The effects of high-intensity exercise on cardiometabolic health in persons with spinal cord injury

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Farrow, Matthew

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Thesis Abstract

Individuals with a spinal cord injury (SCI) are at an increased risk of developing cardiovascular disease (CVD) in comparison to the general population. Despite convincing evidence in non-injured humans that high-intensity interval training (HIIT) can offer similar or superior metabolic advantages to moderate-intensity continuous training (MICT), the efficacy of this form of exercise has yet to be comprehensively studied in individuals with SCI. The aim of this thesis was to determine the acute and chronic training effects of upper-body high-intensity exercise on markers of CVD risk in persons with SCI. In Chapter 4, a systematic review of the available peer-reviewed research concluded that upper-body aerobic exercise training was effective at reducing waist circumference and improving hepatic insulin sensitivity. However, it was not sufficient to improve fasting glycaemia, the blood lipid profile, or resting blood pressure when performed in isolation. The addition of upper-body resistance training appeared to elicit positive changes in the lipid profile. In Chapter 5, an acute bout of upper-body high-intensity interval exercise (HIIE) or moderate-intensity continuous exercise (MICE) performed in the fasted state had no effect (in comparison to a no-exercise control condition) on subsequent postprandial glucose, insulin, or triglyceride responses in individuals with chronic paraplegia. In Chapter 6, an acute bout of iso-energetic HIIE or MICE performed the evening prior to a mixed macronutrient meal test had no effect (in comparison to a no-exercise control condition) on postprandial lipaemia in healthy non-injured adults. Finally, in Chapter 7, a randomised controlled trial found that six-weeks of home-based upper-body HIIT improved fasting insulin resistance and physical capacity, with a trend towards an improvement in postprandial insulin sensitivity in individuals with chronic paraplegia. Further, very high compliance rates were reported, and it was demonstrated that home-based upper-body HIIT is feasible, safe, and enjoyable for this population. An increase in low-density lipoprotein cholesterol was observed following upper-body HIIT, although the reason for this was unclear. This thesis has shown that an acute bout of upper-body exercise, irrespective of timing or intensity, does not appear to improve postprandial metabolism. However, upper-body HIIT is feasible and enjoyable for individuals with chronic paraplegia and leads to an increase in fitness. Additionally, unlike upper-body MICT, this form of exercise may also improve postprandial measures of insulin sensitivity.

Relevant Publications

The following manuscripts were published (or accepted) in peer-reviewed journals:

Farrow, M., Nightingale, T., Maher, J., McKay, C., Thompson, D., Bilzon, J. L. J. (2020). Effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: a systematic review. *Archives of Physical Medicine and Rehabilitation,* 101(12), 2177-2205.

Farrow, M., Maher, J., Nightingale, T., Thompson, D. & Bilzon, J. L. J. (2021). A single bout of upper-body exercise has no effect on postprandial metabolism in persons with chronic paraplegia. *Medicine & Science in Sports & Exercise,* 53(5), 1041-1049.

Farrow, M., Maher, J. Thompson, D. & Bilzon, J. L. J. (2021). Effect of high-intensity interval training on cardiometabolic component risks in persons with paraplegia: Protocol for a randomized controlled trial*. Experimental Physiology*, 106(5), 1159-1165.

Farrow, M., Maher, J. Oaten, J. R., Kreutzfeldt, S., Thompson, D. & Bilzon, J. L. J. (2022). Prior arm crank exercise has no effect on postprandial lipaemia in non-disabled adults*. Applied Physiology, Nutrition, and Metabolism,* 47*(6),* 681-689.

The following abstracts were presented at conferences:

Farrow, M., Nightingale, T., Maher, J., McKay, C., Thompson, D., Bilzon, J. L. J. (2019). The effect of exercise on cardiometabolic syndrome risk factors in adults with chronic spinal cord injury: A systematic review*. 58th International Spinal Cord Society (ISCOS) Annual Scientific Meeting*, Nice, France.

Table List

Figure List

List of abbreviations

The list of below abbreviations are defined upon first appearance in the text.

ACE	Arm Crank Exercise
AMPK	AMP Activated Protein Kinase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASIA	American Spinal Cord Injury Association
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood Pressure
CI	Confidence Interval
CMS	Cardiometabolic Syndrome
CO_2	Carbon Dioxide
CON	Control Group
CRF	Cardiorespiratory Fitness
CT	Computed Tomography
CV	Coefficient of Variation
CVD	Cardiovascular Disease
DALEEDS	Disability-Associated Low Energy Expenditure Deconditioning Syndrome
DEXA	Dual- Energy X-ray Absorptiometry
DIT	Diet-Induced Thermogenesis
EE	Energy Expenditure
EI	Energy Intake
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EPOC	Excess Post-Exercise Oxygen Consumption
FES	Functional Electrical Stimulation
FM	Fat Mass
FFM	Fat-Free Mass
GLUT-4	Glucose Transporter Protein 4
HDL-C	High-Density Lipoprotein Cholesterol
HEC	Hyperinsulinemic Euglycaemic Clamp
HIIE	High Intensity Interval Exercise
HIIT	High Intensity Interval Training
HOMA-IR	Homeostatic Model Assessment- Insulin Resistance
HR	Heart Rate
HRR	Heart Rate Reserve
iAUC	Incremental Area Under Curve
IL-6	Interleukin-6
IVGTT	Intravenous Glucose Tolerance Test
IMF	Intramuscular Fat
MJ	Megajoule
LDL-C	Low-Density Lipoprotein Cholesterol
LPL	Lipoprotein Lipase
MET	Metabolic Equivalent
MICE	Moderate Intensity Continuous Exercise
MICT	Moderate Intensity Continuous Training
MMTT	Mixed Meal Tolerance Test
MRI	Magnetic Resonance Imaging
NEFA	Non-Esterified Fatty Acids

NMES	Neuromuscular Electrical Stimulation
O_2	Oxygen
OFTT	Oral Fat Tolerance Test
OGTT	Oral Glucose Tolerance Test
QUICKI	Quantitative Insulin-Sensitivity Check Index
PAEE	Physical Activity Energy Expenditure
PAL	Physical Activity Level
PPL	Postprandial Lipaemia
PPO	Peak Power Output
RCT	Randomised Controlled Trial
RER	Respiratory Exchange Ratio
RMR	Resting Metabolic Rate
RPE	Rating of Perceived Exertion
RT	Resistance Training
SCI	Spinal Cord Injury
SD	Standard Deviation
SIE	Sprint Interval Exercise
SIT	Sprint Interval Training
T2D	Type 2 Diabetes
TG	Triglyceride
TAUC	Total Area Under Curve
TC	Total Cholesterol
TDEE	Total Daily Energy Expenditure
TNF-α	Tumor Necrosis Factor Alpha
TRL	Triglyceride-Rich Lipoprotein
TSI	Time Since Injury
VAT	Visceral Adipose Tissue
$\dot{V}CO_2$	Cardon Dioxide Consumption
VLDL	Very-Low Density Lipoprotein
$\dot{V}O_2$	Oxygen Consumption
$\dot{V}O_{2PEAK}$	Peak Aerobic Capacity
WHO	World Health Organization

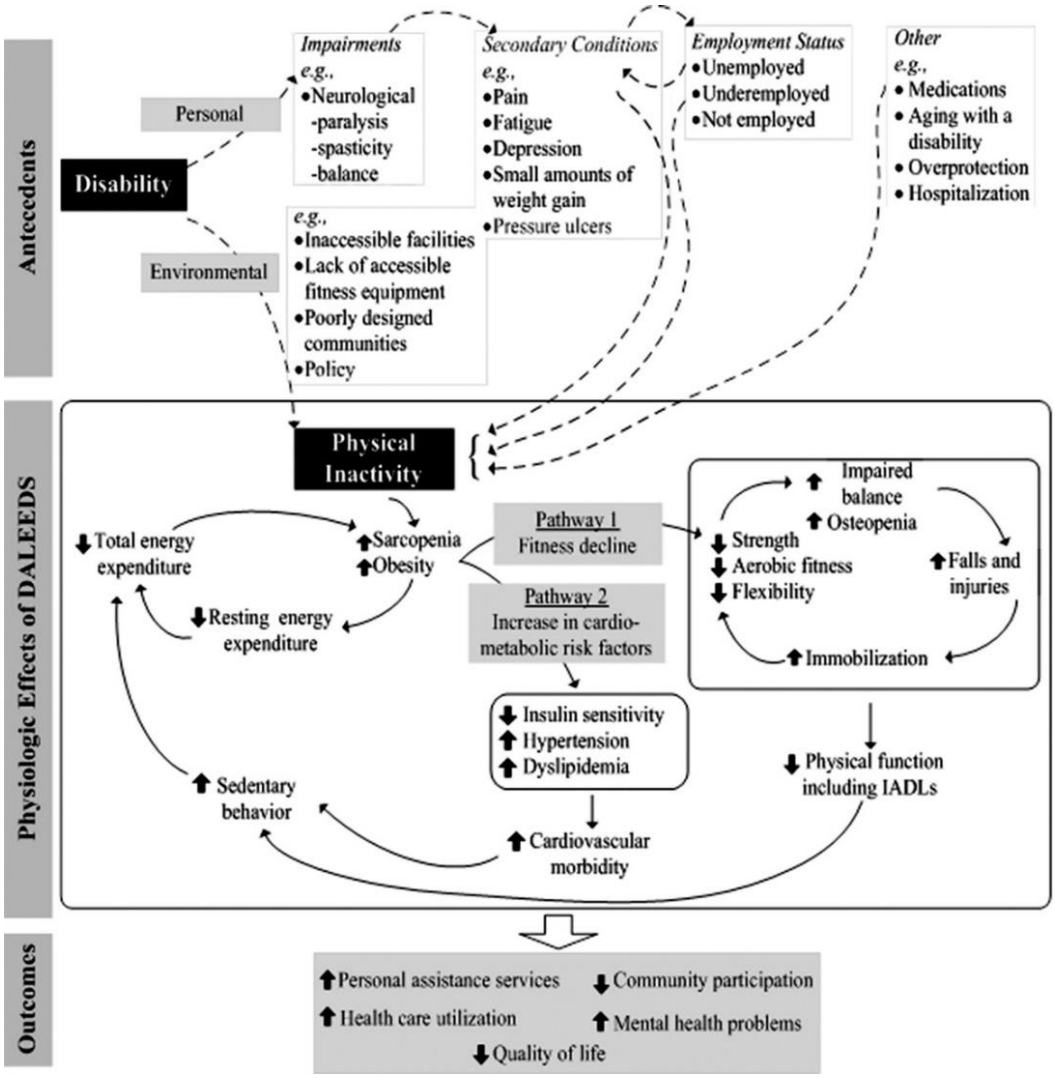
Chapter 1 – Introduction

The World Health Organization (WHO) estimates that ~15% of the world's population live with some form of disability, of whom 2-4% experience significant difficulties in functioning (e.g., spinal cord injury [SCI], multiple sclerosis, stroke, Parkinson's disease, intellectual disabilities). Individuals living with a disability have a greater risk of premature death, largely due to the increased prevalence of non-communicable diseases, such as cardiovascular disease (CVD) and type-2 diabetes (T2D) (World Health Organization, 2011).

The hypothetical link between individuals with a neuromuscular disability and increased cardiovascular morbidity is described by the Disability-Associated Low Energy Expenditure Deconditioning Syndrome (DALEEDS) model (C1 Figure 1) (Rimmer, Schiller and Chen, 2012). The DALEEDS model states that physical inactivity in individuals with disability ensues from various personal (e.g., paralysis, balance, pain) and environmental (e.g., lack of accessible equipment and facilities) barriers to physical activity participation. Sport England estimate that people living in the UK with a disability are twice less likely to meet physical activity recommendations compared to people without a disability (Sport England, 2021). This physical inactivity leads to an increase in fat mass (FM) (i.e., obesity) and decrease in skeletal muscle mass (i.e., sarcopenia), and this initiates a cycle of sedentary behaviour, low total energy expenditure (EE) and cardiovascular morbidity. This is hypothesised to occur through two pathways: Pathway 1, a decline in fitness and physical function, and Pathway 2, an increase in cardiometabolic risk factors (e.g., insulin resistance, dyslipidaemia) (Rimmer, Schiller and Chen, 2012). Ultimately, the development of chronic diseases such as CVD and T2D, lead to a decreased societal role and lower quality of life for persons with a disability, and increased healthcare costs.

It is well-established in the general population that physical inactivity is a major cause of chronic diseases, and therefore the WHO recommends individuals engage in regular physical activity and/or structured exercise (Booth, Roberts and Laye, 2012; Bull et al., 2020). Specifically, adults should perform at least 150-300 minutes of moderate-intensity or 75-150 min of vigorous intensity aerobic physical activity, or equivalent combination of both intensities each week for substantial health benefits (Bull et al., 2020). Whilst meeting the minimum volume of physical activity

is key, it appears that individuals performing a greater proportion of vigorous physical activity to total physical activity time have a lower all-cause mortality rate (Lopez et al., 2019; Wang et al., 2021). In fact, even small doses of high-intensity exercise can reduce CVD mortality risk (Samitz, Egger and Zwahlen, 2011), and high-intensity interval training (HIIT) appears to be an effective method to improve a range of biomarkers in adults at high risk of cardiometabolic disease (Campbell et al., 2019).



