had elevated serum creatine kinase (PRE: 650 U/L vs. POST: 504 U/L) and low creatinine concentrations (PRE: 51 µmol/l vs. POST: 47 µmol/l), consistent with muscle damage and low muscle mass. However, no abnormalities in either fasted glucose or lipid profiles were identified to suggest an elevated cardiovascular disease risk.
**Lower limb strength performance**

Functionally, the subject was unable to move from sitting to standing without the use of aids and this did not change following exercise intervention. The subject’s left leg strength could not be assessed using an isokinetic dynamometer due to limited knee range of movement. However, maximal right knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test with interquartile range. There was a statistically significant reduction in the average isometric force although multiple outliers were present (PRE: 33.97 Nm (0.40) vs. POST: 32.61 Nm (0.65), p = 0.005) but no change in the weight-adjusted peak strength ratio (0.4).

**Mental well-being and health-related quality of life**

When the subject was asked to describe his fitness prior to exercise intervention, he indicated that knee problems “prevented... physical exercises” and limited his fitness. During the HIIT programme he reported palpable change in his quadriceps muscle bulk and improvement in his walking. Following intervention, the subject said he felt “reasonably fit and healthy” and was able to do most things for himself although he was not as fit as 15-20 years ago.

Fatigue Impact scores increased marginally following exercise training (38/160 to 40/160) despite a reduction in reported symptoms of psychological distress according to the Hospital Anxiety and Depression Scale (HADS). This subject consistently demonstrated an above threshold subscale score for depressive mood (≥ 8/22) before and after HIIT intervention, while anxiousness decreased below threshold following intervention (Figure 5-10).
Figure 5-10. Case Twelve: Hospital Anxiety and Depression Scale scores for Anxiety (HADS-A) and Depression (HADS-D) PRE and POST interval training intervention.

Ratings on the Warwick-Edinburgh Mental Well-being Scale (PRE: 41/70 vs. POST: 42/70) and mental components of the 36-Item Short Form Health Survey (SF-36v2) remained similar and below average before and after HIIT intervention. Meanwhile, the subject’s overall physical aspects of quality of life declined with worsening pain but better perceived general health (Table 5-4).

Table 5-4. Case Twelve: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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<tr>
<td>POST</td>
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<td>42.7</td>
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</tbody>
</table>
Summary of findings

Degenerative knee joint changes and progressive leg muscle weakness severely affected this subject’s movement and everyday function. Diagnostic blood tests and muscle biopsy confirmed evidence of inflammatory changes and mitochondrial abnormalities that were expected to be a secondary manifestation of inclusion body myositis. In addition, this subject showed ECG evidence of cardiac ischaemia and abnormal EMG findings in the quadriceps muscle that had not been identified previously. It was postulated that denervation may have occurred within the quadriceps muscle. This process is associated with reduced muscular force, atrophic changes, loss of microvasculature and increased interstitial connective tissue (Carlson 2004).

There was insufficient evidence to conclude whether macro-EMG changes occurred in response to HIIT, altered disease activity or methodological sampling error. However, there was a small, significant decline in isometric quadriceps leg strength following HIIT intervention. Despite considerable disability, this subject demonstrated excellent adherence to the 16-week HIIT programme. It is anticipated that health benefits from the HIIT programme were less adequately captured due to outcome measure limitations. Also, the subject indicated that he had tried to lose weight during the exercise programme, which could have affected exercise outcomes. Results suggested a reduction in total fat and lean body mass in excess of the precision error. However, proportion of total body fat remained at the upper end of a reference population spectrum, which was expected to reflect abnormal soft tissue distribution due to muscle disease, as well as obesity (BMI > 30kg/m²) (WHO 2004).

As the primary outcome measure, peak oxygen consumption increased following training yet the pre-intervention active recovery oxygen consumption exceeded peak exercise oxygen consumption post-intervention. Peak stroke volume also declined post-intervention despite an increase in work capacity. Although functionally the subject remained unable to move from sitting to standing without the use of aids, self-reported anxiousness and perceived general health did improve following HIIT intervention. Further development of the health outcome measures used to assess adults with neuromuscular conditions could help to capture health improvement more effectively. However, understanding the underlying pathophysiology will also be essential for tailoring therapeutic assessment.
Key findings

- Only 2/24 adults with sporadic Inclusion Body Myositis (IBM) entered and completed the exercise study, demonstrating a very low recruitment rate. Crucially, the nature and severity of many adults’ disability was given as the reason for declining exercise participation.

- Both adults who completed the study had multiple comorbidities and used medications that could influence study outcomes and might be considered contraindications in other studies; these include rheumatoid arthritis and treatment with a muscle-disease modifying agent, obesity, evidence of cardiac ischaemia at health review and use of cardiovascular-related medications. Combined with a low recruitment rate, these factors highlight the potential pitfalls of assessing therapeutic potential in complex neuromuscular conditions, such as IBM.

- Macro-EMG and muscle biopsy investigations provided supplementary evidence of myopathic changes and mitochondrial abnormalities in excess of normal ageing for one of the two subjects. Normal EMG findings and fatty replacement of biopsied muscle in the other subject support the need for developing a specific biomarker for IBM.

- In terms of similarities, neither subject was able to rise from sitting without using their upper limbs. As a component of functional outcome measurement, this movement limitation did not change following exercise intervention. The subjects described leg weakness and knee problems as the reasons for their exercise limitation. However, both managed either regular upper limb exercises or outdoor physical activity prior to intervention. These subjects reported at least 90% gym attendance over 16 weeks of HIIT intervention.
Both subjects showed increased peak work capacity, oxygen consumption and arterio-venous oxygen difference following intervention. However, oxygen consumption continued to increase immediately after incremental exercise testing despite reductions in workload and heart rate. Also, peak cardiac stroke volume and cardiac output declined following HIIT intervention, as a measure of cardiovascular training effect.

Isometric knee extensor/flexor torque could not be assessed in the male subject’s more affected leg due to range of movement restrictions. No improvement was recorded in his dominant leg strength, whereas weight-adjusted peak torque increased bilaterally for the female subject post-intervention.

No subjective improvement in fitness was reported following exercise intervention despite improved peak aerobic exercise capacity. In terms of quality of life, most physical aspects remained the same or declined for these two subjects following HIIT intervention. Meanwhile, mental aspects of quality of life were consistently above average for the female subject and below average for the male subject. In fact, results from the Hospital Anxiety and Depression Scale suggested that the male subject had a sub-clinical depressive mood although his scores improved post-intervention.

Overall, there was a lack of consistency in exercise outcomes both within and between subjects following HIIT intervention. In part, this inconsistency could be attributed to individual differences in health status and pathophysiology, identified through extensive clinical and histological assessment. However, there were also major limitations found in applying and interpreting outcome measures that are more commonly used to evaluate interventions in healthy populations, such as DEXA body composition and physiological exercise capacity. It is anticipated that further development and validation of IBM biomarkers will be essential for understanding the impact of therapeutic intervention. Abnormal oxygen consumption responses following incremental exercise testing may also require further investigation.
Chapter 6. Results from Adults with Mitochondrial Disorders

Recruitment and health screening
During the recruitment phase of this study, four individuals with mitochondrial disorders were excluded for using beta-blocker medication and three individuals were excluded for ischaemic heart disease. Seven potential subjects also declined taking part due to other commitments and medical issues.

On medical consultation, two individuals were withdrawn from the study due to exercise risk associated with (i) hypertensive responses and (ii) poorly controlled diabetes combined with a below average body mass index. These individuals, carrying an RRM2B mutation and mitochondrial RNA mutation respectively, were referred for further clinical investigations and follow-up.

In total, six people with mitochondrial disease (3 males and 3 females) completed baseline assessments and proceeded to HIIT intervention. Strict exclusion criteria contributed to a low recruitment rate. Following screening, however, all six subjects completed exercise intervention (Figure 6-1).

Baseline characteristics
Subjects recruited into HIIT were aged 62 ± 15 years, Caucasian and living in different regions of England at the time of the study (Tyne and Wear; Northumberland; Lancashire; Greater Manchester; Merseyside and Norfolk). The three female subjects who completed HIIT were aged 60-66 years and two of the three males were over 70 years old. Only one of the six subjects was in employment at the time of the study.

Four of the subjects who completed HIIT previously participated in regular exercise or were recreationally active. The eldest subject performed no structured exercise but engaged in regular moderate-to-vigorous activities, such as home renovation. Two subjects reported having a family history of heart disease, including one obese, non-exercising female. This subject also had a family history of stroke and had experienced an ischaemic brain haemorrhage and trans-ischaemic attack in the past.
The subjects’ baseline characteristics highlight a spectrum of musculoskeletal impairments and exercise tolerance. Six of the eight subjects with mitochondrial disease had a mitochondrial DNA maintenance disorder, exhibiting a relatively mild phenotype in which progressive external ophthalmoplegia (PEO) and ptosis were primary neurological features. The other two subjects presented with additional neurological manifestations, associated with single and multiple mitochondrial DNA deletions. Baseline characteristics of the six subjects recruited into HIIT are summarised in Table 6-1 and detailed in the following case studies.

Figure 6-1. A flow diagram of the recruitment of adults with mitochondrial disorders into interval training intervention.
Table 6-1. Baseline characteristics of adults with mitochondrial disorders who completed high-intensity interval training intervention (FH = parent/grandparent family history).

<table>
<thead>
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</tbody>
</table>
Case Three.

Abstract

*Rationale:* To assess how high-intensity interval training (HIIT) affects the health of a retired 60-year-old female with mitochondrial disease.

*Presenting condition:* This subject presented with asthma and symptoms of ataxia, bilateral ptosis and chronic progressive external ophthalmoplegia.

*Intervention:* Three times per week of perceptually-regulated HIIT was completed on a gym bicycle for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

*Outcomes:* This subject reported 89% attendance of gym sessions and demonstrated increased peak exercise capacity along with substantial weight loss.

*Implications:* HIIT intervention was completed without complication but findings did not reflect a clear enough training effect to support changing the subject’s usual exercise. Further pulmonary function testing might help to tailor exercise therapy more effectively.
Background

This subject was a 60-year-old female and retired pharmacy assistant. Presenting concerns were balance and visual impairments associated with the mitochondrial disorder (ataxic gait, bilateral ptosis and chronic progressive external ophthalmoplegia). This subject had a clinical diagnosis of multiple mitochondrial DNA deletions. She had a history of unsteady gait, tripping and tiredness on prolonged exertion but did not use a walking aid. She also had lifelong asthma, for which she was prescribed becotide and ventolin inhalers twice daily. This subject reported a family history of stroke. She enjoyed hiking occasionally and attended 2 x 45-minute aqua-aerobic sessions and a gym session with weights each week.