C1 Figure 1 Conceptual model of Disability-Associated Low Energy Expenditure Deconditioning Syndrome (DALEEDS)

Taken (with permission) from Rimmer, Schiller and Chen (2012). IDALs *instrumental activities of daily living*

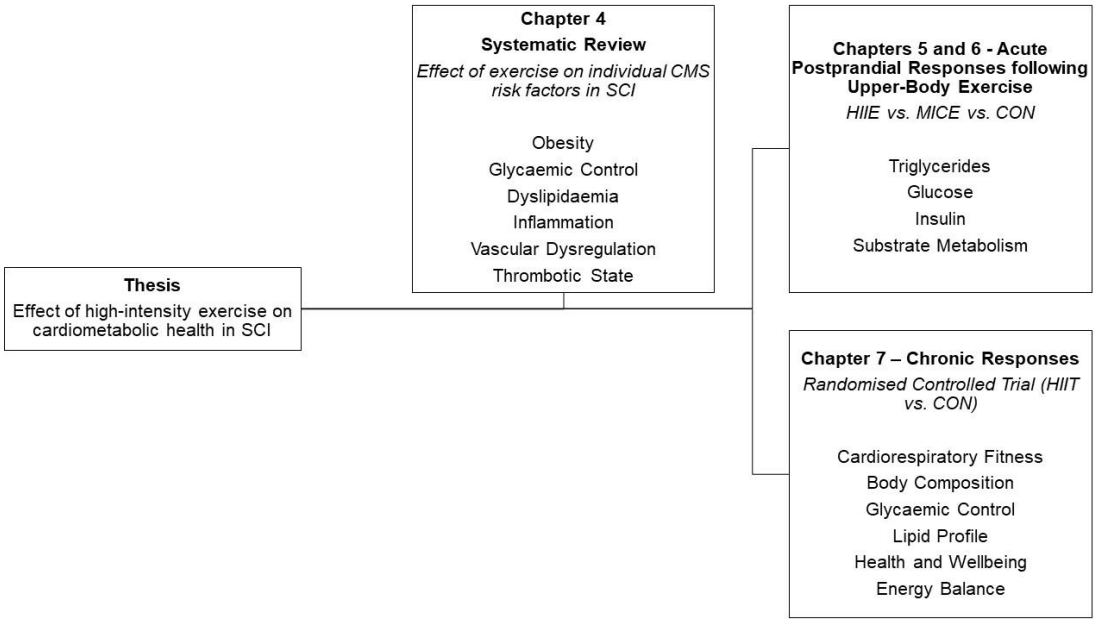
In contrast to the wealth of evidence pertaining to the role of physical activity on chronic disease prevention in the general population, there is a substantial lack of

this research for people living with a disability. The latest systematic review by the WHO concluded that there was insufficient research to determine the relationship between physical activity and the risk of developing chronic diseases for people with a disability (Carty et al., 2021). For example, it has been calculated that fewer than 5% of published articles in high-impact medical journals focused on people living with a disability, and less than 7% of these addressed the effect of physical activity on chronic diseases (Martin Ginis et al., 2021). Consequently, the WHO recommends that individuals with a disability should meet the general population physical activity guidelines (Bull et al., 2020). They also highlight that for "upper-body-led physical activities, less is known about the health risks and benefits, and the extrapolations from the general population are mostly based on lower-body or a combination of upper- and lower-body physical activities" (Carty et al., 2021). This thesis aims to address this research gap, by investigating the health benefits of upper-body exercise (with a particular focus on high-intensity exercise) which is vital for individuals with a disability (e.g., SCI, cerebral palsy, lower-limb amputations, knee osteoarthritis) who may be reliant on wheelchair use for daily physical activity, and handcycling or arm cranking for structured exercise.

Depending on the level and severity of damage, a SCI causes paralysis of the lower-limbs (paraplegia) or all four limbs (tetraplegia) and approaches the most extreme form of human physical inactivity (Booth et al., 2017). The disability is characterised by low EE, due to the loss skeletal mass muscle below the level of injury, and reliance on the upper body (at least for paraplegia) for physical activity and structured exercise. The majority of individuals with an SCI perform no leisure-time physical activity (Ginis et al., 2010), and are three times more likely to develop CVD and twice as likely to develop T2D compared to the general population (Cragg et al., 2013a; Cragg et al., 2013b). SCI-specific exercise guidelines have recently been published, and state that to improve cardiometabolic health, adults with SCI should perform at least 30 min of moderate-to-vigorous intensity aerobic exercise three times per week (Martin Ginis et al., 2018). However, the potential health benefits of upper-body high-intensity exercise for individuals with an SCI have yet to be established. Therefore, the findings from this thesis will help inform SCI-exercise guidelines.

The overarching aim of this thesis was to determine the effect of high-intensity exercise on biomarkers associated with CVD risk (i.e., cardiometabolic health) in

persons with SCI (C1 Figure 2). This was approached initially by performing a systematic review of the available evidence to determine the effect of various exercise training modalities (including upper-body exercise) on individual CVD risk factors in this population (Chapter 4). The postprandial (i.e., post meal) responses to a single bout of upper-body high-intensity interval exercise (HIIE) were then assessed in persons with an SCI (Chapter 5) and non-injured adults (Chapter 6) to determine if this form of exercise is effective at improving postprandial glucose control and lipid metabolism, in comparison to moderate-intensity continuous exercise (MICE) and a no-exercise control condition. Finally, the chronic training effects of home-based upper-body HIIT on key CVD risk factors including glycaemic control, fasting lipid profile, and body composition in persons with SCI were assessed in a randomised controlled trial (RCT) (Chapter 7).



C1 Figure 2 Overview of this thesis

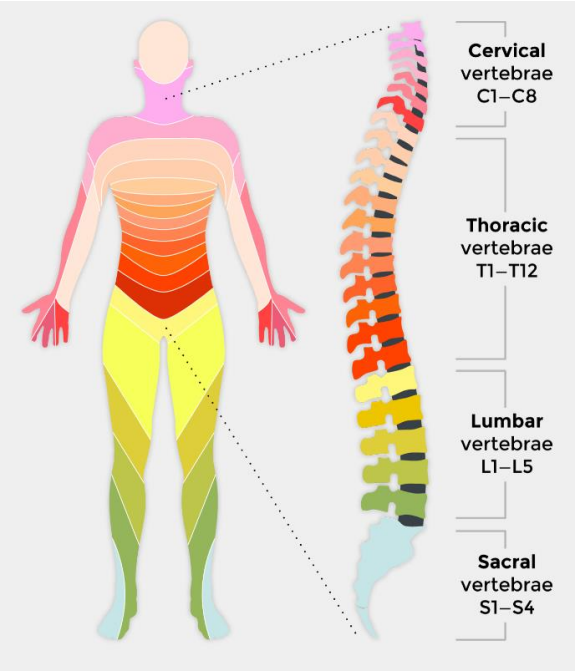
CMS *cardiometabolic syndrome*, HIIE *high-intensity interval exercise*, MICE *moderate-intensity continuous exercise*, CON *control*, HIIT *high-intensity interval training*

Chapter 2 - Review of the Literature

The purpose of this literature review is to: i) describe the physiological changes following an SCI and explain how CVD ensues from these, ii) describe and explain how an acute bout of exercise can improve carbohydrate and lipid metabolism, iii) review the acute and chronic responses to HIIT in the general population, and iv) describe the available evidence relating to the acute and chronic responses to upper-body HIIT in persons with SCI.

2.1 Spinal Cord Injury

The central nervous system consists of the brain and the spinal cord, and controls most of the functions of the body. The spinal cord is a cylindrical bundle of nerve fibres surrounded by the vertebrae of the spinal column. It extends from the medulla oblongata of the brain and terminates near the second lumbar vertebrae. There are 31 pairs of spinal nerves that connect the spinal cord to the peripheral tissues. There are eight cervical, 12 thoracic, five lumber, five sacral and one coccygeal nerve(s) (C2 Figure 1).



C2 Figure 1 The spinal column and functions associated with each level of the spinal cord

Image taken (with permission) from Back Up Trust (www.backuptrust.org.uk)

A SCI is a life-changing neurological event that can have profound effects on body system functioning, mobility, independence, and the societal role of the individual. The cause can be of traumatic (e.g., direct result of a car crash or fall) or non-traumatic (e.g., as a result of degeneration from cancer or transverse myelitis) origin. Dependent on the area of the spinal cord that is damaged, the injury results in the loss of sensory and/or motor control to the lower-extremities (paraplegia) or all four extremities (tetraplegia). Paraplegia occurs if the level of lesion is at or below T1, whilst tetraplegia occurs if the level of lesion is at or above C8. The American Spinal Injury Association (ASIA) clinical scoring system is typically used to describe the completeness of the SCI, and can be classified as complete (ASIA = A, no sensory or motor function remains below the level of injury) or incomplete (ASIA = B to E, some sensory or motor function remains below the level of injury) (Roberts, Leonard and Cepela, 2017).

2.2 Epidemiology of SCI

The global incidence of traumatic SCI is estimated to be 23 cases per million, and 16 cases per million in Western Europe (Lee et al., 2014). The prevalence of traumatic SCI varies across the globe, ranging from 250 to 906 cases per million (Singh et al., 2014). The latest figures from the Spinal Injuries Association (2021) suggest that ~2,500 people become paralysed each year, with an estimated ~50,000 people living with an SCI in the UK. Unfortunately, there is a lack of centralised UK-wide data available on SCI demographics. However, there is data available from a review of traumatic cases in Scotland between 1994 and 2013 (McCaughey et al., 2016). The mean age at which the injury occurred was 47 years, with 75% of all injuries occurring in males. The three most common causes of injury were: falls (52%), road traffic collisions (24%), and sports (10%). Data regarding the level and severity of injury are not readily available in the UK. In the USA, it has recently been reported that 45% of injuries can be classified as incomplete tetraplegia, 21% as incomplete paraplegia, 20% as complete paraplegia, and 13% as complete tetraplegia (National Spinal Cord Injury Statistical Center, 2021). The substantial lifetime costs of an SCI place an economic burden on the NHS, estimated to be on average £1.12 million per SCI case (McDaid et al., 2019). This includes the treatment of various chronic complications associated with an SCI (e.g., pressure sores, urinary and bowel problems, respiratory and cardiovascular issues)

(Sezer, Akkus and Ugurlu, 2015), the higher prevalence of depression and obesity (Graupensperger, Sweet and Evans, 2021), and costs associated with rehabilitation and home care.

2.3 Chronic Disease and Mortality

The acute survival rate after sustaining an SCI has steadily improved over recent decades, due to advancements in critical care (DeVivo, 2012). Despite this, it is well-established that individuals who have survived the first year following an SCI have a higher mortality rate and reduced life expectancy than the general population (Frankel et al., 1998). This varies globally and is largely dependent on income status of the country. The standardised mortality rate has been estimated to be 2.07 (95% confidence interval [CI]: 1.47-2.92) for paraplegics and 2.53 (95% CI: 2.00-3.21) for tetraplegics (Chamberlain et al., 2015). The leading causes of death relate to secondary complications from an SCI, including CVD (van Den Berg et al., 2010). In the UK, a retrospective analysis of mortality over the last 70 years in individuals with chronic SCI (>1 year post-injury) established that 27% of deaths could be attributed to CVD (Savic et al., 2017). The susceptibility of this population to CVD is alarming; a cross-sectional study of 60,000 individuals found that the risk of developing CVD is three times higher for those with an SCI compared to the general population (Cragg et al., 2013b). The risk of developing CVD increases with age, level of SCI (greatest for tetraplegics), and severity of SCI (greater for complete injuries) (Groah et al., 2001). This can be explained, at least partially, by the disruption to the cardiovascular autonomic system that occurs following a SCI (at or above T6), which results in autonomic dysreflexia, cardiac arrythmias, BP instability, and increased heart rate (HR) variability (Phillips and Krassioukov, 2015), which have all been associated with an increased risk of CVD (Bauman et al., 1999; Myers, 2007).

Individuals with a SCI are also at higher risk from developing other chronic conditions. For T2D, the hazard ratio (after adjustment for basic demographics) has been reported to be between 1.16 and 1.66 times higher for persons with an SCI than without (Cragg et al., 2013a; Lai et al., 2014; Peterson et al., 2021). This is significant due to the strong association between T2D and CVD in the general population, equating to a two-fold increased CVD risk (Sarwar et al., 2010).

Furthermore, the 4-year incidence of all cardiometabolic morbidities, including cardiac dysthymias, heart failure, atherosclerosis, non-alcoholic fatty liver disease, hypercholesterolemia, hypertension, and T2D have recently reported to be higher in those with SCI compared to adults without a SCI (Peterson et al., 2021). Therefore, the rate of secondary complications in persons living with a chronic SCI is high and requires intervention.

2.4. Pathophysiology of SCI

The DALEEDS conceptual model (presented in C1 Figure 1) can be used to explain the increased CVD risk for individuals with a SCI (Rimmer, Schiller and Chen, 2012). Specifically, following an SCI, there is substantial skeletal muscle atrophy (i.e., sarcopenia) and increased adiposity, which both result in reduced physical fitness. As a consequence, there is an increase in cardiometabolic syndrome (CMS) risk factors and ultimately, increased cardiovascular morbidity. Therefore, this section will firstly describe these changes in body composition and cardiorespiratory fitness (CRF) and their implications for CVD risk. Then, it will describe the low physical activity rates in this population, which underpin this cycle of positive energy balance and cardiovascular morbidity. Finally, it will define CMS and describe its prevalence in individuals with chronic SCI.

2.4.1 Skeletal Muscle Atrophy

As a result of immobilisation, disuse, and an inability to innervate skeletal muscle below the level of lesion, individuals who suffer a SCI are likely to experience a rapid and significant loss of skeletal muscle mass below the level of injury (Gorgey et al., 2014). For example, in patients with a complete SCI, skeletal muscle cross-sectional area has been shown to be 18-46% smaller at six weeks post-injury, and 45-80% smaller at six months post-injury compared to non-injured controls (matched for age and body mass) (Castro et al., 1999). This rate of muscle atrophy is fastest in the first year of injury. Individuals with a chronic SCI (mean time since injury [TSI]: 16 ± 10 yrs) have been shown to have ~32% lower calf muscle cross-sectional area compared to non-injured controls (Moore et al., 2015). This skeletal muscle atrophy is likely to have clinical implications given that skeletal muscle accounts for ~75% of whole-body insulin-stimulated glucose uptake (Björnholm and Zierath, 2005). In

addition to skeletal muscle atrophy, the quality of the remaining muscle begins to deteriorate following an SCI. Gorgey and Dudley (2007) reported that intramuscular fat (IMF) was three-fold higher at six weeks post-injury in individuals with an incomplete SCI compared to non-injured controls (matched for age, height and body mass). Moreover, IMF further increased by 26% in the SCI group at three months compared to six weeks post-injury. This is significant given the strong relationship between IMF percentage and glucose tolerance (Elder et al., 2004). There is also a rapid shift from type I and type IIA (i.e., slow twitch) to type IIx (i.e., fast twitch) fibres that begins four to seven months following a SCI, reaching a plateau to predominately type IIx by 20-70 months post-injury (Biering-Sørensen et al., 2009). This results in a reduction in peak torque and a low resistance to fatigue in the paralysed muscles, and thus characterises local physical deconditioning (Bickel, Slade and Dudley, 2004).

2.4.2 Obesity

It is estimated that two in three individuals with a chronic SCI are obese (Gorgey et al., 2014), which is substantially higher than the general population. For example, around one in four of the general population in England can be classified as obese (Baker, 2021). Body mass index (BMI) is the most-widely used criterion method to classify those who are overweight (25-30 $kg \cdot m^{-2}$) and obese (>30 $kg \cdot m^{-2}$) in the general population. However, due to the significant loss of skeletal muscle mass below the level of injury, these BMI cut-offs are not valid for individuals with SCI (Silveira et al., 2017). A revised definition of obesity (BMI ≥22 $kg \cdot m^{-2}$) for those with SCI has been proposed (Laughton, 2009), although it is not widely used, and due variations in completeness and level of injury, BMI is unlikely to be adequate as a measure of obesity (Raguindin et al., 2021). In fact, a recent scoping review of the available body composition tools for adults with SCI concluded that dual-energy x-ray absorptiometry (DEXA) was the only tool with acceptable test-retest reliability and convergent validity (van der Scheer et al., 2021a). DEXA uses low-dose radiation to estimate FM and soft-tissue fat-free mass (FFM). Using this method, Spungen et al. (2003) reported that persons with a chronic SCI were 13% fatter per unit of BMI compared with non-injured controls (matched for age, height, and ethnicity).

The prevalence of abdominal obesity, as characterised by visceral adipose tissue (VAT) also appears to be high in those with chronic SCI. Abdominal obesity is a

CVD risk factor even after the adjustment for BMI (Pischon et al., 2008) and has been strongly associated with impaired glucose and lipid metabolism in those with SCI (Gorgey, Mather and Gater, 2011; Sumrell et al., 2018). Waist circumference is the most-widely used measure of abdominal obesity in the general population. It is typically measured in the supine position for wheelchair users, however there is some debate as to which cut-off should be used in individuals with SCI, ranging from 86.5 to 94 cm (Ravensbergen, Lear and Claydon, 2014; Sumrell et al., 2018; Gill et al., 2020). The gold-standard measures of VAT are computed tomography (CT) and magnetic resonance imaging (MRI). Edwards, Bugaresti and Buchholz (2008) reported that persons with chronic SCI had 58% more VAT (measured via CT) than non-injured controls (matched for age, sex, and waist circumference), despite the participants being young (39 ± 8 yrs) and self-reporting as physically active.

This high prevalence of general and abdominal obesity in those with chronic SCI, is ultimately due to a sustained positive energy balance (energy intake [EI] greater than total daily energy expenditure [TDEE]). As per the first law of thermodynamics, energy can neither be created nor destroyed, and therefore any surplus energy must be stored within the human body. Therefore, if a positive energy balance is maintained for a prolonged period, surplus energy is ultimately stored as triaglycerol in adipose tissue (Frayn, 2010). Despite issues with the measurement tools available to measure free-living energy balance, a recent meta-analysis in individuals with chronic SCI (n=606) reported a pooled EI of 1876 kcal·day^{-1} and an estimated TDEE of 1791 kcal·day^{-1}, equating to a ~600 kcal·week^{-1} energy surplus (Farkas et al., 2019).

TDEE can be divided into basal metabolic rate (BMR), diet-induced thermogenesis (DIT), and physical activity energy expenditure (PAEE). BMR represents the minimum number of calories required to support life, and accounts for 70-80% of TDEE in persons with SCI (Gorgey et al., 2015a). However, the measurement of BMR is time-consuming, requiring the participant to stay overnight, and the use of a metabolic chamber. Therefore, resting metabolic rate (RMR) is typically measured as an alternative to BMR using indirect calorimetry under fasted conditions, and represents the number of calories expended during quiet rest. Due to the loss of skeletal muscle mass below the level of injury, RMR is reduced by 14-27% following an SCI compared to non-injured controls (Monroe et al., 1998; Buchholz, McGillivray and Pencharz, 2003a). DIT is the least variable component of TDEE, and represents the energy expended above BMR due to the ingestion of food, accounting for ~6%

of TDEE in persons with SCI (Buchholz, McGillivray and Pencharz, 2003a; Westerterp, 2004). PAEE is the most variable and malleable component of TDEE, and represents the energy expended above BMR during any movement produced by skeletal muscle (Westerterp, 2013). However, due to a reduced RMR, the energetic cost when performing the same physical activities (i.e., PAEE) is reduced for those with SCI in comparison to non-injured individuals (Collins et al., 2010).

2.4.3 Cardiorespiratory Fitness

CRF refers to the ability of the circulatory, respiratory, and vascular system to supply oxygen (O_2) during sustained exercise. It is commonly termed peak aerobic capacity ($\dot{V}O_{2PEAK}$) or peak oxygen consumption and is measured during an incremental exercise test to exhaustion. For individuals with SCI, this test is typically performed using wheelchair or arm crank ergometry. CRF has a strong inverse relationship with all-cause and CVD mortality in non-injured individuals (Lee et al., 2011). However, individuals with chronic paraplegia (median $\dot{V}O_{2PEAK}$: 16 $mL \cdot kg^{-1} \cdot min^{-1}$) and tetraplegia (median $\dot{V}O_{2PEAK}$: 8.8 $mL \cdot kg^{-1} \cdot min^{-1}$) are near the lowest end of the human fitness spectrum (Simmons, Kressler and Nash, 2014). For reference, the median $\dot{V}O_{2PEAK}$ for non-injured humans performing cycling based $\dot{V}O_{2PEAK}$ tests has been reported to be 36 $mL \cdot kg^{-1} \cdot min^{-1}$ (men) and 30 $mL \cdot kg^{-1} \cdot min^{-1}$ (women) for individuals aged 40-49 years (Rapp et al., 2018). Multiple studies have demonstrated that persons with chronic paraplegia have a substantially lower CRF compared to non-injured controls (Baumgart et al., 2018; Farkas et al., 2020). A low CRF increases CVD risk for this population, but also impacts their quality of life (Nightingale et al., 2018), and one in four individuals with paraplegia are unable to reach a sufficient $\dot{V}O_{2PEAK}$ to perform essential activities of daily living (Noreau et al., 1993). The reduced CRF levels are dependent on the level of injury and are a result of the blunted haemodynamic responses (i.e., HR, stroke volume, and cardiac output) to exercise that this population experience (Jehl et al., 1991). However, and importantly, physical activity is strongly and inherently linked to CRF, and is the only modifiable factor known to influence CRF (Church, 2009; Nightingale et al., 2017c).

2.4.4 Physical Inactivity

The available evidence from self-report questionnaires supports the notion that physical activity levels are reduced in individuals with SCI compared to the general

population (Soriano et al., 2022). For example, the proportion of individuals performing no leisure-time physical activity whatsoever is reported to be as high as 50% (n=695) (Ginis et al., 2010). However, there are complex challenges to objectively measuring physical activity levels in persons with a SCI, as a result of the variations in the level of injury, efficiency and type of movements, and body mass, which often preclude the accurate calculation of EE (Nightingale et al., 2017b). Consequently, there is currently a sparsity of objectively measured physical activity data for this population.

An individual's habitual physical activity level (PAL) can be calculated by dividing their TDEE by RMR. For non-injured humans, this value can typically range from 1.20 to 2.40, with a sedentary or light activity lifestyle classified as a PAL between 1.40 and 1.69 (Nocito, Ballard and Shaw, 2005). Buchholz, McGillivray and Pencharz (2003b) reported an average PAL of 1.56 ± 0.34 in 27 adults with chronic paraplegia following three days of habitual lifestyle monitoring. This low PAL occurred despite 15 participants performing structured physical activity (1.46 ± 0.86 times) for 49 ± 31 minutes per session. Additionally, Nightingale et al. (2017f) reported very low physical activity levels (mean PAL: 1.40 ± 0.15, range: 1.20-1.85) in 33 adults with chronic paraplegia following seven days of monitoring. The intensity of physical activity can also be characterised by expressing its energy cost as a multiple of RMR, referred to as a metabolic equivalent (MET). Nightingale et al. (2017f) reported that this population performed 12 $min \cdot day^{-1}$ of moderate-to-vigorous physical activity (≥3 METs) and spent a high proportion (~87%) of the day in a sedentary state (<1.5 METs). Furthermore, just 13% of participants performed any vigorous physical activity (≥6 METs). Despite the relatively small sample sizes in these studies, these data support the notion that this population are habitually physically inactive and need to perform a greater volume or higher intensity of structured physical activity to live a sufficiently physically active lifestyle (i.e., PAL >1.69).

The reasons for the low physical activity rates among persons with chronic SCI are complex and multifaceted, however, and in brief, they have been attributed to both real and perceived barriers and divided into two broad categories: socio-environmental and intrinsic barriers. Socio-environmental barriers include a lack of access to appropriate and affordable facilities and equipment, and knowledge of where and how to exercise (Scelza et al., 2005; Kehn and Kroll, 2009). Intrinsic barriers include a lack of motivation, energy, low enjoyment of exercise, and

perceived low return on physical investment (Scelza et al., 2005; Kehn and Kroll, 2009; Cowan, Nash and Anderson, 2013). These antecedents of disability are depicted in the DALEEDS model (C1 Figure 1) (Rimmer, Schiller and Chen, 2012).

2.4.5 Cardiometabolic Syndrome

The consequence of the cycle of physical inactivity and obesity in persons with SCI is an increase in the prevalence of CMS risk factors, as highlighted by the DALEEDS conceptual model. Often referred to as "syndrome X", CMS is a clustering of multiple CVD risk factors, namely abdominal obesity, insulin resistance, hypertension and dyslipidaemia (either as hypertriglyceridemia or reduced high-density lipoproteinemia) (Després et al., 2008). There is no universally accepted definition of CMS, although it is generally referred to as the co-occurrence of three (or more) of these risk factors. A meta-analysis of prospective cohort and observational studies, which included 951,083 non-injured individuals, revealed that those presenting with CMS had a two-fold increased risk of CVD mortality (Mottillo et al., 2010). Suggested cut-points for individuals with SCI have recently been proposed by Paralysed Veterans of America (PVA) Consortium and are presented in C2 Table 1. These include adjustments for the definition of abdominal obesity, which have been suggested as suitable cut-points for individuals with SCI (Laughton, 2009; Ravensbergen, Lear and Claydon, 2014).