On examination, pulmonary function tests suggested the subject had a low to borderline normal forced vital capacity (FVC), consistent with a restrictive lung disorder. She attained 73-82% of the predicted normal FVC based on age, gender and height (2.06-2.31 l/2.83 l) (Bellamy, Booker et al. 2005). Biopsy and histopathological analysis of the right vastus lateralis showed approximately 9% ragged red fibres and 1-2% cytochrome c oxidase deficient muscle fibres.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 90-109% (159 bpm) of the maximum NICOM heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject managed to progress from five to eight sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 24 minutes. According to the exercise diary, this subject completed 89% of the training programme (42/47 sessions). Despite exercise progression, she recorded “getting fed up” and “need change” by weeks 4 to 5 of the programme. She recorded missed sessions due to holiday and highlighted that her exercise exertion was limited by the heat at times. Interim health review visits in weeks 6 and 12 were completed without complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 14% (79-90 W) following HIIT intervention. Post-intervention minute ventilation and oxygen consumption volumes appeared markedly higher during early-stage exercise and then converged with pre-intervention values towards peak exercise capacity (Figure 6-2 and Figure 6-3). There was an 8% increase in peak oxygen consumption (0.965-1.041 l/min) following HIIT intervention. When adjusted by weight, these results supported greater exercise capacity post-intervention (16-19 ml/kg/min).

At baseline, the subject’s oxygen consumption continued to rise for 30 seconds during post-test active recovery, while the post-intervention volume increased for 20 seconds beyond the peak exercise volume (Figure 6-4). Minute ventilation also continued to increase during post-test active recovery. These changes are critical because pre-intervention oxygen consumption increased to 1.050 l/min during recovery, which exceeds the peak exercise oxygen consumption post-intervention.

Cardiac output and stroke volume

NICOM showed a 14% increase in stroke volume (81.7-93.2 ml) and 19% improvement in cardiac output (12.0-14.3 l/min) with 8 bpm difference in peak heart rate (146-154 bpm).

Resting heart rate variability

There was a decrease in the mean resting heart rate post-HIIT intervention (PRE: 68 ± 13 bpm vs. POST: 59 ± 3 bpm) and an increase in the RR interval duration (RRI) (PRE: 909 ± 105 ms vs. POST: 1020 ± 54 ms). As a measure of heart rate variability, the RRI standard deviation decreased by 51 ms.
Figure 6-2. Case Three: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-3. Case Three: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.
Body composition and blood profile

This subject lost 6.6 kg in body mass post-intervention, lowering her from the 82nd to 57th centile for the proportion of body fat when compared with an age- and gender-matched population. Regional fat distribution was also affected by this weight loss, with more than 10% reduction in abdominal fat (android % PRE: 47.2 vs. POST: 34.8) and attenuation of the AG ratio (0.83-0.69). Both fat (25909 - 19918g) and lean mass (32393 - 31830g) were lost over the course of the study and in excess of Lunar iDXA precision error estimates. Fasted lipid profiles highlighted elevated low and high-density lipoprotein at baseline, and a reduction in LDL following HIIT intervention (Table 6-2).

<table>
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<tr>
<th>Blood measures (mmol/l)</th>
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<tbody>
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<td>0.6</td>
</tr>
<tr>
<td>HDL</td>
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<td>2.5*</td>
</tr>
<tr>
<td>LDL</td>
<td>4.4*</td>
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</table>
Lower limb strength performance

There was a small, statistically significant reduction in left leg torque when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test with interquartile range (PRE right: 89.5 Nm (7.7) vs. POST right: 88.89 Nm (4.20), p = 0.415; PRE left: 82.04 Nm (7.80) vs. POST left: 77.57 Nm (3.56), p = 0.0021). Conversely, there was an increase in weight-adjusted peak torque ratios post-intervention for the right leg (PRE: 1.6 vs. POST: 1.9) and the left leg: (PRE: 1.5 vs. POST: 1.6). Functionally, the subject was able to perform > 8 unassisted chair-stand repetitions but appeared to avoid full extension in standing to maintain balance.

Mental well-being and health-related quality of life

This subject was minimally affected by fatigue and psychological distress according to the Fatigue Impact Scale (5/160 to 2/160) and the Hospital Anxiety and Depression Scale (3/42 to 0/42). At baseline the subject described her fitness as “good overall” and she reported feeling “fairly fit” after finishing the 16-week study. Her perceived exercise limitations specifically related to standing balance.

Mental and physical component summary scores for health-related quality of life were above average in the 36-Item Short Form Health Survey (SF-36v2) and remained stable following intervention (Table 6-3). Total scores on the Warwick-Edinburgh Mental Well-being Scale also remained high and unchanged post-intervention (67/70).

Table 6-3. Case Three: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

<table>
<thead>
<tr>
<th></th>
<th>PF</th>
<th>RP</th>
<th>BP</th>
<th>GH</th>
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<tr>
<td>POST</td>
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</table>
Summary of findings

This subject safely completed 16 weeks of high-intensity interval training intervention. Exercise diary entries suggest the HIIT programme may not have been varied enough for this subject, despite high adherence. Entries also highlight a potential limitation of intensity-based exercise in that over-heating affected vigorous exertion.

Other findings from the case study include increased peak work capacity, oxygen consumption and cardiac stroke volume despite less training time per week than her previous exercise commitments. However, the subject’s peak oxygen consumption increased during the active recovery after incremental exercise, such that pre-intervention recovery volumes exceeded the peak exercise value post-intervention. This finding could compromise evidence of an improvement in cardiopulmonary fitness. Furthermore, the reduction in heart rate variability following training appears to contradict evidence for improved cardiovascular function.

In terms of exercise capacity, the subject showed negligible change in isometric knee extensor/flexor strength following training, and she was minimally affected by fatigue and psychological distress that might affect exercise tolerance. Balance impairment appeared to limit functional lower limb performance more than strength, in conjunction with previous findings that multiple physiological and psychological processes affect this transfer skill (Lord, Murray et al. 2002). Meanwhile, the subject’s marked weight loss and reduction in fat mass suggest dietary modification during exercise intervention, which is expected to affect exercise performance.

HIIT intervention did not give sufficient evidence to advocate changing this subject’s usual exercise habits. However, further investigation of the subject’s pulmonary function could help to tailor aerobic exercise therapy and maximise cardiopulmonary fitness.
Case Four.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a 47-year-old male with mitochondrial disease.

Presenting condition: This subject had a single large-scale mitochondrial DNA deletion.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: HIIT intervention was completed safely with access to a network of health professionals. The subject reported 70% attendance of gym sessions and demonstrated increased exercise capacity and physical aspects of health-related quality of life.

Implications: HIIT intervention can have therapeutic potential in complex chronic health conditions provided there is sufficient clinical support.
Background

This subject was a 47-year-old male and self-employed engraver. His presenting concerns were manifestations of mitochondrial disease including ataxia, fatigue, chronic progressive external ophthalmoplegia and bilateral ptosis. Nutritional co-enzyme Q10 supplements were taken regularly as part of mitochondrial disease management. He also had epilepsy, for which he was prescribed tegretol twice daily (500 mg). This subject was diagnosed with mitochondrial myopathy caused by a single mitochondrial DNA deletion. Biopsy and histopathological analysis of the right vastus lateralis showed more than 40% cytochrome c oxidase deficient muscle fibres and analyses were consistent with his diagnosis. Multi-systemic manifestations in the previous 12 months included worsening of visual acuity, gastro-intestinal symptoms, seizure, migraine headaches and mild gait impairment. Despite difficulty managing prolonged exertion, this subject exercised regularly, attending the gym three times per week for approximately 30 minutes of weight-training primarily. He was a smoker (10-20 daily) and did not drink alcohol.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 90-98% (150-163 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject managed to progress from five to six sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 18 minutes. According to the exercise diary, this subject completed 70% of the training programme (33/47 sessions). He recorded a lot of stress delaying him starting exercise training and careful pacing of exertion and activities during the programme. He completed interim health review visits safely but experienced a seizure the day after his second review. His epilepsy medication was changed to a slow-release form of tegretol and he was allowed to continue the exercise programme following medical review and an additional joint session with the study physiotherapist. He recorded “feeling nervous, worried and unconfident” on returning to exercise but then described gradually re-gaining confidence and motivation to complete the programme.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 11% (146-162 W) following HIIT intervention. Trends in exercising heart rate and minute ventilation were similar pre- and post-training (Figure 6-5 and Figure 6-6) but the oxygen consumption was greater following HIIT intervention (Figure 6-7). There was a 26% increase in peak oxygen consumption (1.724-2.174 l/min) following HIIT intervention. When adjusted by weight, these results supported greater exercise capacity following HIIT intervention (21-26 ml/min). At baseline, the subject’s oxygen consumption continued to rise for 20 seconds during post-test active recovery but there was an immediate decline in the post-intervention volumes (Figure 6-8). These differences in oxygen consumption indicate only 6% change in overall peak volumes following intervention (0.106 l/min).

Cardiac output and stroke volume

Following HIIT, there was a 55% increase in NICOM stroke volume (95.0-147.3 ml) and 64% improvement in cardiac output (15.1-24.7 l/min) with 9 bpm difference in peak heart rate (159-168 bpm).

Resting heart rate variability

There was a marginal decrease in the mean resting heart rate post-HIIT intervention (PRE: 60 ± 3 bpm vs. POST: 59 ± 3 bpm) and an increase in the RR interval duration (RRI) (PRE: 1011 ± 52 ms vs. POST: 1014 ± 56 ms) post-HIIT intervention. As a measure of heart rate variability, the RRI standard deviation increased by 4 ms.
Figure 6-5. Case Four: heart rate responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-6. Case Four: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.
Figure 6-7. Case Four: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-8. Case Four: oxygen consumption during active recovery (PRE-training: 0-20 W; POST-training: 0 W) following peak exercise workload.
**Body composition and blood profile**

This subject was on the 100th centile for whole body fat when compared with an age- and gender-matched population. Total body mass increased by 2.2 kg following HIIT, with increased fat mass in excess of precision error estimates (30147 - 32204 g) and negligible change in lean mass (47830 - 48000 g). Abdominal fat constituted less than half of the regional tissue mass (android % PRE: 44.3 vs. POST: 48.3) but contributed to an AG ratio ≥ 0.89. Whole body bone mineral density (BMD) was found to be below a normal age-matched range with a z-score of -2.0, indicating osteopenic changes in excess of normal ageing.

Meanwhile, as a biomarker for low muscle mass, serum creatinine levels were below normal following HIIT intervention. The fasted glucose and lipid profiles did not identify any abnormalities except for elevated high-density lipoprotein pre- and post-intervention (PRE: 2.3 mmol/l vs. POST: 1.9 mmol/l).

**Lower limb strength performance**

The subject was able to move from sitting to standing unaided and consistently managed more than 8 stands in the 30-second chair-stand test despite muscle and balance impairments. There was a statistically significant increase in right leg torque with multiple outliers (PRE right: 176.6 Nm (7.40) vs. POST right: 197.3 Nm (5.83), \( p = 0.007 \)) and a decrease in left leg force (PRE left: 142.52 Nm (14.72) vs. POST left: 120.62 Nm (14.84), \( p = 0.005 \)) when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test. The peak knee extensor/flexor torque showed similar trends following intervention and these were supported by weight-adjusted strength ratios for the right leg (PRE: 2.2 vs. POST: 2.7) and the left leg (PRE: 1.9 vs. POST: 1.6).
Mental well-being and health-related quality of life

When asked to describe his fitness prior to HIIT intervention, the subject said “compared to a ‘normal’ person, I suppose I am not fit but bearing in mind my mitochondrial condition I feel that I am not in too bad condition for my age.” Specific exercise limitations related to his elderly parents needing more help and support as well as time commitments with voluntary work and housework. The subject reflected that if he felt less motivated he sometimes missed a session “because I know that I will suffer for pushing myself.” Following HIIT intervention, the subject said “On the whole I think my level of fitness is not too bad... Compared to friends my age I am in reasonable shape.” When asked again about exercise limitations, the subject stated that “The obvious issue is Mitochondrial disease...” He expressed frustration about losing his driving licence following an epileptic seizure, which affected habitual exercise.

The Hospital Anxiety and Depression Scale (HADS) showed this subject experienced above average levels of psychological distress, which worsened following intervention. He consistently demonstrated an above threshold subscale score for anxiousness (≥ 8/22) (Figure 6-9). The impact of fatigue on this subject was also evident in the Fatigue Impact Scale and worsened following intervention (73/160 to 90/160).

Figure 6-9. Case Four: Hospital Anxiety and Depression Scale scores for Anxiety (HADS-A) PRE and POST interval training intervention.
Total scores on the Warwick-Edinburgh Mental Well-being Scale remained below average before and after HIIT intervention (42-40/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) also showed below average mental component summary scores for quality of life, which declined following HIIT intervention. Physical component summary scores were markedly below the norm but increased post-intervention; perceived physical functioning remained unchanged, while physical role was the aspect of this subject’s quality of life that improved most following the HIIT programme. Conversely, perceived emotional role was the aspect of quality of life that declined most following HIIT intervention (Table 6-4).

Table 6-4. Case Four: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training intervention (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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<td>30.3</td>
<td>30.2</td>
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</table>
Summary of findings

This subject’s functional capacity was affected by multiple chronic health problems associated with mitochondrial disease. Despite symptoms of fatigue and loss of confidence following an epileptic seizure, the subject managed to complete 70% of a 16-week high-intensity interval training programme. Key findings from the case study were an increased peak work capacity, peak oxygen consumption and stroke volume even though the subject exercised regularly prior to intervention. While these changes support a cardiopulmonary training effect, the peak stroke volume was recorded at a higher peak heart rate post-intervention. Also, incremental exercise tests showed a continued increase in baseline oxygen consumption during active recovery, reducing the overall difference in peak oxygen consumption. Resting heart rate variability improved as a surrogate measure for cardiac function. However, ECGs, body composition scans and blood tests did not consistently indicate an elevated cardiovascular disease risk that could be targeted with HIIT intervention.

Body composition analysis showed this subject had osteopenic changes that were in excess of normal ageing, increasing his fracture risk. As a 47-year-old male, such decline in bone mineral density might be a side of effect of anti-convulsant medication. DEXA scans also highlighted a proportion of total body fat that was at the upper end of a reference population despite having a normal body mass index. It is anticipated these soft tissue results partially reflect muscle atrophy, secondary to mitochondrial dysfunction. Functionally, lower limb strength performance was not impaired to the extent that the subject had difficulty performing movements such as rising from sitting although there was marked evidence of mitochondrial dysfunction in the quadriceps muscle. While mitochondrial disease strongly impacted on this subject’s activities of daily life, he seemed to perceive limitations in terms of meeting other people’s needs. Responses to health-related questionnaires showed elevated anxiousness and below average quality of life.
Case Seven.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of an active 60-year-old female with mitochondrial disease.

Presenting condition: This subject presented with a mitochondrial DNA maintenance disorder associated with a familial p.Leu381pro PEO1 gene mutation.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 96% attendance of gym sessions and demonstrated enhanced exercise tolerance but persisting muscle symptoms.

Implications: HIIT intervention demonstrated therapeutic potential for increasing the functional capacity of a physically active adult with mitochondrial disease.
**Background**

This subject was a 60-year-old female and housewife. Her presenting condition included symptoms of leg stiffness, soreness, burning and cold sensations. She had chronic progressive external ophthalmoplegia, bilateral ptosis, proximal myopathy and gastrointestinal symptoms associated with the mitochondrial disorder. She was medication-free but used nutritional co-enzyme Q10 supplements regularly. Biopsy of the right vastus lateralis showed approximately 8% cytochrome c oxidase deficient muscle fibres and 3% ragged red fibre-type accumulations, consistent with a genetic diagnosis of familial p.Leu381pro PEO1 (Twinkle) mutation. In the previous 12 months, multisystemic manifestations included mild gait impairment but she reported no difficulties in managing everyday functional activities. This subject also had a family history of heart disease. She was physically active, playing 2-hour sessions of badminton three times per week and fell-walking once weekly.

**HIIT and health review**

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 93% (158 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject progressed from five to eight sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 24 minutes. According to the exercise diary, this subject completed 96% of the training programme (45/47 sessions) with missed sessions due to holiday. Interim health review visits in weeks 6 and 12 were completed without complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 25% (114-143 W) following HIIT intervention. Exercising minute ventilation and heart rate were lower post-training (Figure 6-10 and Figure 6-11), while the oxygen consumption was higher following HIIT intervention (Figure 6-12). There was a 28% increase in peak oxygen consumption (1.277-1.638 l/min) following HIIT intervention. When adjusted by weight, these results supported greater exercise capacity post-intervention (23-31 ml/kg/min). During active recovery, the subject’s baseline oxygen consumption continued to rise for 30 seconds although there was an immediate decline in the post-intervention volumes on lowering the exercise workload (Figure 6-13). Crucially, these differences in oxygen consumption supported only 8% change in overall peak volumes following intervention (0.068 l/min).

Cardiac output and stroke volume

NICOM showed an 8% reduction in stroke volume (64.6-59.2 ml) and 9% lower cardiac output (10.9-9.9 l/min) with the same peak heart rate (168 bpm). According to Fick’s Principle, the arterio-venous oxygen difference at peak exercise increased by 5 ml/100ml blood post-HIIT intervention.

Resting heart rate variability

There was no change in the mean resting heart rate post-HIIT intervention (PRE: 62 ± 3 bpm vs. POST: 62 ± 3 bpm) and negligible change in RR interval duration (RRI) (PRE: 972 ± 40 ms vs. POST: 973 ± 45 ms). As a measure of heart rate variability, the RRI standard deviation increased by 5 ms.
Figure 6-10. Case Seven: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-11. Case Seven: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Figure 6-12. Case Seven: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-13. Case Seven: oxygen consumption responses during active recovery (PRE-training: 10-25 W; POST-training: 0 W) following peak exercise workload.
**Body composition and blood profile**

At baseline, this subject was on the 28th centile for whole body fat when compared with an age- and gender-matched population. She had a normal BMI (22.4 kg/m²) and an AG ratio < 0.78. This subject’s total body mass decreased only marginally following HIIT (0.4 kg) with a reduction in fat mass (16882 – 16036 g) but an increase in lean mass (35196 - 35687 g) in excess of the Lunar iDXA precision error. Her fasted blood tests showed that high-density lipoprotein (HDL) was consistently elevated (PRE: 2.3 mmol/l vs. POST: 2.4 mmol/l) and post-intervention creatinine levels were below average, as an indicator of low muscle mass.

**Lower limb strength performance**

Functional lower limb strength performance improved following HIIT intervention according to performance in the 30-second sit-to-stand test following HIIT intervention (PRE: 10 stands vs. POST: 14 stands). Yet, average knee extensor/flexor force was significantly lower post-intervention (PRE right: 80.50 Nm (5.4) vs. POST right: 71.46 Nm (6.07), p = 0.013; PRE left: 80.01 Nm (4.78) vs. POST left: 69.70 Nm (4.06), p = 0.005), as were weight-adjusted peak torque ratios for the right leg (PRE: 1.6 vs. POST: 1.5) and left leg (PRE: 1.6 vs. POST: 1.5).

**Mental well-being and health-related quality of life**

The subject described her baseline fitness as “moderate to good, but declining” and following training said that she felt “active, fit and healthy.” She stated “taking part in the H.I.T. research has made my level of fitness and endurance better.” However, she reported persisting symptoms of muscles hurting and tiring with exercise following intervention. The effect of fatigue on this subject’s everyday activities remained similar following training, according to the Fatigue Impact Scale (34/160 to 36/160). In the Hospital Anxiety and Depression Scale (HADS), symptoms of anxiousness increased above a subscale threshold post-intervention (> 8/21) (Figure 6-14).
Figure 6-14. Case Seven: Hospital Anxiety and Depression Scale scores for Anxiety (HADS-A) PRE and POST interval training intervention.

Total scores on the Warwick-Edinburgh Mental Well-being Scale remained stable before and after HIIT intervention (52-53/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) also remained stable and indicated that the case perceived having better mental than physical components of health-related quality of life (Table 6-5).

Table 6-5. Case Seven: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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Summary of findings

The 16-week high-intensity interval training programme was completed safely and with a high level of adherence. This subject described an improvement in her fitness and endurance following HIIT intervention despite being physically active prior to the study. These comments were supported by a lower sub-maximal exercise heart rate, greater resting heart rate variability and increased cycling capacity post-intervention. Yet, baseline peak oxygen consumption continued to increase during the active recovery following incremental exercise, reducing the overall increase in oxygen consumption from 28% to 8% post-intervention. Peak heart rate recorded by the NICOM device remained the same, while the corresponding stroke volume and cardiac output decreased following training, which could support greater work capacity with less cardiac exertion. However, these results also suggest that peak cardiac capacities during intense cycling may have been under-estimated, with lower peak heart rates recorded compared with 12-lead electrocardiography.

Alongside increased peak work capacity, the subject showed an increase in lean body mass with marginal weight loss following intervention. These changes were not reflected in peak isometric knee/extensor flexor torque although functionally she increased chair-stand repetitions in the 30-second sit-to-stand test. Also, blood tests highlighted low creatinine levels post-intervention, which can be a sign of decreased muscle mass associated with myopathy despite DEXA evidence of increased overall lean mass following HIIT intervention.

In terms of clinical symptoms, it was postulated that high-intensity interval training would demonstrate therapeutic potential in the management of fatigue. While the subject showed enhanced cycling exercise tolerance with training, her muscle symptoms persisted and experienced fatigue levels remained similar. There was no evidence of hypoglycaemia or anaemia that might contribute to more generalized fatigue symptoms and mental well-being remained stable. Micro-trauma of the subject’s skeletal muscle fibres with intense exertion perhaps contributed to secondary leg soreness. In conclusion, this subject’s clinical symptoms did not appear to improve with high-intensity interval training although there was evidence of improved exercise tolerance.
Case Eleven.

Abstract

**Rationale:** To assess how high-intensity interval training (HIIT) affects the health of a non-exercising 60-year-old female with mitochondrial disease.

**Presenting condition:** This subject presented with a mitochondrial DNA maintenance disorder associated with a PEO1 gene mutation.

**Intervention:** Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

**Outcomes:** This subject reported 70% attendance of gym sessions and showed a lack of improvement in exercise capacity but improved hyperglycaemia and aspects of mental well-being.