C2 Table 1 Paralysed Veterans of America (PVA) Consortium definition of CMS.

Risk Factor	Diagnosis
Abdominal obesity	>22% body fat percentage when using 3 or 4-comparment modelling or BMI ≥ 22 $kg \cdot m^{-2}$
Hypertriglyceridemia	Plasma triglycerides ≥1.7 $mmol \cdot L^{-1}$
Reduced HDL-C	Males: <1.03 $mmol \cdot L^{-1}$ Females: <1.29 $mmol \cdot L^{-1}$
Hyperglycaemia	Fasting glucose ≥5.6 $mmol \cdot L^{-1}$ or use of medication for hyperglycaemia
Hypertension	Blood pressure ≥130/85 mmHg or use of medication for hypertension

Adapted from Nash et al. (2019)

The prevalence of CMS in the general population is estimated to be ~25%, although this varies according to the definition of CMS used, and the ethnicity, age, and sex of the population studied (O'Neill and O'Driscoll, 2015). In the largest cohort to date (n=473), the prevalence of CMS in chronic SCI has been reported to be as high as 57.5% (Gater et al., 2019). Despite, the relatively small sample size of this study, it is likely that the prevalence of CMS is high across the chronic SCI community considering the prevalence of the individual CMS risk factors.

A meta-analysis reported that compared with non-injured controls, individuals with SCI had a significantly depressed high-density lipoprotein-cholesterol (HDL-C) and increased total cholesterol (TC)/HDL-C ratio (Gilbert et al., 2014). This review reported no differences in triglyceride (TG) concentrations between groups, although a recent analysis of the unique relationship between HDL-C and TG in individuals with a SCI, suggests that the threshold for hypertriglyceridemia should be reduced to 1.3 $mmol \cdot L^{-1}$ and 1.55 $mmol \cdot L^{-1}$ for individuals with an injury at or above T4 and at or below T5 respectively (La Fountaine et al., 2018). Furthermore, as described earlier, individuals with a chronic SCI are at a two-fold increased risk of developing T2D in comparison to the general population (Cragg et al., 2013a; Peterson et al., 2021), with an estimated obesity prevalence of 66% (Gorgey et al., 2014). Finally, whilst individuals with an injury at or above T6 are more likely to suffer from hypotension (Zhu et al., 2013), there is also evidence of a higher prevalence of hypertension in those with lower injuries compared to the general population (Peterson et al., 2021).

2.5 Disorders of Carbohydrate and Lipid Metabolism in SCI

The CMS risk factors highlighted in Section 2.4 can be summarised as an impairment in metabolic control, or metabolic dysregulation. This section will discuss disorders of carbohydrate (e.g., hyperglycaemia and insulin resistance) and lipid (e.g., postprandial lipaemia [PPL]) metabolism, which are strongly associated with increased CVD risk.

2.5.1 Metabolic Regulation

Metabolic control refers to the regulated flow of metabolites to deliver energy to tissues (e.g., skeletal muscle, adipose tissue) and organs (e.g., liver, brain) as

required, thus achieving energy homeostasis. This is primarily regulated by the endocrine (e.g., insulin release from the pancreas) and nervous (e.g., signalling the release of adrenaline) systems. In the fasted state, plasma glucose concentrations are relatively stable, and are largely maintained through hepatic glycogenolysis and gluconeogenesis. The oxidation of non-esterified free-fatty acids (NEFA) is prioritised over glucose, which is released into the blood stream following the hydrolysis of triacylglycerol with adipose tissue. These processes are primarily regulated by low concentrations of plasma insulin. In response to the ingestion a meal, there is a rapid rise in availability of glucose and lipids. Consequently, glucose is preferentially oxidised by tissues, and is stored as glycogen within skeletal muscle and the liver. This is regulated by increasing insulin concentrations, which also suppresses adipose tissue lipolysis and hepatic gluconeogenesis. Impairments in the ability to modulate these rapid changes in energy availability is termed 'metabolic inflexibility' and is observed in individuals with chronic diseases including obesity (Astrup, 2011) and T2D (Kelley and Simoneau, 1994).

2.5.2 Insulin Resistance

Insulin is a peptide hormone that is produced by the β-cells of the pancreas. It is a pivotal regulator of metabolism, particularly in the fed-state, and has roles across multiple organs, including the, i) stimulation of glucose uptake at skeletal muscle via glucose transporter type 4 (GLUT4), ii) suppression of hepatic glucose production, iii) stimulation of glucose and lipid uptake at adipose tissue, and iv) vasodilation of the vascular endothelium to facilitate glucose uptake (Wilcox, 2005). Insulin resistance is a pre-cursor to T2D and is an independent CVD risk factor (Eddy et al., 2009). It can be defined as an impaired ability of insulin to suppress hepatic glucose production and facilitate peripheral glucose uptake (McGarry, 2002). Consequently, impaired fasting glycaemic control or prediabetes (fasting glucose: 5.6 – 6.9 $mmol \cdot L^{-1}$) can eventually ensue (American Diabetes Association, 2020). The gold standard methods for estimating insulin resistance and sensitivity are the intravenous glucose tolerance test (IVGTT) and the hyperinsulinemic euglycaemic clamp (HEC) (DeFronzo, Tobin and Andres, 1979; Bergman, 1989). Briefly, the HEC method involves the infusion of exogenous insulin to reach a steady-state plasma insulin concentration. Exogenous glucose is also infused to hold plasma glucose concentrations constant. The rate of glucose infusion is then used as a measure of the whole-body glucose uptake and represents peripheral insulin sensitivity. The

IVGTT involves the injection of a glucose bolus (standardised to body mass) with regular samples taken for 3 h to calculate glucose effectiveness. The injection of a standardised bolus of insulin is used to estimate whole-body insulin sensitivity. However, these techniques are rarely used in a clinical context due to the lack of appropriate equipment and experienced clinical staff.

Instead, the oral glucose tolerance test (OGTT) is widely used in clinical practice and is used to diagnose impaired glucose tolerance and provide an estimate of insulin sensitivity (American Diabetes Association, 2020). The OGTT involves the consumption of a drink containing 75 g of glucose, following an overnight fast. Blood samples are taken at regular intervals for 2 h, with plasma glucose and insulin concentrations determined. For the purposes of this thesis, the total area under the curve (TAUC) and incremental area under the curve (iAUC) for glucose and insulin are used to characterise responses to an OGTT. Various indices of insulin sensitivity and resistance can also be calculated from an OGTT. The Homeostasis Model Assessment (HOMA), and updated model (HOMA2) are widely used clinical tools to estimate insulin resistance, beta cell function, and insulin sensitivity (Matthews et al., 1985; Levy, Matthews and Hermans, 1998). These indices are calculated using fasting concentrations of insulin and glucose, and are strongly correlated with the HEC (Sarafidis et al., 2007). The calculation of HOMA2 is based on the principle of a feedback loop between glucose production in the liver and insulin produced by the pancreas, and therefore represents hepatic insulin sensitivity (Holman and Turner, 1979). Similarly, the Quantitative Insulin-sensitivity Check Index (QUICKI) is determined from the log-transformation of fasting plasma glucose and insulin concentrations and has been reported to have the greatest agreement with IVGTT derived insulin sensitivity in persons with chronic SCI (Farkas et al., 2021a). Additionally, the Matsuda Index ($ISI_{Matsuda}$), defined as the ratio of plasma glucose to insulin concentrations during the OGTT, is highly correlated with glucose disposal (r=0.73) during HEC (Matsuda and Defronzo, 1999). It can therefore be used as an estimate of both peripheral and hepatic insulin sensitivity.

As previously described, persons with a chronic SCI are at high risk of T2D. Multiple studies have reported a high prevalence of impaired glucose tolerance, as defined using OGTT cuff-offs, in previously undiagnosed individuals (Duckworth et al., 1980; Bauman and Spungen, 1994). This appears to occur in individuals presenting with normal fasting glucose concentrations, and therefore likely reflects a reduction in glucose uptake and/or insulin sensitivity at the peripheral tissues (Duckworth et al.,

1980; Segal, Thompson and Tayek, 2007). Whole-body insulin sensitivity has been reported to be ~50% lower for individuals with an SCI vs non-injured controls (Aksnes et al., 1996; Yarar-Fisher et al., 2013). The reasons for this difference are multi-factorial, and likely include a reduced volume and quality of lower-body muscle mass and physical inactivity (and associated increase in obesity).

Skeletal muscle is a major site for insulin-stimulated glucose disposal, and muscle atrophy is profound following an SCI (as described in Section 2.4.1). Aksnes et al. (1996) demonstrated a 43% decrease in whole-body insulin-sensitivity (using HEC) in tetraplegics (compared to age-matched non-injured controls). This was observed despite there being no differences in insulin-stimulated glucose uptake at the individual muscle fibre level (vastus lateralis) and supports the importance of reduced skeletal muscle mass in explaining impaired glucose tolerance for individuals with SCI. Additionally, Yarar-Fisher et al. (2013) reported GLUT4 protein content of the vastus lateralis was 25% lower for SCI compared to non-injured controls, suggesting that reduced glucose uptake at skeletal muscle (i.e. reduced peripheral insulin sensitivity) is partially responsible for impaired glycaemic control in this population. The quality of skeletal mass also appears to be important. Elder et al. (2004) reported that ~70% of the variance in OGTT responses could be explained by IMF in individuals with and without a SCI. A recent one-legged physical inactivity model also highlighted a link between a reduction in mitochondrial oxidative capacity, IMF accumulation and lower insulin sensitivity (Bilet et al., 2020). This is likely due to the increased fatty acid flux, which causes a disruption to insulin signalling pathways (Petersen and Shulman, 2018).

Physical inactivity (and subsequent fat accumulation) is likely an important driver of the development of insulin resistance and progression to T2D in persons with SCI. Large prospective studies have reported strong associations between daily physical activity and increased risk of developing T2D in the general population (Venables and Jeukendrup, 2009). Additionally, smaller cross-sectional studies in individuals with chronic SCI have reported associations between physical activity levels and fasting glucose and insulin concentrations (Manns, McCubbin and Williams, 2005; Buchholz et al., 2009; D'Oliveira et al., 2014). Studies restricting physical activity in non-injured individuals can also provide a useful model for understanding the role of physical inactivity on insulin sensitivity (Bowden Davies et al., 2019). For example, a 17% reduction in peripheral (but not hepatic) insulin sensitivity was reported when step-count was reduced from ~10,000 to 1,500 steps per day for 2

weeks in healthy men (Krogh-Madsen et al., 2010). This study reported a reduction in insulin stimulated Akt phosphorylation, and therefore it is suggested that a lack of AMP Activated Protein Kinase (AMPK) activation within skeletal muscle may, at least partially, be responsible for short-term reductions in insulin sensitivity (Bowden Davies et al., 2019). Step reduction models have also reported concomitant increases in total, central, and liver fat content (Bowden Davies et al., 2021). During periods of prolonged physical inactivity, it is likely that these deposits are further increased due to fat deposition (e.g., through de-novo lipogenesis). Both central adiposity and hepatic fat accumulation have been associated with insulin resistance in humans with and without an SCI (Hocking et al., 2013; Rankin et al., 2017). Inflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor alpha (TNF)-α that are released from the adipose tissue have been implicated in interfering with skeletal muscle insulin signalling and contributing to the development of insulin resistance (Trayhurn, Drevon and Eckel, 2011; Hotamisligil, 2017). Furthermore, the increase in these deposits can lead to higher secretion of NEFA (from adipose tissue), and TG (from the liver), which can further exacerbate insulin resistance and lead to the progression of T2D (DeFronzo and Tripathy, 2009).

2.5.3 Postprandial Lipaemia

Fasting TG concentrations are a well-established biomarker of CVD (Sarwar et al., 2007), however in a typical Western eating pattern, most individuals consume three or more meals a day, meaning they can spend ~18 hours per day in a postprandial (fed) state. For a typical meal containing 30-40 g of fat, plasma TG concentrations can take three to five hours to peak, and six to eight hours to return to baseline (Frayn, 2010). Therefore, individuals will likely spend most of the day presenting with non-fasting TG concentrations. Importantly, large scale prospective cohort studies have identified non-fasting TG concentrations as a stronger predictor of the incidence of CVD than fasting concentrations (Bansal et al., 2007; Nordestgaard et al., 2007).

The term PPL is given to the prolonged elevation of triglyceride-rich lipoproteins (TRLs) following digestion and absorption of a meal containing fat. Dietary fats are absorbed and re-esterified in the small intestine into TRLs (Frayn, 2010). These TRLs are released into circulation by the lymphatic nodes and hydrolysed by the enzyme lipoprotein lipase (LPL) in skeletal muscle and adipose tissue, with chylomicron remnants being released into systematic circulation (Frayn, 2010).