**Implications:** Exercise intervention showed therapeutic potential for managing cardio-metabolic risk in mitochondrial disease. However, the effectiveness of intensity-regulated exercise may require further investigation into the exercise motivation of previously non-exercising adults with chronic health conditions.
Background

This subject was a 60-year-old female, recently made redundant. Her presenting condition included symptoms of fatigue, hypertension and an above average BMI (31.8 kg/m²). Specific manifestations associated with the mitochondrial condition included ataxia, progressive external ophthalmoplegia and bilateral ptosis. The subject was diagnosed with a Twinkle helicase mutation (PEO1 gene). In the previous 12 months, her gait stability was affected by occasional falls but she was able to walk without an aid. She had a ventriculoperitoneal shunt inserted following intraventricular haemorrhage 10-11 years before the study. She also experienced a transient ischaemic attack seven years prior to the study, and was prescribed daily aspirin at the time of the study. She was prescribed adipine, bendrofluazide and atorvastatin for hypertension and elevated blood cholesterol. Nutritional coenzyme Q10 supplements were taken regularly as part of mitochondrial disease management. This subject had a family history of heart disease and stroke. At the time of the study she engaged in no regular exercise or habitual physical activities.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. Exercise intensity was adjusted primarily by pedal resistance (wattage) with exercise tolerance limiting initial heart rate responses to 82% (131 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. After an initial delay starting exercise, the subject managed five sets of intervals throughout the programme, with an interval training time of 15 minutes. According to the exercise diary, this subject completed 70% of the training programme (33/47 sessions) with some missed sessions due to holiday. Interim health review visits were completed without complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity declined by 10% (93-84 W) following HIIT intervention. The oxygen consumption dipped unexpectedly during submaximal cycling post-intervention (Figure 6-15). There was a 29% decrease in peak oxygen consumption (1.519-1.080 l/min) following HIIT intervention. When adjusted by weight, these results again indicated lower exercise capacity post-intervention (20-14 ml/kg/min). During active recovery, the subject’s baseline oxygen consumption continued to rise for 10 seconds up to 1.573 l/min, further increasing the overall oxygen consumption difference between pre- and post-intervention tests.

Cardiac output and stroke volume

NICOM showed a 15% decrease in stroke volume (96.3-81.7 ml) and 24% reduction in cardiac output (15.2-11.5 l/min) with a 17 bpm difference in peak heart rate (158-141 bpm).

Resting heart rate variability

There was a reduction in the mean resting heart rate (PRE: 78 ± 2 bpm vs. POST: 74 ± 2 bpm) and increased RR interval duration (RRI) (PRE: 772 ± 17 ms vs. POST: 816 ± 23 ms) post-HIIT intervention. As a measure of heart rate variability, the RRI standard deviation increased by 6 ms.
Body composition and blood profile

This subject had a baseline BMI of 31.8 kg/m² and was on the 88th centile for whole body fat when compared with an age- and gender-matched population. Total body mass increased by 1.8 kg following HIIT, with increased fat mass in excess of precision error estimates (33919 - 35436 g) and negligible change in lean mass (38864 - 39064 g). Abdominal fat constituted more than half of the regional tissue mass (android % PRE: 58.4 vs. POST: 60.1) and contributed to an AG ratio > 0.89. Fasted lipid profile did not show an elevated cardiovascular disease risk but pre-diabetes was diagnosed from the fasted glucose and glycated haemoglobin; this hyperglycaemia decreased by 0.6 mmol/L following HIIT intervention along with a reduction in glycated haemoglobin. Meanwhile, cardio-protective high-density lipoprotein was consistently elevated before and after HIIT intervention (Table 6-6).
Table 6-6. Case Eleven: fasted blood measures for cardiovascular disease risk PRE and POST interval training intervention (* = above normal).

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<th>Blood measures (mmol/l)</th>
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Lower limb strength performance

Functionally, this subject was able to complete 14 chair-stands in 30 seconds at baseline and 13 stands post-intervention. There were no statistically significant changes in right and left leg torque (PRE right: 98.2 Nm (14.2) vs. POST right: 101.29 Nm (5.97), p = 0.878; PRE left: 96.07 Nm (5.29) vs. POST left: 98.99 Nm (6.51), p = 0.093) when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test. Weight-adjusted peak torque ratios also supported unchanged strength performance (right leg: 1.5; left leg: 1.4).

Mental well-being and health-related quality of life

Prior to HIIT intervention, this subject demonstrated above threshold subscale scores for anxiousness and depressive mood in the Hospital Anxiety and Depression Scale (HADs) (≥ 8/22) (Figure 6-16). Along with a reduction in symptoms of psychological distress following training, her Fatigue Impact scores decreased markedly (65/160 to 30/160). When asked about baseline fitness and exercise limitations, the subject said she had “no excuses for not exercising” and felt that “[she’d] like to put that right”. She described going to the gym regularly “as part of Research [she’d] been doing for Newcastle” and consequently felt her fitness was “quite good.”
Figure 6-16. Case Eleven: Hospital Anxiety and Depression Scale scores for Anxiety (HADS-A) and Depression (HADS-D) PRE and POST interval training intervention.

The subject showed below average but improved mental well-being and mental components of quality of life following intervention, according to the Warwick-Edinburgh Mental Well-being Scale (36-41/70) and the 36-Item Short Form Health Survey (SF-36v2). Emotional and physical role were aspects of quality of life that improved most following intervention (Table 6-7).

Table 6-7. Case Eleven: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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Summary of findings

The 16-week high-intensity interval training programme was completed safely and with reasonable adherence considering this subject did no previous exercise and had multiple chronic health conditions. Key findings from the case study included identification of pre-diabetes and a reduction in hyperglycaemia following high-intensity interval training intervention. This outcome is consistent with previous findings in adults with diabetic hyperglycaemia (Little, Gillen et al. 2011).

In addition to evidence of pre-diabetes, this subject had an android: gynoid ratio greater than 0.89 and was obese (≥ 30 kg/m²), supporting increased cardiovascular disease risk (WHO 2004). Although elevated high density lipoprotein suggested a cardio-protective effect, the subject’s family history of heart disease and own past history of transient-ischaemic attack and intraventricular haemorrhage increased her non-modifiable risk of coronary artery disease. High-intensity interval training showed therapeutic potential in reducing hyperglycaemia although there was an increase in fat mass and weight following intervention.

In terms of exercise capacity, the subject showed a lack of improvement in lower limb strength and a reduction in peak cycling performance, oxygen consumption and cardiac stroke volume. As she was feeling well at the time of assessment and engaged in no exercise prior to intervention, these findings might suggest less vigorous exertion post-intervention, and possibly during training also. Exercise intolerance limited heart rate responses during training such that the subject may not have consistently reached a near-maximal heart rate. Motivational aspects of perceptually-regulated exercise performance may need to be considered more closely to deliver intensity-based exercise recommendations.

This subject entered the training programme following a recent redundancy from work and described feeling that she ought to do more exercise. Following training, she related a fitness benefit to her contribution to research. Indeed, the aspects of her health-related quality of life that improved most following intervention were perceived physical and emotional role. Improvement in mental well-being following intervention also represented a statistically important change based on established individual responsiveness to change (≥ 3 change score) (Maheswaran, Weich et al. 2012).
Case Thirteen.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a non-exercising 71-year-old male with mitochondrial disease.

Presenting condition: This subject presented with a mitochondrial DNA maintenance disorder associated with a Twinkle helicase mutation (PEO1 gene).

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 70% attendance of gym sessions and demonstrated increased cycling work load capacity, weight loss and improved physical aspects of quality of life.

Implications: HIIT intervention was completed without complication and showed therapeutic potential for managing cardiovascular disease risk.
Background

This subject was a retired 71-year-old male and carer for his disabled wife. He had an above average BMI (29.1 kg/m²) and engaged in no regular exercise. The manifestations of his mitochondrial disorder included chronic progressive external ophthalmoplegia and bilateral ptosis. Biopsy findings from the left vastus lateralis supported a diagnosis of mitochondrial DNA maintenance disorder and showed that approximately 1% of muscle fibres were cytochrome c oxidase deficient, consistent with age-related changes.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. Exercise intensity was adjusted by cycling speed and pedal resistance (wattage). Heart rate was not used by the subject to guide exercise intensity due to inconsistent functioning of a portable heart rate monitor and lack of monitor integrated into the gym bicycle. This subject managed five sets of intervals throughout the programme, with an interval training time of 15 minutes. According to the exercise diary, this subject completed 70% of the training programme (33/47 sessions). There was an initial delay starting the exercise programme and the subject also missed some sessions due to holiday. He sustained a shoulder injury while on holiday but was able to continue the exercise programme safely. Interim health review visits were completed without complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 15% (97-112 W) following HIIT intervention. Submaximal exercising minute ventilation remained similar, while exercising heart rate was lower post-intervention except for an early spike (Figure 6-17 and Figure 6-18). The submaximal oxygen consumption was also lower following HIIT although incremental exercise was tolerated for longer, which resulted in an increased peak oxygen consumption (1.543-1.566 l/min) (Figure 6-19). When adjusted by weight, these results again supported marginally increased exercise capacity following HIIT intervention (21-22 ml/kg/min). The subject’s oxygen consumption continued to rise over 30 seconds during active recovery, such that the difference was lower than the difference in peak exercise oxygen consumption (1.579-1.595 l/min) (Figure 6-20).

Cardiac output and stroke volume

NICOM showed a 23% decrease in stroke volume (122.3-94.4 ml) and 27% reduction in cardiac output (16.8-12.2 l/min) with a 7 bpm difference in peak heart rate (137-130 bpm). According to Fick’s Principle, the arterio-venous oxygen difference at peak exercise increased by 4 ml/100ml blood) post-HIIT intervention.
Figure 6-17. Case Thirteen: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-18. Case Thirteen: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Figure 6.19. Case Thirteen: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6.20. Case Thirteen: oxygen consumption responses during active recovery (PRE and POST-training: 0 W) from peak exercise work load.
**Body composition and blood profile**

This subject had a baseline BMI of 29.1 kg/m$^2$ and was on the 98\textsuperscript{th} centile for whole body fat when compared with an age- and gender-matched population. Total body mass decreased by 3.8 kg following HIIT, with a reduction in fat (24897 - 21735 g) and lean mass (45631 - 45005 g) in excess of the Lunar iDXA precision error. Abdominal fat constituted less than half of the regional tissue mass (android % PRE: 46.3; POST: 40.8) but contributed to an AG ratio > 0.89. Other cardiovascular disease risk factors, the fasted glucose and lipid profile, remained within normal laboratory ranges.

**Lower limb strength performance**

Functionally, the subject was able to complete 12 chair-stands in 30 seconds at baseline and 10 stands post-intervention. There was a statistically significant improvement in left leg torque (PRE left: 87.12 Nm (4.07) vs. POST left: 118.38 Nm (14.27), p = 0.005) and negligible change in the dominant right leg force (PRE right: 145.0 Nm (17.3) vs. POST right: 142.05 Nm (12.34), p = 0.799) when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test. Peak knee extensor/flexor torque reflected similar changes although weight-adjusted torque ratios supported relative improvement in the left leg (PRE: 1.3 vs. POST: 1.9) and the right leg (PRE: 2.1 vs. POST: 2.2).