Although the exact mechanistic link between PPL and CVD remains unclear, a prominent theory, first proposed by Zilversmit (1979) states that these cholesterol ester-rich chylomicron remnants are likely to cause a build-up of atherosclerotic plaques. Since this theory was highlighted, a pro-inflammatory pathway that links chylomicron remnants to the increased recruitment of macrophages to the vascular endothelium has been identified (Jackson, Poppitt and Minihane, 2012).

PPL is typically assessed using an oral fat tolerance test (OFTT). For clinical diagnosis of postprandial hypertriglyceridemia, expert statements have recommended an OFTT should be performed following an 8 h fast and consist of a single meal (75 g of fat, 25 g of carbohydrate, and 10 g of protein), with a single blood measurement at 4 h (Kolovou et al., 2019). However, in a research setting, and for the purposes of this thesis, PPL is defined as either the TG TAUC or iAUC following the consumption of a high-fat meal. A wide range of protocols have been used to assess PPL, however, typically the test will last four to eight hours (blood samples taken hourly), with the meal containing 40-100 g of fat and 700-1500 kcal (total calories for each participant is often normalised to per kilogram of body mass or FFM) (Teeman et al., 2016). There are many factors that can effect the magnitude of PPL, including age, sex, body composition, habitual diet, meal composition, and fasting lipid/glycaemic markers (Berry et al., 2020). In Chapters 5 and 6 of this thesis, a mixed-meal tolerance test (MMTT) will be used to allow us to concurrently assess postprandial glycaemic and lipaemic responses. The MMTT is being increasingly used in research settings as it is viewed as providing a metabolic challenge that is more ecologically valid than the feeding of a single macronutrient (i.e, OGTT and OFTT) (LaBarre, Singer and Burant, 2021).

In persons with chronic SCI, there is some evidence of impaired PPL. Nash et al. (2005) originally reported that total PPL response was greater in individuals with paraplegia (n=3) than non-injured (n=21) individuals during an OFTT. However, follow-up studies with larger sample sizes suggest that there is no difference in the total PPL response between those with a SCI and non-injured controls (Emmons et al., 2010; Emmons et al., 2014). Emerging evidence from lipid isotope tracer studies is likely to aid understanding of the fat trafficking responses in persons with SCI. McMillan et al. (2021a) demonstrated that lesion level was positively correlated with time-to-peak exogenous TG concentration in eight paraplegics (T2-T12), following the ingestion of a standardised liquid meal (35% calories from fat, 20 kcal per kg of

fat free mass). It is possible that this represents an impaired ability to absorb dietary fats in individuals with SCI.

2.6 Glycaemic Control and Lipid Metabolism following Exercise

In the general population, there is overwhelming evidence that physical inactivity, or lack of exercise, is a major cause of a wide range of chronic diseases, including CVD and T2D (Booth, Roberts and Laye, 2012). Furthermore, exercise can prevent and/or delay the onset of these diseases (Booth, Roberts and Laye, 2012) and can target every CMS risk factor presented in C2 Table 1 (Ostman et al., 2017). This has formed the basis for global physical activity and exercise guidelines (Bull et al., 2020). Exercise also has a profound acute effect on metabolism, and this section will explain how exercise can improve glycaemic control and PPL.

2.6.1 Exercise and Glycaemic Control

Exercise has a potent effect on glycaemic control and insulin sensitivity. This occurs during exercise, after acute exercise, and in response to chronic exercise training. During exercise, glucose uptake in contracting skeletal muscle increases in an intensity and duration-dependent manner (Richter and Hargreaves, 2013). This occurs via insulin-independent mechanisms, namely an increase in blood flow to the active skeletal muscle, increased GLUT4 translocation to the plasma membrane, and an increase in intracellular glucose metabolism to facilitate glucose diffusion across the cell membrane (Sylow et al., 2017). These mechanisms explain how exercise performed in a postprandial state is effective at reducing glucose concentrations for individuals with T2D (Borror et al., 2018). This insulin-independent uptake of glucose can persist for up to 4 h after exercise (Frøsig et al., 2007).

A single bout of exercise can improve peripheral insulin sensitivity for up to 48 h, in adults with and without insulin resistance (Devlin and Horton, 1985; Mikines et al., 1988). This effect has been reported following both aerobic (45 min at 65% $\dot{V}O_{2PEAK}$) (Perseghin et al., 1996) and two-leg resistance (Koopman et al., 2005) exercise. Consequently, there are multiple studies demonstrating that prior exercise improves 24 h glycaemic control for individuals with T2D and obesity (Praet et al., 2006; van Dijk et al., 2012; Oberlin et al., 2014). The insulin-sensitizing effect of exercise

appears to be local and isolated to the exercised skeletal muscle. For example, Richter et al. (1989) demonstrated that glucose uptake was higher for the exercised leg compared to non-exercised leg during a HEC performed 4 h after exercise. The mechanisms responsible for this effect are linked to muscle glycogen re-synthesis. Specifically, there is i) an increase in insulin mediated upregulation of microvascular flow, enabling an increased delivery of glucose to the exercising muscle and, ii) enhanced sensitivity of proteins involved in the insulin signalling pathway, leading to an increase in GLUT4 translocation (Sjøberg et al., 2017; Richter, Sylow and Hargreaves, 2021).

Whilst the insulin-sensitizing effect of a single bout of exercise only lasts for a maximum of 48 h, exercise training (of sufficient duration and intensity) has been shown to increase insulin sensitivity by ~25-50%, including for individuals who are physically inactive, obese, pre-diabetic or have T2D (Conn et al., 2014; Way et al., 2016; Bird and Hawley, 2017). This effect appears to be volume and intensity-dependent, with greater exercise volumes (>1,900 kcal per week) (Malin et al., 2013) and higher exercise intensities (e.g., HIIT) producing greater improvements in insulin sensitivity. Additionally, the combination of aerobic exercise and resistance exercise appears to be effect than either exercise modality alone (Bird and Hawley, 2017). Emerging evidence suggests that weight-loss may also be an important factor to consider. Ryan et al. (2020) reported that improvement in peripheral insulin sensitivity (measuring using a HEC) observed the day after 12 weeks of exercise training (MICT and HIIT) was abolished after four days of detraining in sedentary adults who maintained their body mass. Mechanisms linked to the increase in insulin sensitivity following exercise training include increased muscle capillarisation, an increased expression of GLUT4 and hexokinase II (responsible for phosphorylation of glucose to glucose-6-phosphate within skeletal muscle), and mitochondrial biogenesis (Richter, Sylow and Hargreaves, 2021).

2.6.2 Exercise and PPL

Exercise training, at least in the absence of a recent exercise bout, appears to have no effect on PPL (Herd et al., 1998; Herd et al., 2000). However, there is consistent evidence from meta-analyses and systematic reviews that a single bout of aerobic exercise prior to meal consumption can reduce PPL in non-injured humans (Petitt and Cureton, 2003; Maraki and Sidossis, 2013; Freese, Gist and Cureton, 2014). This effect is transient (lasting <24 h) highlighting the importance of performing

regular exercise (Zhang, Thomas and Ball, 1998). The magnitude of the PPL lowering effect is moderated by the energy expended during aerobic exercise (Petitt and Cureton, 2003; Freese, Gist and Cureton, 2014), with a threshold of ~2-2.5 MJ (~480-600 kcal) proposed to reduce PPL (Maraki and Sidossis, 2013). It also appears that exercise intensity and energy balance play an important moderating role in this effect (Maraki and Sidossis, 2013; Freese, Gist and Cureton, 2014). Specifically, HIIT appears to reduce PPL to a greater extent than MICT (see Section 2.8.4), and the effect of exercise on PPL is diminished or abolished when the calories expended during exercise are replaced (Burton et al., 2008; Harrison et al., 2009).

The primary mechanism responsible for the PPL lowering effect of exercise is believed to differ depending on the timing of exercise in relation to the meal tolerance test. Studies in this area typically employ a design whereby exercise is performed either; i) immediately prior to the assessment of PPL (i.e., in a fasted state), or, ii) the evening prior to the assessment of PPL (i.e., 12-18 h post-exercise). For exercise performed immediately prior to meal consumption, it is thought that PPL is attenuated largely due to decreased hepatic secretion of very low density lipoproteins (VLDLs) (Gill and Hardman, 2003). This theory has been supported by experimental work demonstrating that VLDL secretion rate was significantly reduced during 90 min of cycling at 50% $\dot{V}O_{2PEAK}$, and this persisted during the subsequent 2 h recovery period (Sondergaard et al., 2011). For exercise performed 12-18 h prior to meal consumption, it is likely that PPL is attenuated largely due to increased expression of tissue-specific skeletal muscle LPL, and therefore an increased hydrolysis of TRLs (Gill and Hardman, 2003). The activation of LPL is delayed, with peak expression and mass (i.e., activity) of LPL occurring 4 h and 8 h post-exercise respectively, before returning to baseline at 20 h post-exercise (Kiens et al., 1989; Seip et al., 1997). This likely explains findings that exercise performed 12 h prior to meal assessment reduced PPL to a greater extent than exercise performed 1 h prior (Zhang, Thomas and Ball, 1998), and consequently most studies in this area have performed exercise the evening prior to PPL assessment.

2.7 Exercise and CVD risk in SCI

The modes of exercise available to individuals with a SCI are limited to voluntary upper-body exercise (e.g., hand-cycling, arm crank ergometry, wheelchair

propulsion, and resistance training), lower extremity, or hybrid functional electrical stimulation (FES), neuromuscular electrical stimulation (NMES), and body weight supported, or exoskeleton assisted treadmill walking. The evidence presented herein in will focus on upper-body exercise only, as these other exercise modalities were deemed unsuitable (e.g., expensive equipment, limited applicability for personal use) for the experimental chapters of this thesis. These alternative interventions are reviewed elsewhere (Gorgey et al., 2015b; Nam et al., 2017; van der Scheer et al., 2021b). This section will describe the current exercise guidelines for individuals with an SCI and evaluate the best available evidence pertaining to the effect of upper-body exercise training on CVD risk factors in this population.

2.7.1 Exercise Guidelines for SCI

The latest SCI-specific exercise guidelines recommend that adults should engage in at least 30 min of moderate-to-vigorous intensity aerobic exercise three times per week for cardiometabolic health benefits (Martin Ginis et al., 2018). For CRF and muscle strength benefits, this recommendation is at least 20 min of moderate-to-vigorous intensity aerobic exercise two times per week, in addition to three sets of strength exercises for each major functioning muscle group, at a moderate-to-vigorous intensity. These guidelines were recommended following a systematic review of the available literature (van der Scheer et al., 2017) and a rigorous process of consultation with scientists, clinicians and persons with SCI (Martin Ginis et al., 2018). However, these guidelines have been met with some contention (Tweedy et al., 2018), specifically over the quality of evidence available to determine the minimum threshold of exercise for fitness and health benefits. Instead, a position statement published by Exercise and Sports Science Australia (ESSA) recommends adults with SCI perform ≥30 min of moderate aerobic exercise on ≥5 days per week or ≥20 min of vigorous exercise on ≥3 days per week, in addition to performing strength and flexibility training on ≥2 days per week (Tweedy et al., 2017). These recommendations are based on the standpoint that there is a lack of a sufficient high-quality studies in people with SCI, and therefore in the “absence of compelling evidence to the contrary, exercise guidelines for people with SCI should be consistent with those for the general population” (Tweedy et al., 2017).

This standpoint is in line with guidelines issued by WHO, which recommended that all adults with a disability should perform 150-300 min of moderate-intensity, and/or 75-150 min of vigorous-intensity physical activity per week, in addition to regular

muscle strengthening exercises (Bull et al., 2020). These guidelines were issued following a systematic review of the available evidence in disabled adults (including SCI), which also concluded that due to evidence gaps in the dose-response relationship between volume and/or intensity of physical activity and health outcomes, guidelines for disabled individuals should be in line with those for the general population. Similar to the ESSA and WHO guidelines, the latest UK guidelines recommend adults with a disability should perform at least 150 min per week of moderate intensity physical activity, in addition to two sets of strength and balance activities on ≥2 days per week (UK Chief Medical Officers, 2019). The associated rapid evidence review concluded that there was moderate to strong evidence that for adults with physical and cognitive impairments, physical activity was associated with increased CRF, muscular strength, and reduced disease risk (Smith et al., 2018).

2.7.2 Effect of Exercise on CMS Risk Factors

The evidence pyramid states the highest level of evidence comes from systematic reviews and meta-analyses, particularly those containing results from high quality RCT's (Murad et al., 2016). Unfortunately, due to the relatively small SCI prevalence in society, and the large heterogeneity (due to variations in level and completeness of injury) of the SCI population, the number of high-quality RCT's to assess the effect of exercise on markers of CVD risk is low. The first systematic review in this area concluded that the evidence was insufficient to determine whether exercise improves carbohydrate and lipid metabolism orders amongst adults with SCI (Carlson et al., 2009). Since this, the quality of studies has slowly improved, with the most recent systematic review concluding there was low to moderate confidence in evidence that three to five sessions per week of upper-body aerobic exercise at a moderate-to-vigorous intensity for 20-44 minutes can improve CRF, body composition, and CVD risk (van der Scheer et al., 2017). However, this review did not assess the effect of exercise on the individual component risk factors for CVD, which forms the rationale for the systematic review performed in Chapter 4 of this thesis. The reader is encouraged to see Chapter 4 for a detailed summary of the available literature relating to exercise and markers of CVD risk in those with SCI. However, several pertinent RCT's that have examined upper-body exercise are discussed below.

There are only a small number of RCT's assessing the effect of upper-body aerobic exercise on CVD risk factors that also include a 'true' control (CON) group whereby participants are instructed to continue their habitual physical activity patterns (Rosety-Rodriguez et al., 2014; Kim et al., 2015). This is an important comparison due to the natural time course changes that can be expected in this population. For example, these studies have reported a reduction in the mean CRF and insulin sensitivity of the CON group across a six week period (Rosety-Rodriguez et al., 2014; Kim et al., 2015; Nightingale et al., 2017d). Kim et al. (2015) reported improvements in CRF and fasting insulin sensitivity (fasting insulin and HOMA-IR) with 132 min per week of hand-cycling exercise at 70-80% peak heart rate (HR_{PEAK}) for six weeks. Similarly, Nightingale et al. (2017) reported an improvement in CRF and insulin sensitivity (fasting insulin and HOMA-IR) following 180 min per week of arm crank exercise at 60-65% $\dot{V}O_{2PEAK}$ for six weeks. These RCT's suggest upper-body exercise (of moderate and moderate-to-vigorous intensity) improves CRF and fasting insulin sensitivity in individuals with chronic SCI.

However, Nightingale et al. (2017) observed no other changes in the fasting lipid profile, DEXA-derived measures of body composition, resting BP, or postprandial glycaemic control. This is significant as the study is arguably the most rigorous RCT involving upper-body exercise to date. Participants were all habitually physically inactive (PAL ≤1.60) and therefore were representative of the wider SCI population. The majority of studies in the area lack a-priori sample size calculations, however, this study was sufficiently powered to detect changes in the main outcome measure (fasting insulin). The exercise and CON groups were also matched for key characteristics (age, body mass, level of injury, and PAL), and consequently, there were no significant differences in markers of CVD risk between groups at baseline. Finally, physical activity was objectively measured (tri-axial accelerometery combined with HR) in addition to EI (food diary) in the final week of the intervention (or control period), which allowed any physical activity 'substitution' or changes in EI to be quantified. It should be noted that the exercise training programme was relatively short in duration (six weeks), which may be insufficient to elicit other metabolic adaptations. However, the total volume of exercise (180 min per week) was considerably higher than the latest SCI-specific exercise guidelines (90 per week) (Martin Ginis et al., 2018) and higher than WHO physical activity guidelines for the general population (150 min per week) (Bull et al., 2020). This would suggest that either a higher volume and/or intensity of upper-body exercise may be needed

to achieve further cardiometabolic benefits in people with chronic SCI. Given the numerous and complex barriers to exercise participation in this habitually inactive population, as previously discussed, promoting a higher volume of exercise (i.e., ≥180 min per week) may be an unrealistic message to promote. Instead, it may be possible to achieve further cardiometabolic benefits in individuals with SCI by exercising at a higher intensity, or by performing HIIT, as proposed by Nightingale et al. (2017a).

This call to action for research assessing the effect of HIIT in SCI, was formed primarily on the basis of i) the effectiveness of HIIT in comparison to traditional moderate-intensity continuous training (MICT) in the general population, and ii) preliminary evidence from two pre-post study designs in persons with SCI that upper-body high-intensity exercise was more effective than moderate-intensity exercise for improving CMS risk factors (Hooker and Wells, 1989; de Groot et al., 2003). For example, de Groot et al. (2003) reported greater improvements in $\dot{V}O_{2PEAK}$ following eight weeks of arm crank exercise at 70-80% heart rate reserve (HRR) compared to 40-50% HRR, in addition to a reduction in TG and improvement in insulin sensitivity, in adults with acute SCI.

2.8 High-Intensity Interval Training

2.8.1 Definitions

This section will firstly introduce and define HIIT, and then review the available evidence from the general population regarding its' effectiveness for reducing CVD risk (chronic and acute effects). Where possible, this will be compared to traditional MICT.

In the general population, cohort studies have consistently demonstrated that there is an inverse relationship between physical activity intensity and cardiovascular/all-cause mortality (Samitz, Egger and Zwahlen, 2011), independent of the total volume of physical activity performed (Tanasescu et al., 2002). High-intensity exercise, even in small volumes has a potent effect, with a single weekly bout of high-intensity exercise sufficient to reduce cardiovascular mortality in individuals free from known CVD and those with coronary heart disease (Wisløff et al., 2006; Moholdt et al., 2008). These findings formed the basis for early studies demonstrating that HIIT can

improve biomarkers of CVD risk to a greater extent than traditional MICT (Tjønna et al., 2008; Trapp et al., 2008).

MICT has been defined as exercise of typically 30-60 min in duration at an intensity of 64-76% HR_{PEAK} (Medicine et al., 2018). There is no standardised definition of HIIT, but it can generally be characterised as repeated short intervals of near maximal exercise, eliciting ≥80% (but often 85-95%) of HR_{PEAK} (MacInnis and Gibala, 2017). It is important to distinguish HIIT from sprint interval training (SIT), which involves 'all-out' or supramaximal efforts at an intensity ≥100% peak power output (PPO) (Weston, Wisløff and Coombes, 2014). Both HIIT and SIT involve intense exercise that cannot be maintained for a sustained period, and therefore the work intervals are separated by low-intensity exercise or resting recovery, to allow for a greater volume of high-intensity exercise to be performed. Although there is a wide range of HIIT protocols used in the literature, two of the most common protocols can be classified as 'high-volume' HIIT (e.g., 4 x 4 minute intervals at 85-95% HR_{PEAK}) (Wisløff et al., 2007) and 'low-volume' HIIT (e.g., 10 x 60 s intervals at 100% PPO) (Little et al., 2011). SIT protocols typically involve Wingate sprints, including four to six repeated 30-s sprints interspersed with two to five minutes of complete rest (Gibala et al., 2006). Given the high prevalence of undiagnosed ischaemic heart disease in persons with chronic SCI (Bauman et al., 1994), and the lack of available evidence regarding the safety of SIT in this population, it was decided not to investigate SIT in the experimental chapters of this thesis. However, SIT is discussed in this literature review intermittently as it is directly relevant to the primary goal of this thesis (i.e., to examine high-intensity exercise).

2.8.1 Efficacy of HIIT

There is a rapidly growing body of evidence demonstrating that HIIT can elicit a variety of benefits to cardiometabolic health. The first extensive meta-analysis of these studies revealed that HIIT performed at least three times per week for 12 weeks provides improvements to CRF, body composition (waist circumference, body fat percentage), and vascular function (resting HR, systolic and diastolic BP) in overweight and obese populations (Batacan et al., 2016). Despite a smaller time-commitment, meta-analyses have reported that HIIT offers similar (lipid profile, inflammatory markers, body composition) (Campbell et al., 2019; Wood et al., 2019; Khalafi, 2020) and often superior improvements (CRF, vascular function, insulin resistance) (Weston, Wisløff and Coombes, 2014; Jelleyman et al., 2015; Ramos et

al., 2015) to MICT across a range of cardiometabolic health outcomes. Importantly, these effects are observed in overweight and obese populations, and those with metabolic disorders.

2.8.2 Safety of HIIT

HIIT has been evaluated in a wide variety of clinical populations, including those with CVD, metabolic syndrome, T2D, heart failure, and chronic obstructive pulmonary disease (Weston, Wisløff and Coombes, 2014). It appears that HIIT is a safe form of exercise in these populations, with one study reporting one major cardiovascular adverse event per 17,083 training sessions for HIIT, and no events for MICT, during cardiac rehabilitation across 1,117 patients (Wewege et al., 2018). Furthermore, the Generation 100 study reported no cardiovascular adverse events for twice-weekly MICT or HIIT in 1,567 older adults across a 5-year period (Stensvold et al., 2020). Despite this, some safety concerns remain, and guidelines for the prescription of HIIT in these clinical populations were recently published (Taylor et al., 2019).

2.8.3 Adherence and Enjoyment of HIIT

HIIT is tolerable and acceptable in previously sedentary individuals, at least in a laboratory setting, with a recent meta-analysis reporting a drop-out rate of 17.6% across 67 studies (Reljic et al., 2019). However, adherence to HIIT in a free-living setting is less well understood, and there is some debate over the promotion of HIIT as a public health strategy (Biddle and Batterham, 2015). In the short to medium term (<24 weeks), adherence rates to HIIT have been reported to be similar (Vella, Taylor and Drummer, 2017) or greater (Locke et al., 2018) than MICT in small pilot studies. In a follow-up study amongst 250 overweight and obese individuals, adherence to regular unsupervised HIIT declined from 60.8% at baseline to 19.6% at 12 months, although this was no different to MICT (Roy et al., 2018). The longest RCT to date to compare HIIT and MICT, suggests that HIIT is achievable in the long-term, with an adherence rate of 47% to twice-weekly HIIT, compared to 51% for MICT in older adults across a 5 year period (Stensvold et al., 2020).

There is a lack of evidence regarding free-living adherence to HIIT. However, several studies have characterised the psychological responses to a single-bout of HIIE in comparison to MICE to provide indications of long term free-living adherence

to HIIT. For example, and in brief, affective valence (i.e., how an individual feels during exercise), exercise enjoyment, and exercise self-efficacy (i.e., an individual's belief in their capacity to perform exercise) can all predict future physical activity behaviour and adherence to exercise programmes (Williams et al., 2008; Lewis et al., 2016). These outcomes have been extensively summarised in recent scoping and systematic reviews, with HIIE reported to be more enjoyable than MICE, despite affect being lower during HIIE (Stork et al., 2017; Oliveira et al., 2018; Niven et al., 2021). Qualitative research has highlighted the reasons individuals tend to enjoy and prefer HIIE over MICE, which include perceiving HIIE as less monotonous, the feelings of accomplishment fostered during HIIE, and the presence of recovery intervals to overcome fatigue and exhaustion (Stork, Williams and Ginis, 2020). Given these positive psychological responses to a single-bout of HIIE, it is likely that long-term adherence to HIIT is at least comparable to MICT.

2.8.4 Glycaemic Control and Lipid Metabolism following HIIE

As discussed in Section 2.6, a single bout of aerobic exercise can have a potent transient (0-48 h) effect on glucose and lipid metabolism, specifically by reducing hyperglycaemia, enhancing insulin sensitivity, and reducing PPL. This also appears to be true for HIIE, and there is some evidence that HIIE is more effective than MICE at targeting these CVD risk factors.

In comparison to a no-exercise condition, a single bout of HIIE (10 x 60 s cycling at 90% HR_{PEAK}) performed in the fasted state can reduce 24 h postprandial glucose concentrations in individuals with T2D (Gillen et al., 2012). Furthermore, this effect has been reported to be greater than a work-matched MICE session in overweight and obese individuals (Little et al., 2014), and those with insulin resistance (Francois et al., 2014) and T2D (Karstoft et al., 2014). A single bout of HIIE elicits a strong insulin-sensitizing effect, with a recent study reporting that insulin sensitivity (measured using HEC) was significantly increased ~22 h after a bout of HIIE (15 x ~2 min at 84% $\dot{V}O_{2PEAK}$) in comparison to a no-exercise condition in untrained women (Fisher et al., 2019). This difference was observed under rigorously controlled energy-balanced conditions, with no difference in insulin sensitivity observed following MICE (1 h at 50% $\dot{V}O_{2PEAK}$) in comparison to no-exercise.

A single bout of HIIE also has the potential to improve lipid metabolism for a transient period (0-48 h). This topic has been extensively studied; a meta-analysis reported

that HIIE induced a larger reduction in the TG iAUC (*d*=-1.49) compared to MICE (*d*=-0.58) (Freese, Gist and Cureton, 2014). Although importantly, this analysis did not distinguish between HIIE and sprint interval exercise (SIE). There are a small number of studies that have assessed the effect of sub-maximal HIIE on postprandial lipid metabolism. Burns, Miyashita and Stensel (2015) concluded from five available studies that HIIE reduced PPL to a similar extent as MICE, although noted that a substantial time commitment, and thus EE was required to elicit this reduction. For example, Trombold et al. (2013) found that a bout of HIIE (intervals of 2 min at 90% $\dot{V}O_{2PEAK}$) performed the evening prior, reduced PPL in comparison to a no-exercise condition, and to a greater extent than an iso-energetic (~660 kcal) bout of MICE (50% $\dot{V}O_{2PEAK}$ for 1 h) in six healthy young men.