**Mental well-being and health-related quality of life**

This subject felt he was “very fit” at baseline but he “[did] not get much time to exercise.” Following HIIT intervention he reported having no limitations to exercise. The subject was minimally affected by fatigue prior to, and after HIIT intervention according to the Fatigue Impact Scale (PRE: 7/160 vs. POST: 4/160). He also reported minimal symptoms of psychological distress in the Hospital Anxiety and Depression Scale (PRE: 2/42 vs. POST 1/42).
Total scores on the Warwick-Edinburgh Mental Well-being Scale were very high above average at baseline and increased following HIIT intervention (65-70/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) also showed the subject’s mental and physical component summary scores were above average when compared to a reference population. Vitality and low impact of pain were the highest scoring aspects of this subject’s quality of life, while perceived general health improved most following HIIT intervention (Table 6-8).

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Summary of findings

The 16-week high-intensity interval training programme was completed safely and with reasonable adherence. At baseline, this subject was physically active as a carer, and felt that he was very fit. Indeed, this subject expressed no health concerns associated with his mitochondrial disorder or any other chronic health condition. He had no known family history of heart disease and fasted blood tests did not identify any increased cardio-metabolic risk. However, the subject was overweight, increasing his risk of cardiovascular disease. Following high-intensity interval training, the subject lost fat mass in excess of precision error estimates and increased cycling workload capacity.

The subject showed an increase in weight-adjusted peak torque for isometric knee extensors/flexors following training, which might suggest skeletal muscle conditioning. Yet, as a primary measure of cardiopulmonary fitness, the weight-adjusted peak oxygen consumption increased by only 1% following HIIT intervention. Combined with a lower peak cardiac stroke volume, this finding suggests negligible change in aerobic fitness with exercise intervention. It is possible that unsupervised, perceptually-regulated training failed to induce a sufficiently elevated heart rate for cardiovascular adaptation. However, the cardiac stroke volume may also have been underestimated as
corresponding heart rates were lower in bioreactance recordings than in 12-lead electrocardiography recording.

In terms of mental well-being, this subject reported minimal psychological distress and scored above average for health-related quality of life. Nevertheless, improvement in mental well-being following intervention represented a statistically important change based on established individual responsiveness to change (≥ 3 change score) (Maheswaran, Weich et al. 2012).
Case Twenty Two.

Abstract

Rationale: To assess how high-intensity interval training (HIIT) affects the health of a retired 80-year-old male with mitochondrial disease.

Presenting condition: This subject presented with a mitochondrial DNA maintenance disorder associated with a familial heterogeneous c.1075G>A PEO1 gene mutation.

Intervention: Three times per week of perceptually-regulated HIIT was completed on a cycle ergometer for 16 weeks. Diagnostic and performance measures were undertaken before, during and after training to monitor the safety and efficacy of HIIT intervention.

Outcomes: This subject reported 98% attendance of gym sessions and demonstrated increased peak work capacity, oxygen consumption and cardiac stroke volume, as well as improved lower limb strength performance.

Implications: HIIT intervention demonstrated therapeutic potential for increasing the functional capacity of a physically active, older adult with mitochondrial disease.
Background

This subject was an 80-year-old male and retired painter and decorator. He presented with marked genu varum and leg stiffness, as well as mild hearing loss and gastrointestinal symptoms. The subject engaged in no structured exercise but kept physically active through home renovation, gardening and wood-chopping. He reported sometimes suffering from tripping but never from tiredness after prolonged exertion. Specific manifestations associated with the subject’s Twinkle helicase mutation (familial heterogeneous c.1075G>A PEO1 gene) included chronic progressive external ophthalmoplegia and bilateral ptosis. Nutritional coenzyme Q10 supplements were taken regularly although the subject was medication-free. Biopsy findings from the left vastus lateralis were consistent with a diagnosis of familial heterogeneous c.1075G>A PEO1 gene mutation and showed approximately 3% cytochrome c oxidase deficient muscle fibres. The subject reported no family history of heart disease, diabetes or stroke but he had an elder sibling with the same mitochondrial DNA mutation.

HIIT and health review

Three times per week of gym-based, recumbent cycling was undertaken over 16 weeks, according to the protocol detailed in Chapter Three. During programme familiarization, heart rate responses peaked at 93% (137 bpm) of the maximum heart rate attained in the baseline incremental cardiopulmonary exercise test. The subject progressed from five to eight sets of intervals by the end of the programme, increasing interval training time from 15 minutes to 24 minutes. According to the exercise diary, this subject completed 98% of the training programme (46/47 sessions) despite ice and snow conditions affecting gym access at times. During the programme he reported improvement in his leg stiffness with exercise; interim health review visits in weeks 6 and 12 were completed without injury or complication.
Exercise outcome assessment

Aerobic exercise capacity

Incremental cardiopulmonary exercise tests showed that peak work capacity improved by 16% (106-123 W) following HIIT intervention. Submaximal minute ventilation, heart rate and oxygen consumption were lower post-intervention (Figure 6-21, Figure 6-22 and Figure 6-23). As incremental exercise was tolerated for longer post-HIIT, there was a 34% increase in peak oxygen consumption (1.480-1.988 l/min. When adjusted for weight change, these results again supported greater exercise capacity following HIIT intervention (20-28 ml/min). The subject’s baseline oxygen consumption continued to rise for 20 seconds during active recovery, such that the overall difference in oxygen consumption was 16% following HIIT intervention (1.665-1.988 l/min) (Figure 6-24).

Cardiac output and stroke volume

Following HIIT, there was a 5% increase in stroke volume (131.6-138.3 ml) and 1% change in cardiac output (18.3-18.5 l/min) with 6 bpm lower peak heart rate (139-133 bpm). According to Fick’s Principle, the arterio-venous oxygen difference at peak exercise increased by 3 ml/100ml blood post-HIIT intervention.

Resting heart rate variability

There was a reduction in the mean resting heart rate post-HIIT intervention (PRE: 61 ± 3 bpm vs. POST: 55 ± 3 bpm) and an increase in RR interval duration (RRI) (PRE: 991 ± 53 ms vs. POST: 1086 ± 47 ms). As a measure of heart rate variability, the RRI standard deviation decreased by 6 ms.
Figure 6-21. Case Twenty Two: minute ventilation responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-22. Case Twenty Two: heart rate responses during incremental exercise tests PRE and POST interval training intervention.
Figure 6-23. Case Twenty Two: oxygen consumption responses during incremental exercise tests PRE and POST interval training intervention.

Figure 6-24. Case Twenty Two: oxygen consumption responses during active recovery (PRE-training: 0-15 W; POST-training: 20 W).
**Body composition and blood profile**

At baseline, this subject was on the 26th centile for whole body fat when compared with an age- and gender-matched population. He had a normal BMI (24.4 kg/m²) and an AG ratio < 0.89. Whole body bone mineral density (BMD) was also found to be within a normal population-matched range with a t-score of 0.2. This subject’s total body mass decreased marginally following HIIT, with a loss of fat (16281-15414 g) and lean mass (53092 - 51907 g) in excess of the Lunar iDXA precision error. Fasted blood tests showed that cardio-protective high-density lipoprotein (HDL) was consistently elevated (2.1 mmol/l) and pre- and post-intervention urea concentrations were above average also.

**Lower limb strength performance**

There were statistically significant improvements in right leg torque (Figure 6-25) and left leg torque when maximal isometric knee extensor/flexor contractions were performed and the changes assessed using Wilcoxon’s Signed-Rank Test although multiple outliers were evident for the dominant left leg (PRE left: 171.81Nm (4.98) vs. POST left: 182.45Nm (4.07), p = 0.017). The peak knee extensor/flexor torque also increased in both legs following intervention and these changes were supported by weight-adjusted strength ratios for the left leg (PRE: 2.5 vs. POST: 2.8) and right leg (PRE: 2.1 vs. POST: 2.3). In addition, functional lower limb strength performance showed improvement in the 30-second chair-stand test following HIIT intervention (PRE: 17 stands vs. POST: 23 stands).
Mental well-being and health-related quality of life

At baseline, the subject reported that “apart from some stiffness in my legs I feel quite fit.” He did not think he was prevented in any way regarding exercise. Following HIIT intervention, this subject stated “I feel very fit and happy and I love physical tasks...” In terms of specific issues limiting exercise, the subject re-iterated having some leg stiffness but that “I don’t let that get in the way at all.” This subject was minimally affected by fatigue and psychological distress prior to, and after HIIT intervention according to the Fatigue Impact Scale (0/160 to 2/160) and the Hospital Anxiety and Depression Scale (4/42 to 3/42).

Total scores on the Warwick-Edinburgh Mental Well-being Scale were very high above average at baseline and increased following HIIT intervention (67-70/70). Responses to the 36-Item Short Form Health Survey (SF-36v2) also showed the subject’s mental and physical component summary scores were above average when compared to a reference population. Vitality was consistently the highest scoring aspect of this subject’s quality of life (Table 6-9).
Table 6-9. Case Twenty Two: The 36-Item Short Form Health Survey (SF-36v2) scale/summary scores for health-related quality of life PRE and POST interval training (PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; MCS = mental component summary score; PCS = physical component summary score).

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Summary of findings

The 16-week high-intensity interval training programme was completed safely and with clear exercise progression. Despite a reduction in resting heart rate variability, peak work capacity, oxygen consumption and cardiac stroke volume all increased following HIIT intervention, supporting a cardiopulmonary training effect. As the intensity of training was perceptually-regulated, this subject’s self-motivation was particularly important in driving exercise progression. He engaged in no structured exercise prior to the study but enjoyed regular physical activity without any pain, cardiovascular co-morbidity or other perceived exercise barrier. He also reported minimal symptoms of psychological distress and above average quality of life. It is anticipated these factors contributed to the subject’s high exercise adherence. Nevertheless, improvement in mental well-being following intervention represented a statistically important change based on established individual responsiveness to change (≥ 3 change score) (Maheswaran, Weich et al. 2012). Having a sibling with the same mitochondrial disorder perhaps shaped this subject’s health perceptions and questionnaire responses, comparatively.
Key findings

- Only 6/22 adults with mitochondrial disease entered and completed the exercise study. Most subjects were recreationally active and half of the subjects were taking no medications other than supplements at the time of the study. A number of adults were excluded from the study for taking beta-blocker medication, which might suggest that the subjects selected for exercise intervention were relatively healthy.

- Novel findings from the study related in particular to Cases Four and Eleven, who presented with major neurological co-morbidities, epilepsy and previous intra-cranial haemorrhage. Body composition analyses showed Case Four had the most histopathological evidence of mitochondrial dysfunction in the quadriceps muscle and also marked osteopenia. He presented with sub-clinical anxiety before and after exercise intervention, according to the Hospital Anxiety and Depression Scale. Similarly, Case Eleven reported sub-clinical psychological distress prior to exercise intervention. She was obese and newly identified as pre-diabetic during study assessments. At the time of the study, only one other subject was overweight (Case Thirteen); he was also the only subject who did not present with elevated high-density lipoprotein levels in the fasted lipid profile. All six subjects exhibited an altered total body fat mass in excess of the Lunar iDXA precision error. However, only Cases Four and Eleven gained fat mass following training intervention.

- Exercise adherence ranged from 70-98% with variable training progression, demonstrating individual differences in training volume that could affect study outcomes. The subjects with major neurological co-morbidities showed the lowest exercise adherence. Missed sessions were mostly attributed to holiday or illness.
As an indicator of exercise tolerance, all subjects apart from Case Eleven increased their peak work capacity and peak exercise oxygen consumption following HIIT intervention. However, the subjects also showed increased overall oxygen consumption during the active recovery following incremental exercise tests, affecting the validity of endpoint measures for cardiopulmonary fitness in this patient population.

Mental and physical aspects of health-related quality of life were below average for Cases Four and Eleven. These subjects scored particularly low on perceived physical role and general health although there was some improvement in these aspects of quality of life following HIIT intervention.

Three subjects specifically made positive reference to their fitness in relation to taking part in the exercise programme although only one subject (Case Seven) described fitness improvement. These subjects included two previous exercisers (Cases Three and Seven) and one subject who did no previous exercise (Case Eleven) and showed a decline in exercise performance following intervention but improved psychological distress and fatigue impact. As an anchor for MCID in peak exercise oxygen consumption, the subjective fitness improvement highlights that perceived exercise benefits may not be adequately reflected in peak exercise performance measures alone.

The eldest subject (Case Twenty Two) presented with no co-morbidities and reported the highest exercise adherence. He was the only person to improve peak work capacity, exercising oxygen consumption, cardiac stroke volume, arterio-venous oxygen difference, weight-adjusted isometric torque for knee extensors/flexors and functional performance in the 30-second chair-stand test. However, he also showed a reduction in total lean body mass following training that was in excess of precision error estimates; two other subjects presented with reduced total lean mass in excess of the Lunar iDXA precision error.
The main implications from these case findings are firstly that subjects with mitochondrial disorders were able to safely perform high-intensity interval training with access to clinical support. However, only one subject demonstrated consistently improved exercise capacity across a range of assessments. Secondly, exercise adherence was lowest for those subjects who had major neurological co-morbidities, limiting the therapeutic potential of HIIT in more severely disabled adults. Those with neurological co-morbidities were also more affected by fatigue, psychological distress and poorer health-related quality of life. As there was some evidence for statistically important individual improvement in mental well-being following training, it may be appropriate to use perceptually-regulated exercise to help promote self-efficacy.
Chapter 7. Group Analysis

Background
In Chapter Two, it was reported that the existing literature on cycling training supports a general improvement in aerobic exercise capacity with different training regimes and across different clinical and non-clinical populations. However, there is a lack of evidence to support other functional gains, improvement in mental well-being and reduction in cardiovascular disease risk in adults with IBM and mitochondrial disorders. On this basis, the following analysis (1) identifies those outcome measures that all subjects were able to complete (2) compares individual responses across clinical and non-clinical populations, and (3) assesses HIIT at group-level for the adults with neuromuscular disease to identify potential trends for investigation on a larger scale.

Selection of exercise outcome measures
As part of this study, subjects’ baseline level of exercise and physical inactivity was determined by self-report. Background information was also collected on neuromuscular signs and symptoms using the Neuromuscular Symptom Score, the Newcastle Mitochondrial Adult Scale and the Newcastle Mitochondrial Quality of Life Scale.

At least one of the twelve recruited subjects was unable to complete the 30-second chair-stand test, non-dominant leg strength assessment, muscle biopsy and macro-electromyography due to the test requirements. However, all recruited subjects completed an exercise diary, incremental exercise tests, fasted blood tests, a DEXA body scan, cardio-autonomic monitoring, dominant leg strength assessment and a series of health-related questionnaires. Completed outcome measures were selected for the comparison of subject responses to HIIT intervention.
Exercise tolerance and cardiopulmonary fitness

Over 16 weeks of high-intensity interval training, adults with IBM and mitochondrial disorders reported exercise adherence equivalent to 84% of the exercise programme (41 ± 7 sessions attended). Incremental cardiopulmonary exercise tests showed a statistically significant increase in these subjects’ peak work capacity following HIIT intervention (PRE: 97 ± 26 W vs. POST: 109 ± 32 W, p = 0.014), as shown in Figure 7-1. The mean increase in peak work capacity was 12.6 Watts with a 95% confidence interval ranging from 3.4 to 21.8 Watts. The eta squared statistic (0.6) indicated a large effect size. However, there was no significant change found in the peak absolute exercise oxygen consumption (PRE: 1.323 ± 0.302 l/min vs. POST: 1.500 ± 0.420 l/min, p = 0.148) or peak relative oxygen consumption (PRE: 20 ± 4 ml/kg/min vs. POST: 23 ± 6 ml/kg/min, p = 0.141). Also, the peak oxygen consumption increased further during post-exercise recovery for all eight of these subjects at baseline and half of all subjects following training intervention. Perceived improvement in fitness was reported by one of the eight subjects following HIIT intervention.

Figure 7-1. Improvement in peak work capacity for subjects with inclusion body myositis and mitochondrial disorders following high-intensity interval training intervention (p = 0.014).

In terms of cardiovascular adaptation, there was no statistically significant improvement in peak exercise stroke volume of subjects with IBM and mitochondrial disease (PRE: 104.4 ± 31.6 ml vs. POST: 103.3 ± 34.7 ml, p = 0.905). The standard deviation of RR interval as a measure of heart rate variability (n = 7) did not change significantly following HIIT intervention (PRE: 46 ± 29 ms vs. POST: 39 ± 15 ms, p = 0.376). Also, Fick’s arterio-venous difference remained similar following HIIT intervention as an indicator of oxygen utilisation during intense exercise (PRE: 9 ± 2 ml vs. POST: 11 ± 4 ml, p = 0.135).
Inter-subject variation may have been too large for clinically meaningful analysis of heart rate variability and cardio-autonomic functioning at group-level. Across all subjects, the youngest adult with no myopathy (Case Six) consistently demonstrated much greater heart rate variability except for an apparent measurement artefact affecting Case Thirteen’s baseline results. Figure 7-2, Figure 7-3 and Figure 7-4 compare the changes in heart rest variability for sedentary adults and subjects with IBM and mitochondrial disease, except for Case Thirteen.

Figure 7-2. Individual change in sedentary females’ heart rate variability (SDRRI) following high-intensity interval training intervention.

Figure 7-3. Individual change in the heart rate variability (SDRRI) of adults with inclusion body myositis following high-intensity interval training intervention.
Lower limb strength performance
There was no significant improvement in the peak isometric knee extensor/flexor torque of subjects with IBM and mitochondrial disorders following HIIT intervention (PRE: $111.65 \pm 57.59$ Nm vs. POST: $118.58 \pm 68.13$ Nm, $p = 0.259$). Muscle weakness was most apparent in the strength assessment of adults with IBM, where peak torque generated by the dominant leg was consistently less than 50 Nm. In terms of functional limitation, the two adults with IBM were also the only subjects unable to perform an unassisted chair-stand.

Body composition
There were no significant changes in total body mass (PRE: $69.8 \pm 13.6$ kg vs. POST: $68.2 \pm 14.1$ kg, $p = 0.169$) or lean tissue mass (PRE: $41209 \pm 7827$ g vs. POST: $40857 \pm 7486$ g, $p = 0.191$) for subjects with IBM and mitochondrial disorders following HIIT intervention.
**Blood biomarkers for cardiovascular disease risk**

Fasted lipid profiles identified no statistically significant changes in the concentration of low-density lipoprotein (PRE: 2.9 ± 0.8 mmol/l vs. POST: 2.9 ± 1.0 mmol/l, p = 0.772) or high-density lipoprotein (PRE: 1.9 ± 0.5 mmol/l vs. POST: 2.0 ± 0.4 mmol/l, p = 0.732). There was also no significant change in non-normally distributed triglyceride levels following HIIT intervention. Only one subject presented with hyperglycaemia in this study, which decreased following HIIT intervention. However, the mean fasted glucose did not decrease significantly across subjects with IBM and mitochondrial disease (PRE: 5.2 ± 0.9 mmol/l vs. POST: 5.1 ± 0.7 mmol/l, p = 0.515).

**Psychological symptoms and mental well-being**

Levels of psychological distress, measured using the Hospital Anxiety and Depression Scale, did not change significantly following HIIT intervention (PRE: 10/42 ± 7 vs. POST: 9/42 ± 7, p = 0.225). There was also no significant change in non-normally distributed ratings of perceived fatigue impact. All subjects in the study who had FIS scores of ≥ 35/160 also presented with symptoms of depressed mood and, or anxiousness in the HAD Scale.

Despite the lack of change in symptoms, subjects with IBM and mitochondrial disease showed a statistically significant improvement in mental well-being following training, according to the Warwick-Edinburgh Mental Well-being Scale (PRE: 53/70 ± 13 vs. POST: 55/70 ± 13, p = 0.049), as shown in Figure 7-5. The mean increase in WEMWBS scores was 2.13 with a 95% confidence interval ranging from 0.01 to 4.24. The eta squared statistic (0.5) indicated a large effect size. Results were also found to be statistically significant across the larger study group upon exclusion of the youngest, sedentary adult (n = 11), who stopped taking medication for clinical depression during the study (PRE: 53/70 ± 13 vs. POST: 55/70 ± 13, p = 0.018).
Figure 7-5. Improvement in mental well-being on the Warwick-Edinburgh Mental Well-being Scale (WEMWBS) following high-intensity interval training intervention in subjects with inclusion body myositis and mitochondrial disorders (p = 0.049).

Health-related quality of life
For subjects with IBM and mitochondrial disease, improvement in mental well-being was not reflected in the 36-Item Short Form Health Survey for health-related quality of life. According to this questionnaire, the mean physical component summary score remained below average before and after HIIT intervention (PRE: 46.6 ± 9.6 vs. POST: 46.8 ± 8.8, p = 0.894). The mental component summary scores were slightly above average but also did not change significantly following HIIT intervention (PRE: 52.6 ± 9.1 vs. POST: 51.1 ± 10.6, p = 0.531).
Summary of findings
There was a high attrition rate during the recruitment phase of this exercise study, particularly in the non-clinical population. While exclusion criteria were less extensive than in many previous studies, the assessments involved considerable time commitment, as well as invasive procedures. Multiple assessment measures provided insight into individual case presentations but were not found to be practicable as exercise outcome measures across a heterogeneous sample population.

Exercise training was well-tolerated based on self-reported programme adherence over sixteen weeks. For adults with IBM and mitochondrial disorders incremental exercise tests also provided evidence of increased peak work although no statistically significant improvement in aerobic exercise capacity following HIIT intervention. There was also no clear evidence found to support cardiovascular adaptation or cardiovascular disease risk reduction after HIIT intervention. However, changes in the WEMWBS suggest that subjects experienced an improvement in mental well-being following HIIT intervention.