More recently, several studies have examined the effect of lower-volume HIIE protocols involving a smaller time commitment. For example, Bailey et al. (2019) reported that a bout of HIIE (10 x 60 s at 90% $\dot{V}O_{2PEAK}$) significantly reduced PPL in comparison to a no-exercise condition in sedentary adults, when exercise was performed between a standardised breakfast and lunch meal test. Furthermore, Lee, Kuo and Cheng (2018) reported that a single bout of HIIE (10 x 60 s at 85% $\dot{V}O_{2PEAK}$) performed the evening prior was more effective at reducing postprandial TG concentrations in comparison to a no-exercise condition, and a bout of MICE (50 min at 65% $\dot{V}O_{2PEAK}$) in physically active men. However, such findings are not consistent across the literature. Tucker et al. (2018) reported no differences in postprandial TG concentrations between a no-exercise condition, and two different HIIE protocols (4 x 4 min at 85-95% HR_{PEAK}, 16 x 1 min at 85-95% HR_{PEAK}) in non-exercise trained men. The reason for this discrepancy is unclear, however it should be noted that blood samples were only taken at baseline, 2 h, and 4 h post-meal consumption. Overall, it appears that a single bout of HIIE has the potential to reduce PPL to a similar extent as MICE.

Furthermore, the reduction in PPL following HIIE appears to be due to factors stemming from the most recent exercise bout, and not from chronic training adaptations. This is evident from a four week HIIT intervention (10 x 60 s at 90% $\dot{V}O_{2PEAK}$), which reported no change in postprandial TG concentrations when assessed >72 hours after the final exercise session (Wilhelmsen et al., 2019). Time-course studies have also demonstrated that the PPL lowering effect of HIIE and SIE is present at 24 h post-exercise but abolished at 48 h post-exercise (Bellou et al., 2013; Gabriel et al., 2013).

2.9 Upper-body Exercise Metabolism

As described in Section 2.8, there is convincing evidence from the general population that an acute bout of HIIE is equally, and in some cases, more effective than MICE, at reducing postprandial lipaemia and glycaemia, and increasing insulin sensitivity. However, the cardiorespiratory and metabolic stress of upper-body exercise is profoundly different from whole and/or lower-body exercise. Therefore, this section will describe the available evidence from studies that have assessed the acute cardiorespiratory and metabolic responses (e.g., to a meal challenge) to upper-body exercise (with a focus on HIIE) in individuals with SCI.

2.9.1 Acute Cardiorespiratory Responses to Upper-body HIIE

Several studies have recently characterised the cardiorespiratory responses to arm crank based HIIE, SIE, and MICE in individuals with SCI (Astorino and Thum, 2018b; Astorino, 2019; McMillan et al., 2021d) (C2 Table 2). Importantly, these studies provide evidence that upper-body exercise protocols can elicit a HR response that meets the definition of HIIE previously described (i.e., ≥80% HR_{PEAK}) (MacInnis and Gibala, 2017). Furthermore, upper-body HIIE (60 to 120 s bouts at 70-85% PPO) elicits ~87-88% of arm-crank specific $\dot{V}O_{2PEAK}$, and this metabolic strain is greater than circuit resistance exercise (42% $\dot{V}O_{2PEAK}$) (Nash et al., 2002), FES-hybrid exercise (~70% $\dot{V}O_{2PEAK}$) (Hettinga and Andrews, 2008), and exoskeleton-assisted walking (36% $\dot{V}O_{2PEAK}$) (Maher et al., 2020). All three of the studies presented in C2 Table 2 demonstrate evidence of a drift in peak HR and $\dot{V}O_2$ during the HIIE working phases, such that the final bout elicits a ~15% higher $\dot{V}O_2$ compared to the first bout (McMillan et al., 2021d). This cardiovascular drift is not present during MICE conditions.

There are also potentially important fluctuations in energy substrate partitioning during upper-body HIIE and SIE, that are not observed during MICE. Mean respiratory exchange ratio (RER) is lower during MICE (0.97 ± 0.04) than HIIE (1.04 ± 0.07) and SIE (1.13 ± 0.11) (Astorino and Thum, 2018b). For upper-body HIIE and SIE, RER initially increases during the first working phase, rising to well above 1.0 during the first recovery phase. RER then returns towards (and sometimes below) 1.0 during each resultant working phase, before rising again during the recovery phases. The dynamic shifts and coupling of RER with recovery and working phases

is also seen in non-injured individuals performing lower-body HIIE (Hetlelid et al., 2015). This is due to an increase in cardon dioxide production ($\dot{V}CO_2$), likely a result of an increase in bicarbonate buffering, as reflected by increasing blood lactate concentrations during upper-body HIIE (Astorino and Thum, 2018b). This likely represents a degree of muscle glycogen breakdown (Astorino and Thum, 2018b; McMillan et al., 2021d). It is well-known that the rate of muscle glycogen breakdown increases during high-intensity exercise (Hargreaves and Spriet, 2020), and this also appears occur during a bout of HIIE in non-injured humans (Scribbans et al., 2014). However, it should be noted that participants in all studies presented in C2 Table 2 were habitually active and appear to have a good level of CRF. This is not representative of the general SCI community, and responses may differ in those unaccustomed to exercise. Furthermore, the assumptions of indirect calorimetry are violated during HIIE and SIE, and therefore caution is needed when interpreting substrate utilisation during these exercise forms.

C2 Table 2 Studies characterising the peak cardiorespiratory responses to upper-body HIIE, SIE, and MICE.

Study	Participants	Protocol	%HR_{PEAK}	%$\dot{V}O_{2PEAK}$	Total EE (kcal)	Duration (min)
Astorino and Thum (2018b)	n=9 8 M, 1 F T6 or ↑: 2 ↓T6: 7 $\dot{V}O_{2PEAK}$: 17.4 ± 4.7 mL·kg^{-1}·min^{-1}	*HIIE* 8 x 60-s at 70% PPO	99%	87%	102 ± 35	25
		SIE 8 x 30-s at 105% PPO	96%	78%	97 ± 32	25
		MICE 25 min at 45% PPO	86%	69%	118 ± 38	30
Astorino (2019)	n=5 5 M T6 or ↑: 3 ↓T6: 2 $\dot{V}O_{2PEAK}$: 21.9 ± 12.6 mL·kg^{-1}·min^{-1}	*HIIE* 60-s at 85% PPO	88%	87%	100 ± 10	28 ± 12
		SIE 30-s at 115% PPO	88%	80%	100 ± 10	24 ± 12
		MICE 35% PPO	74%	53%	100 ± 10	30 ± 13
McMillan et al. (2021d)	n=10 10 M T6 or ↑: 7 ↓T6: 3 $\dot{V}O_{2PEAK}$: 19.2 ± 5.2 mL·kg^{-1}·min^{-1}	*HIIE* 120-s at 70% PPO	86%	88%	117 ± 35	32 ± 6
		MICE 24.6% PPO	62%	53%	116 ± 22	40 ± 5

HIIE *high intensity interval exercise*, SIE *sprint interval exercise*, MICE *moderate intensity continuous exercise*, $\dot{V}O_{2PEAK}$ *peak aerobic capacity*, HR_{PEAK} *peak heart rate,* EE *energy expenditure*, PPO *peak power output*

2.9.2 Metabolic Responses During and Following Upper-Body Exercise

The absolute capacity for upper-body is ~70% of that achieved during lower-body cycling in well-trained subjects (Astrand and Saltin, 1961). Furthermore, and in Section 2.4, both RMR and $\dot{V}O_{2PEAK}$ are lower for those with a SCI than non-injured individuals. Consequently, at a given relative exercise intensity the energy expended during upper-body exercise is substantially lower (30-75%) for those with an SCI (Price, 2010). For example, during 45 min of vigorous-intensity arm crank exercise at 75% $\dot{V}O_{2PEAK}$, individuals with mid-paraplegia (T6-T8), low-paraplegia (T10-L1), and non-injured controls expended 352 ± 52, 429 ± 32, and 558 ± 158 kcal·session^{-1} respectively (Farkas et al., 2020). In the context of the exercise guidelines presented earlier, a typical bout of upper-body MICE lasting 30 min has been reported to elicit an total EE of ~120 kcal in persons with chronic paraplegia (Astorino and Thum, 2018b). This would equate to a total exercise EE of ~620 kcal per week (150 min of MICE) for individuals meeting the WHO and ESSA minimum exercise guidelines, and ~700-800 kcal per week (90 min at 75% $\dot{V}O_{2PEAK}$) for those meeting the latest SCI-exercise guidelines (Tweedy et al., 2017; Ginis et al., 2018; Bull et al., 2020). This falls short of the suggested threshold of 1200 to 2000 kcal per week to promote and maintain health in the general population (Haskell et al., 2007; Donnelly et al., 2009). The low EE of exercise may also be significant in relation to the acute effect of upper-body exercise on PPL and insulin sensitivity, given that EE moderates the magnitude of these effects in non-injured individuals (Magkos et al., 2008; Freese, Gist and Cureton, 2014).

Substrate metabolism during upper-body exercise also differs substantially from whole and lower-body exercise. During treadmill running, as exercise intensity increases the relative contribution of fat metabolism to energy expenditure decreases, and carbohydrate metabolism becomes predominant at ~45-55% $\dot{V}O_{2PEAK}$ (Venables, Achten and Jeukendrup, 2005). During arm crank exercise, this cross-over occurs at a lower intensity (~30-40% $\dot{V}O_{2PEAK}$) for sedentary individuals with paraplegia, with maximal fat oxidation rates occurring at ~41% $\dot{V}O_{2PEAK}$ (Jacobs et al., 2013). This indicates a heavy reliance on carbohydrate metabolism during upper-body exercise, likely a result of a lower rate of O_2 extraction and metabolic efficiency compared to whole and lower-body exercise (Kang et al., 1997; Calbet et al., 2005). This may be significant in contextualising the modest CVD risk benefits of MICT for this population, due to the association between fat oxidation capacity during exercise and markers of cardiometabolic health, including insulin sensitivity,

in the general population (Venables and Jeukendrup, 2008). For non-injured individuals performing arm crank exercise, carbohydrate metabolism was predominant across all exercise intensities, with maximal fat oxidation rates occurring at ~13% $\dot{V}O_{2PEAK}$ (Jacobs et al., 2013). This could indicate that individuals with an SCI have occurred some skeletal muscle adaptations to enable them to oxidise fat to a greater extent.

It is also important to consider the post-exercise period when assessing the effect of upper-body exercise on metabolism, as EE does not immediately return to baseline. This phase is often referred to as excess post-exercise oxygen consumption (EPOC), and it's magnitude is dependent on the exercise intensity and volume (Børsheim and Bahr, 2003). Both the magnitude and duration of EPOC following arm crank exercise appear to be limited. For example, arm crank exercise at 65-70% $\dot{V}O_{2PEAK}$ for 30 min elevates EPOC for ~23 min, equivalent to ~37 kcal in individuals with chronic paraplegia (Sedlock et al., 2004). In non-injured individuals, despite exercising at the same relative intensity (60% $\dot{V}O_{2PEAK}$) to expend 200 kcal, arm crank exercise induced a smaller EPOC magnitude and duration than leg ergometry (Lyons et al., 2007). However, a recent study demonstrated that 45 min of circuit resistance exercise can elevate energy expenditure and fat oxidation for at least 2 h in individuals with chronic SCI (McMillan et al., 2021b). This highlights the possibility that upper-body HIIE may be able to substantially elevate EPOC and potentially provide a greater overall metabolic stress than MICE.

2.9.3 Metabolic Challenge Responses to Upper-Body Exercise

There are a limited number of studies that have assessed the effect of an acute bout of upper-body exercise on carbohydrate and lipid responses to a meal challenge (C2 Table 3). In individuals with chronic SCI, it appears that upper-body exercise may only offer limited benefit to metabolic responses (Bailey et al., 2020; Farkas et al., 2021c; McMillan et al., 2021c). McMillan et al. (2020) reported no change in glucose, insulin, or TG iAUC across the entire postprandial period following arm crank exercise (both MICE and HIIE) and circuit resistance exercise (vs. a no exercise condition). It is possible that the low EE (~120 kcal) of the upper-body exercise protocols may be responsible for these findings. However, the results should also be treated with some caution in view of the study limitations. The postprandial period was short (180 min), and therefore the peak TG concentrations were likely missed (Travers et al., 2017). All of the participants recruited to this study

were metabolically healthy, and a large proportion had a ‘good’ level of CRF (Simmons, Kressler and Nash, 2014), which is not representative of the SCI population. Bailey et al. (2020) reported no change in glucose, insulin, or TG iAUC across the entire 5.5 h postprandial period when sedentary time was interrupted by regular bouts of arm crank based physical activity. There was a significant reduction in glucose iAUC following the lunch meal, although the clinical relevance of this is not clear. The discrepancies between breakfast and lunch responses might mean a ‘threshold’ of EE or muscular contractions is required to elicit a reduction in glucose concentrations.