A crucial and unexpected finding from this study was the increased oxygen consumption during post-exercise recovery in adults with IBM and mitochondrial disease. Also, evidence of elevated high-density lipoprotein in subjects with mitochondrial disease may need further investigation as a potential cardio-protective factor against cardiovascular disease.
Chapter 8. Discussion

Overview
This is an extensive and detailed study of high-intensity interval training in sedentary adults and patients with neuromuscular disorders, exploring individual responses and providing information for larger studies in the future. Major aspects of this work were the recruitment of subjects from clinical and non-clinical populations, as well as the timely assessment and provision of individual exercise guidance over 16 weeks of intervention. The study author managed these aspects of the work, designing, coordinating and leading most exercise assessments and all of the training in order to optimise the consistency of data collection; this factor is expected to greatly improve the validity of the data.

Safety considerations
This study demonstrated that adults with mitochondrial disorders and IBM were able to safely perform perceptually-regulated HIIT in a community setting with access to clinical support. No cardiac events or musculoskeletal injuries were recorded in response to training intervention although long-standing pains were reported to affect the participation of several subjects during this study. Asymptomatic ECG abnormalities were identified in one subject with IBM but he was able to continue training following medical review and completed all of the exercise training sessions. Typically, this subject would be excluded from participation if such ECG changes were identified at baseline (Blumenthal, Emery et al. 1989). However, previous studies do indicate that HIIT can safely improve myocardial function in adults with cardiovascular disease (Wisløff, Støylen et al. 2007). This subject was the only person who asked for a GP exercise referral on completion of the study.

As an indicator of muscle damage, the male subject with IBM was also the one subject with hallmark signs of elevated serum creatine kinase levels before and after HIIT intervention, as well as macro-EMG findings suggestive of muscle denervation. Therefore, inclusion and exclusion criteria for exercise participation demand careful consideration and review in relation to the available clinical resources and expertise. These criteria are expected to have a fundamental impact on study outcomes for the safety and efficacy of high-intensity interval exercise, as well as patients’ longer term exercise habits.
In previous studies, the exclusion of comorbidities, such as overweight/obesity using body mass indices (Short, Vittone et al. 2005; Harber, Konopka et al. 2009 and Harber, Konopka et al. 2012), might not adequately reflect the spectrum of exercise responses across clinical and non-clinical populations, irrespective of the sample size.

Prior to this pilot study, randomised and quasi-randomised trials on the safety of aerobic training were limited to the study of moderate-intensity continuous exercise in muscle disease (Voet, van der Kooi et al. 2013). Furthermore, previous HIIT studies in other clinical populations have mostly involved intervention based in a clinical setting (El Mhandi, Millet et al. 2008 and Weston, Wisloff et al. 2013). In-depth, multi-disciplinary assessment and review facilitated community-based exercise participation across a wide spectrum of functional capacity in this study. No subject with a neuromuscular disorder dropped out of HIIT intervention although there were three-drop-outs from the sedentary adult group around weeks six and twelve. Reasons given for stopping the programme included unrelated illness, increased workload and preference for alternative exercise. These three subjects reported missing multiple training sessions prior to dropping out of the study and they were the only subjects who did not show evidence of exercise diary completion.

**Aspects of fitness**

This is the first known study to investigate the efficacy of high-intensity interval training in mitochondrial disease and inflammatory myopathy. Seven of the eight subjects demonstrated increased peak workload, as an indicator of improved exercise capacity. Across all subjects included in the study, there was also a statistically significant increase in work capacity. These findings are consistent with previous improvements reported following HIIT in both clinical and non-clinical populations (Weber and Schneider 2002; Duffield, Edge et al. 2006; Edge, Bishop et al. 2006; El Mhandi, Millet et al. 2008; Perry, Heigenhauser et al. 2008; McKay, Paterson et al. 2009; Little, Safdar et al. 2010; Talanian, Holloway et al. 2010; Leggate, Carter et al. 2012; Jacobs, Flück et al. 2013 and Weston, Wisloff et al. 2013).
Despite this significant improvement in peak workload, there was no overall change in aerobic capacity following HIIT intervention in adults with IBM and mitochondrial disorders. In addition to the effect of a small sample size, it has also previously been highlighted that improvement in exercise capacity is lower in a real-world setting than in a clinical setting for HIIT intervention (Lunt, Draper et al. 2014).

In contrast to previous investigations of moderate-intensity continuous aerobic exercise in mitochondrial disease (Taivassalo, Shoubridge et al. 2001 and Taivassalo, Gardner et al. 2006), this study found no significant change in the arterio-venous oxygen difference. Inconsistent evidence for change in cardiac stroke volume, from which the a-v difference is calculated, also failed to conclusively demonstrate a cardiovascular or peripheral training adaptation with HIIT intervention. Furthermore, resting measurement of heart rate variability did not show any significant improvement in cardio-autonomic functioning despite a reduction in resting heart rate for the majority of subjects. Similarly, moderate-intensity continuous aerobic exercise has previously been associated with a lowering of resting heart rate and could be induced by exercise training intervention (Zarins, Wallis et al. 2009 and Katch 2011).

Crucially, peak exercise oxygen consumption may be less valid as a measure of fitness in neuromuscular populations, such as IBM and mitochondrial disease, than in non-clinical populations. One of the novel findings from this study was the evidence of delayed oxygen consumption recovery following intense exercise in adults with IBM and mitochondrial disorders. It is not as yet known whether other disease groups exhibit a similar response following intense exercise. However, an excess post-exercise oxygen consumption (EPOC) has previously been associated with an accumulation of lactate, providing a carbon reservoir for oxidative metabolism and a possible substrate for glycogen repletion (Gaesser and Brooks 1984; Brooks 2002 and Brooks 2009). Also, the typically exponential decline in oxygen consumption following intense exercise may reflect a thermic effect of activity (LaForgia, Withers et al. 2006), associated with phosphagen replacement in muscle. Mitochondrial dysfunction may be expected to influence this thermic effect. HIIT intervention appeared to induce a more normal oxygen consumption response in most of the subjects’ exercise recovery.
Yet, atypical oxygen consumption responses were accompanied by concomitant changes in minute ventilation in this study, suggesting a possible mismatch between lung ventilation and perfusion. Whether this potential mismatch implicates the role of oxygen sensors in chemoreceptors (Prabhakar and Peng 2004 and Prabhakar 2011), the effect of vascular density and, or methodological error remains to be known. However, possible angiopathy and delayed exercise-induced angiogenesis have previously been reported in mitochondrial disease (Jeppesen, Schwartz et al. 2006 and Jeppesen, Duno et al. 2009). In terms of methodological error, these atypical oxygen consumption responses have been observed anecdotally in previous assessments of mitochondrial patients but not observed in apparently healthy adults.

Aside from the oxygen consumption responses to training, previous studies also report increased muscular power and mitochondrial oxidative capacity following aerobic training in neuromuscular disease (Taivassalo, Shoubridge et al. 2001; Taivassalo, Gardner et al. 2006; Jeppesen, Schwartz et al. 2006; Adhihetty, Taivassalo et al. 2007 and El Mhandi, Millet et al. 2008). Importantly, change in mitochondrial oxidative capacity is not assumed to correspond with increments in the maximal oxygen consumption (Bassett and Howley 2000). Although oxidative enzyme activities were not interpreted in this study, individual metabolic adaptions might be anticipated given the normalisation of post-exercise oxygen consumption responses in four subjects with mitochondrial disease following HIIT intervention. In addition, there is evidence from other clinical and non-clinical populations to suggest potential for HIIT-induced adaptation in oxidative capacity (Burgomaster, Hughes et al. 2005; Burgomaster, Howarth et al. 2008; Perry, Heigenhauser et al. 2008; McKay, Paterson et al. 2009; Little, Safdar et al. 2010; Talanian, Holloway et al. 2010; Whyte, Gill et al. 2010; Fisher, Schwartz et al. 2011; Hood, Little et al. 2011 and Little, Gillen et al. 2011).
There was no significant change in the averaged maximal isometric knee extensor/flexor torque following 16 weeks of high-intensity interval cycling in this study. In terms of functional capacity, all subjects’ weight-adjusted strength ratios were consistently below 3.5, which is previously associated with an increased likelihood of having difficulty managing chair-stand performance (Ploutz-Snyder, Manini et al. 2002). In patients with Charcot-Marie-Tooth disease, interval training has been associated with improved functional capacity and perceived fatigue (El Mhandi, Millet et al. 2008). Despite improved chair-stand performance for the majority of subjects in this study following training, only two subjects with IBM were consistently unable to perform an unassisted chair-rise, and they both exhibited below 1.0 weight-adjusted strength ratios. These results suggest that severe isometric leg muscle weakness is a component of transfer skill, which is consistent with the understanding that functional capacity is affected by multiple physiological and psychological processes (Lord, Murray et al. 2002).

**Cardiovascular disease risk reduction**

Three subjects with neuromuscular disease and all four sedentary subjects with no myopathy were overweight or obese upon entering this study. There was no evidence of overall weight reduction following HIIT intervention although there were individual variations in the direction of change for total body mass, fat and lean tissue mass. While weight reduction has been reported following HIIT and sprint interval training, (McKay, Paterson et al. 2009 and Whyte, Gill et al. 2010), it is expected that a combination of exercise and dietary change is needed to optimise weight reduction (Jakicic and Otto 2005).

In this study, cardiovascular disease risk factors in the fasted blood profile were mostly within normal laboratory ranges for subjects with IBM and mitochondrial disease; only one subject presented with pre-diabetic hyperglycaemia at baseline, which improved post-intervention. Overall, no evidence was found for a significant reduction in the fasted glucose, triglyceride or LDL levels following HIIT intervention. Similarly, previous HIIT studies in sedentary and overweight/obese adults have also shown no significant reduction in fasted glucose (Hood, Little et al. 2011 and Leggate, Carter et al. 2012). However, improvement in the 24-hour average glucose has been reported following HIIT in adults with hyperglycaemia associated with type II diabetes (Little,
Gillen et al. 2011). As with weight management, it is postulated that change in the lipid profile is optimised through a combination of exercise, diet and pharmacological therapy (Kelley, Kelley et al. 2004 and Kelley and Kelley 2006).

Unexpectedly, five of the six subjects with mitochondrial disease included in this study had consistently elevated HDL levels, which is usually regarded as a cardio-protective factor (ACSM 2010). Aerobic exercise training is also found to be associated with significantly increased HDL in men and women (Kelley, Kelley et al. 2004 and Kelley and Kelley 2006). Due to the small sample size, it is not clear whether elevated HDL in subjects with mitochondrial disorders was simply a random finding or perhaps provided evidence of an antioxidant response to mitochondrial oxidative stress. In turn, elevated HDL might also reflect increased oxidative stress in response to aerobic exercise.

**Exercise training time commitment**

A common argument for high-intensity interval training (HIIT) is that it offers a time-efficient alternative to moderate-intensity continuous training for improving aerobic exercise capacity (Little, Safdar et al. 2010; Gibala, Little et al. 2012 and Shiraev and Barclay 2012). In this study, subjects improved peak work capacity with as little as 75 minutes of exercise per week, which included a five-minute warm-up and five-minute warm-down. However, much larger-scale investigations would be necessary to determine the relative benefits of HIIT compared with moderate-intensity continuous exercise in neuromuscular disease. It is anticipated that a valid comparison of different training intensities would require supervision, which may not be logistically feasible in a sparsely distributed patient population.
**Change in health perceptions**

In Chapter Two, it was found that few previous studies had assessed the impact of aerobic training, such as HIIT, on subjects’ health perceptions. In this study, perceived psychological distress, fatigue impact and health-related quality of life did not change significantly in subjects with IBM and mitochondrial disease despite individual variations. In contrast, interval training in Charcot-Marie-Tooth disease has been associated with improvement in the symptoms of fatigue using a visual analogue scale (El Mhandi, Millet et al. 2008). Meanwhile, moderate-intensity continuous exercise has been associated with some improvement in symptom severity (Cejudo, Bautista et al. 2005) and better health-related quality of life in adults with mitochondrial disease (Taivassalo, Gardner et al. 2006). Also, studies involving subjects with cardio-metabolic disease have identified improvement in self-reported symptoms of anxiety and depression, as well as perceived quality of life following HIIT intervention (Weston, Wisloff et al. 2013).

Despite a lack of self-reported improvement in symptoms of psychological distress, subjects with IBM and mitochondrial disease reported a small, significant improvement in their mental well-being following HIIT intervention. These differences in outcome are also important because improvement was found in subjects who reported being minimally affected by psychological distress. Subsequently, a symptom-based approach to assessing change may be less relevant than a scale of increasing mental well-being. In addition, the Warwick-Edinburgh Mental Well-being Scale has previously demonstrated individual and group-level responsiveness to change in mental health interventions (Maheswaran, Weich et al. 2012). Based on this analysis, half of the subjects with IBM and mitochondrial disease demonstrated individual improvement in mental well-being that was considered to be more than methodological error (≥ 3 change score). However, a higher change score may be regarded as important by the study population, as indicated previously (Maheswaran, Weich et al. 2012). Enhanced exercise confidence and self-efficacy may represent contributing factors in subjects’ improved mental well-being following perceptually-regulated HIIT intervention. Therefore, qualitative interview and completion of questionnaires relating to illness perceptions and self efficacy could help to better understand patients’ health and exercise perceptions (Weinman, Petrie et al. 1996; Moss-Morris, Weinman et al. 2002 and Broadbent, Petrie et al. 2006).
Invasive assessment procedures
In terms of methodology, a high attrition rate during recruitment to this exercise study indicated that invasive procedures, such as muscle biopsy, were a major factor for adults with no known myopathy. Also, the biopsy procedure could not always be completed if subjects were unable to relax the quadriceps muscle. Application of alternative procedures to muscle biopsy for assessing mitochondrial function could help to facilitate recruitment into future exercise studies.

Previous studies involving phosphorus magnetic resonance spectroscopy (P-MRS) have identified abnormal resting ADP in adults with IBM and mitochondrial disorders compared with controls, as well as a slow recovery of ADP post-exercise in adults with mitochondrial disease (Argov, Taivassalo et al. 1998; Lodi, Taylor et al. 1998 and Trenell, Sue et al. 2006). Despite possible reliability issues with this technique (Berneburg, Gremmel et al. 2005), the findings suggest that P-MRS might help to determine the contribution of muscle bioenergetics to the evidence presented in this study for abnormal, but modifiable, post-exercise oxygen consumption in IBM and mitochondrial disorders.

Sample population size
As the main focus of this pilot study was to provide individual response interpretation to exercise training in neuromuscular disease, statistical analysis of outcomes was limited by a small and heterogeneous sample population. Arguably, the level of variation and extent of comorbidity in apparently healthy adults, as well as those with neuromuscular disorders, is such that a reductionist interpretation of performance-based outcomes may fail to elicit clinically meaningful findings. However, the overall effect size of 0.5 for change in mental well-being on the WEMWBS suggests a sample population size of 28 people would be required with 0.80 power and 0.05 α levels (Cohen 1992).
Performance bias
As with perceptually-regulated training, exercise and performance motivation were expected to influence study outcomes. The primary outcome, aerobic exercise capacity (i.e. peak work capacity and oxygen consumption) was determined by a standardised cardiopulmonary exercise test that all subjects were able to perform, irrespective of muscle weakness. The end-point of each cardiopulmonary exercise test was determined voluntarily by subjects according to their rate of perceived exertion. Subsequently, visual and verbal feedback from assessors and exercise modalities could be a critical factor in exercise performance. While attempts were made to identify and standardise these factors, there remains a lack of reporting in many exercise studies regarding the provision of performance feedback. Assessors’ perceptions of the subjects’ rate of perceived exertion may also need to be examined as part of understanding performance outcomes.

Systematic review of exercise studies has highlighted the issue of assessor blinding in exercise studies as a major limitation in evaluating exercise effect (Pfeffer, Majamaa et al. 2012). Yet, for safety reasons it may be imperative that assessors are aware of subjects’ exercise history and any adverse responses prior to each assessment. As a non-performance outcome measure, resting heart rate variability could help to assess the cardiovascular health of subjects before and after training intervention.

In this study, time domain recordings (approximately 10-15 minutes) were screened for statistical outliers but not abnormal heart rhythms. The standard deviation of normalised RR intervals was selected as a simple measure of heart rate variability. Related time-domain and frequency-domain measures may also be evaluated but these are not yet fully understood in terms of physiological relevance and require additional software to screen for ectopy and artefact (TaskForce 1996) (Nunan, Donovan et al. 2009). A variety of non-linear analytical techniques have been developed that could help to interpret heart rate variability in the future but these have so far been advocated only speculatively as standards of measurement (TaskForce 1996).
**Pharmacological therapy**

Medication and a change in dose could potentially have influenced exercise tolerance and capacity in this study. Only three subjects were prescribed no medication at baseline or following HIIT intervention. Beta-blocker medication was contra-indicated as a potential confounding factor for heart rate reduction following HIIT intervention. As the heart rate responses were integral to training intensity and fitness assessments, multiple potential subjects with neuromuscular conditions were excluded from participating in this study, reducing the sample population size.

Drug therapies, such as anti-hypertensive medication, may also be expected to affect exercise tolerance but were not contraindicated in this study. In addition, one subject with IBM was prescribed a muscle disease-modifying agent, which could influence muscle strength performance. Furthermore, several subjects’ medication dose changed during the study and one subject stopped taking anti-depressant medication, which is also expected to have influenced study outcomes. The impact of these factors has often been averted in previous studies that assess HIIT in adults who are medication-free (Leggate, 2012) or medications are unspecified.

**Feasibility, validation and reliability issues**

Methodological review and practical application of the exercise outcome measures helped to identify potential feasibility, validation and reliability issues. These aspects of outcome measurement were not previously established for people with inclusion body myositis or mitochondrial disorders. Findings from this study indicate that physical disability limited the feasibility of performing gold standard laboratory assessments of strength and fitness in some subjects (i.e. isokinetic dynamometry and incremental cardiopulmonary exercise tests).

Potential issues relating to both validity and reliability were highlighted in the cardiopulmonary fitness parameters. These issues included variation in peak exercise heart rate between different measurement devices and tests, as well as the novel evidence of increased post-exercise oxygen consumption. Anchoring peak exercise oxygen consumption to subjective fitness only appeared to reflect a consistent directional change for two of the twelve subjects, suggesting potential mismatch between perceived and physiological fitness outcomes. In addition, questionnaire completion highlighted different timescales, comprehension difficulties and potential
misinterpretation of questionnaire terminology for psychological and neuromuscular symptoms. From a clinical perspective, the WEMWBS was the only outcome measure tested across different study populations and validated for responsiveness to intervention. Yet, apparently unidimensional measures of both psychological distress and mental well-being may still require further internal validation, such as Rasch analysis, in the study population.

The lack of combined validation and reliability assessment in the study population was a limiting factor for interpreting minimal clinically important difference. DEXA body composition analyses included precision error estimates for repeat scans but a distinction between adipose fat mass and fatty infiltration of lean tissue affected by muscle disease was not identified; following intervention, all subjects’ total fat mass increased or decreased in excess of the precision error, which suggests a physiological response although the precision error could be different in this study population.

In terms of reliability, multiple outcome measures demonstrated statistically acceptable test-retest reliability on methodological review. However, performance measures, such as strength testing, involved highly specific protocols, which would also need to demonstrate satisfactory inter-rater reliability for meta-analysis purposes.
**Study impact and contribution to clinical research**

This study provides novel evidence of the effects of HIIT on clinical and physiological outcomes in adults with IBM and mitochondrial disorders. The study also identifies feasibility issues and the importance of quality control in delivering and assessing HIIT intervention. As a feasibility study, it is anticipated this work will inform the design of future exercise studies in adults affected by a spectrum of neuromuscular conditions. Perceptually-regulated HIIT is shown to facilitate exercise participation for patients with a wide range of disability and fitness levels. For patients and clinicians, this study has also shown that clinically supported high-intensity interval training can be performed safely in a community setting. In terms of exercise benefits, this study suggests that patients’ exercise capacity and mental well-being can improve following 16 weeks of training intervention.

The implications of these findings are that clinicians, researchers and service providers need to consider strategies to facilitate access to supported exercise across the wider patient population. In a real world setting, some patients are unable to access community gym facilities and, or receive no clinical input in relation to exercise therapy. Establishing evidence-based exercise recommendations could help to promote therapeutic service provision in inclusion body myositis and mitochondrial disorders.
Concluding remarks

- Sedentary adults and those with neuromuscular disorders safely performed perceptually-regulated high-intensity interval training (HIIT) with clinical support.

- Overall improvement in peak work capacity supported the therapeutic potential of high-intensity interval training to increase exercise tolerance but not cardiopulmonary fitness.

- Overall improvement in perceived mental well-being in subjects with IBM and mitochondrial disease following HIIT intervention supports the therapeutic potential of perceptually-regulated exercise in mental health.

- A personalised approach to exercise intervention is integral not optional due to individual differences in morbidity and exercise responses.

- Targeting mental health through exercise and physical activity may enhance confidence and self-efficacy in clinical and non-clinical populations.
**Recommendations for future exercise research**

Development of an internationally agreed standard of clinical exercise assessment in neuromuscular disorders is recommended to promote greater transparency and comparison between studies. Essential safety considerations could include (1) medical history and examination (2) fasted blood tests (3) resting cardio-autonomic monitoring, and (4) cardiac-monitored incremental aerobic exercise. In addition, increased emphasis on understanding health perceptions through self-reported outcome measurement is expected to provide greater insight into patients’ self-efficacy, while minimising the assessor bias that has been associated with open exercise trials.

Further clinical investigations need to establish the extent of cardiovascular disease risk in neuromuscular populations to tailor appropriate exercise and, or dietary intervention. Also, large-scale incremental exercise testing is recommended to investigate post-exercise oxygen consumption responses and their significance in relation to neuromuscular disease status, bioenergetics and cardiopulmonary fitness. Finally, exploring mental well-being through qualitative interview may help to inform both training programme design and the therapeutic benefits of perceptually-regulated training in adults with IBM and mitochondrial disease.
References


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