Farkas et al. (2021) reported that glucose effectiveness was higher immediately after 45 min of arm crank exercise at 75% $\dot{V}O_{2PEAK}$ in individuals with chronic paraplegia, with no change in insulin sensitivity during an IVGTT. The improvement in glucose effectiveness was not maintained at 24 h post-exercise. This suggests that glucose concentrations were reduced in the immediate post-exercise period due to muscle contraction-stimulated glucose transport (i.e., non-insulin mediated glucose transport) (Sylow et al., 2017). This major strength of this study is the use of an IVGTT to measure glucose tolerance and insulin responsiveness, compared to the consumption of a drink or meal used in other studies (Bailey et al., 2020; McMillan et al., 2021c), which overcomes the delay and variability in postprandial absorption. Therefore, this study provides strong evidence that upper-body aerobic exercise improves glucose metabolism. Similarly, Short et al. (2017) reported that glucose iAUC was lowered following 35-min of moderate-to-vigorous handcycling exercise in adolescents with spina bifida or cerebral palsy, with no change in insulin sensitivity.

C2 Table 3 Studies assessing the effect of an acute bout of upper-body exercise on carbohydrate and/or lipid metabolism.

Study	Participants	Conditions	Meal/Metabolic Assessment	Outcomes
McMillan et al. (2021c)	n=10 (all PARA) 10 M *Age*: 39 ± 10 yr *TSI*: 13 ± 9 yr	CON: 45-min seated rest *MICE:* 40-min ACE at 30% PPO *HIIE:* ~30 min ACE with 2-min intervals at 10% PPO and 70% PPO *CRE:* ~40 min, 6 resistance exercises, interspersed with low-intensity ACE	*Type:* MMTT *Content:* 50% CHO, 35% fat, 15% protein, 600 kcal *Timing*: ≤1 h post-exercise *Duration:* 2.5 h	Glycerol higher in postprandial period for MICE and CRE vs. CON. Lipid oxidation higher for HIIE (until 60-min) and CRE (until 150 min) vs. CON No other differences in glucose, insulin, or TG.
Short et al. (2017)	n=18 (7 with spina bifida or cerebral palsy, 11 ambulatory) 10 M, 8 F *Age:* 11-18 yr *TSI:* N/A	CON: 45-min seated rest *Ex:* 35 min of moderate-to-vigorous handcycling (mostly at 50% HR_{PEAK} with five 30-s intervals at 80% HR_{PEAK})	*Type:* OGTT *Content:* 75 g glucose *Timing:* 30 min post-exercise *Duration:* 2 h	Glucose TAUC 11% lower in EX vs. CON Insulin sensitivity 16% higher for EX vs. CON (ambulatory participants only)
Bailey et al. (2020)	n=14 (all PARA) 6 M, 8 F *Age:* 51 ± 9 yr *TSI:* >1 yr	*CON:* Uninterrupted sitting for 5.5 h *Active:* 120-s of MICE every 20 min for 5.5 h	*Type:* Standardised breakfast and lunch *Content:* 54% CHO, 31-34% fat, 12-15% protein (each meal provided 30% of daily energy requirements) *Timing:* Breakfast at 0 h, lunch at 3 h. *Duration:* 5.5 h	Glucose iAUC 37% lower in Active vs CON during Lunch period. No other differences for glucose, insulin, or TG.

Farkas et al. (2021c)	*SCI:* n=11 (all PARA) 10 M, 1 F *Age:* 34±11 *TSI:* 7±6 yr *Able-bodied:* n=7 4 M, 3 F *Age:* 29±12 yr	*Ex:* 45 min of ACE at 75% $\dot{V}O_{2PEAK}$	*Type:* IVGTT *Content:* N/A *Timing:* Performed 24 h before exercise, immediately post exercise, and 24 h post exercise. *Duration:* N/A	*SCI:* Glucose effectiveness 27% higher immediately post-exercise than baseline. *Able-bodied:* No differences at any time-points.

n *sample size*, TSI *time since injury*, ACE *arm crank ergometry*, MICE *moderate intensity continuous exercise*, CRE *circuit resistance exercise*, HIIE *high-intensity interval exercise*, CON *control*, PPO *peak power output*, HR_{PEAK} *peak heart rate*, $\dot{V}O_{2PEAK}$ *peak aerobic capacity*, TG *triglycerides*, IVGTT *intravenous glucose tolerance test*

2.10 Upper-Body HIIT

HIIT is equally, and for some cardiometabolic health markers, more effective than traditional MICT. Given that upper-body MICT only appears to elicit modest improvements in cardiometabolic health outcomes in persons with chronic SCI, upper-body HIIT may be an effective alternative for this population. Therefore, this section will describe the available evidence from studies that have assessed the chronic training responses to upper-body HIIT in individuals with SCI.

2.10.1 Effect of Upper-Body HIIT on Biomarkers of CVD

C2 Table 4 summarises the studies that have evaluated the effect of upper-body HIIT or SIT on markers of CVD risk in individuals with SCI. These include four RCT's comparing the effect of HIIT/SIT and MICT (de Groot et al., 2003; Gauthier et al., 2018; Graham et al., 2019; McLeod, Diana and Hicks, 2020), four single-group designs (Tordi et al., 2001; Brurok et al., 2011; Hasnan et al., 2013; Koontz et al., 2021), and one case study (Harnish, Daniels and Caruso, 2017). The duration of training programmes ranges from four to 16 weeks, with exercise sessions being performed two to three times per week. Studies have employed a range of protocols, ranging from three 20 s intervals at ≥100% PPO to 20 intervals of 30 to 60 s duration at an RPE of 8-10 (CR-10).

$\dot{V}O_{2PEAK}$ and/or PPO were assessed in all nine studies, with seven studies reporting an increase in one (or both) of these outcomes following HIIT. Koontz et al. (2021) reported no change in $\dot{V}O_{2PEAK}$ or PPO following a six week HIIT programme, with the authors speculating that this was due to either a short interval duration (60-s intervals at 80-90% PPO) or the frequency of sessions (two per week). Gauthier et al. (2018) reported no change in $\dot{V}O_{2PEAK}$ following a home-based HIIT intervention using wheelchair propulsion and speculated that this was due to the lack of exercise supervision and therefore an insufficient intensity of exercise was performed. Overall, it appears that upper-body HIIT/SIT is effective at improving CRF by 8-45%, with no extra benefit compared to MICT. Two (de Groot et al., 2003; Graham et al., 2019) of the three studies to assess measure(s) of insulin sensitivity reported an improvement, suggesting that upper-body HIIT/SIT can elicit positive metabolic adaptations.

The most comprehensive study to date, at least in terms of range of CVD risk markers measured reported a significant improvement in fasting insulin sensitivity (QUICKI) and $\dot{V}O_{2PEAK}$ following six weeks of SIT (twice weekly, 4 x 30 s 'all-out' sprints). These improvements were comparable to that seen in the MICT (three sessions per week, 30 min at 55-65% $\dot{V}O_{2PEAK}$) group. Despite not reaching statistical significance, there was a reduction in TC and low-density lipoprotein-cholesterol (LDL-C) for all participants in the SIT group. No changes were reported for whole-body DEXA measures or OGTT outcomes. Despite the very small sample size (n=4 for SIT), this pilot study provides the strongest available evidence that upper-body high-intensity exercise can improve markers of CVD risk in persons with chronic SCI.

2.10.2 Feasibility and Acceptability of Upper-Body HIIT

Studies assessing responses to upper-body HIIT and SIT in individuals with SCI have largely been limited to those that are laboratory based and/or supervised by a clinician or trainer. Nonetheless, compliance to upper-body HIIT/SIT appears to be high, ranging from 85% (Koontz et al., 2021) to 100% (Graham et al., 2019). To date, only one study has monitored adherence to upper-body HIIT for individuals with SCI in a 'real-world' setting. Gauthier et al. (2018) reported an 86% compliance rate for wheelchair propulsion HIIT, compared to 98% for MICT. Participants were prescribed three sessions of exercise per week, and the authors speculated that due to the higher habitual physical activity levels in the HIIT group, participants in this group had difficulties in scheduling time to perform the intervention. However, all participants completed an acceptable proportion (>75%) of exercise sessions. It therefore appears that upper-body HIIT is feasible for those with an SCI.

The available evidence from acute and chronic training studies demonstrates that upper-body HIIT is acceptable and enjoyable for individuals with SCI. A single bout of arm crank based HIIT (10 x 60 s at 200% PPO) has been reported to be more enjoyable than a work-matched bout of MICT (30 min at 80% PPO) in recreationally active able-bodied males (Hoekstra, Bishop and Leicht, 2017). In individuals with SCI, a single bout of arm crank based HIIE, and SIE have been reported to be more enjoyable than MICE despite a similar time commitment (Astorino and Thum, 2018a). Training studies in individuals with SCI have also demonstrated that

enjoyment levels are high for upper-body HIIT/SIT (Koontz et al., 2021), and are equally enjoyable as MICT (Gauthier et al., 2018; McLeod, Diana and Hicks, 2020).

2.10.3 Safety of Upper-Body HIIT

There are some inherent risks associated with exercise in persons with SCI, including autonomic dysreflexia, hypotension, thermal dysregulation, and musculoskeletal injury (Jacobs and Nash, 2004). These risks should be carefully considered and monitored when intervening in this population. Furthermore, due to the high incidence of undiagnosed coronary heart disease (Bauman et al., 1994) in those with chronic SCI, concerns have been raised regarding the safety of upper-body HIIT. The current evidence, albeit limited in number, from upper-body HIIT studies suggests that there no additional safety concerns for this population. McLeod et al. (2020) reported one adverse event (post-exercise hypotension in the first exercise session) during a five week SIT intervention (3 x 20 s at ≥100% PPO) in ten individuals with acute SCI. Other pilot studies assessing the safety of home-based upper-body HIIT have reported no adverse safety events (Gauthier et al., 2018; Koontz et al., 2021).

Whilst upper-body HIIT appears to be safe, it is possible that HIIT may increase shoulder pain. This is an important consideration for individuals relying on a manual wheelchair for transportation and activities of daily living. Two of the six participants undergoing a wheelchair HIIT programme reported an increase in shoulder pain, which caused one participant to drop-out of the study (Gauthier et al., 2018),. However, this should be interpretated with caution due to the mode of exercise used, which is likely to produce high stress on the shoulder tendons (Collinger et al., 2010). Similarly, two of the six participants undergoing hybrid HIIT reported exacerbation of shoulder dysfunction, although this was alleviated by rest and therapy (Brurok et al., 2011). McLeod et al. (2020) reported no change in shoulder pain following arm crank based SIT, suggesting that low-volume high-intensity exercise doesn't elicit shoulder discomfort.

In summary, the current preliminary evidence suggests that upper-body HIIT is feasible (protocols established that elicit expected HR responses, high compliance), acceptable (enjoyable), safe (at least in terms of cardiovascular adverse events), and effective at improving CVD risk factors ($\dot{V}O_{2PEAK}$ and fasting insulin sensitivity) in individuals with chronic SCI. Therefore, a fully powered RCT, with a wide range

of cardiometabolic health outcomes is warranted to determine its' effectiveness in this population.

C2 Table 4 Studies evaluating the effect of upper-body HIIT on markers of CVD risk in SCI.

Study	Participants				Intervention					Comparator	Outcomes
	n	*LOI*	*Age (yr)*	*TSI (yr)*	*Mode*	*Time (min)*	*Frequency (times per wk)*	*Intensity*	*Duration (wk)*		
Harnish, Daniels and Caruso (2017)	1	C8/T1	42	15	ACE	10-15	3	70-110% PPO	16	N/A	$\dot{V}O_{2PEAK:}$ ↑45% PPO: ↑52% BF%: ↓2%
Hasnan et al. (2013)	8	NR	NR	NR	ACE (+ lower body FES)	32-48	3	80-90% HR_{PEAK}	6	N/A	$\dot{V}O_{2PEAK:}$ ↑20% PPO: ↑ 33% TC: ↔ HDL-C: ↔ LDL-C: ↔ OGTT: ↔
Koontz et al. (2021)	10	C2-S1	39 ± 14	12 ± 11	Handcycling	25	2	10 x 60 s at 90% PPO	6	N/A	$\dot{V}O_{2PEAK:}$ ↔ PPO: ↔
Tordi et al. (2001)	5	T6-L4	27 ± 8	~2	WCE	30	3	6 x 60 s at 80% PPO	4	N/A	$\dot{V}O_{2PEAK:}$ ↑19% PPO: ↑28%
Brurok et al. (2011)	6	C7-T9	40 ± 11	18 ± 8	ACE (+ lower body FES)	NR	3	4 min at 85-90% PPO	8	N/A	$\dot{V}O_{2PEAK:}$ ↑26% PPO: ↑25%
McLeod, Diana and Hicks (2020)	20	C2-L2	46 ± 16	<1	ACE	10	3	3 x 20 s at ≥100% PPO	5	MICT	PPO: ↑ 39%

Gauthier et al. (2018)	9	C6-T11	38 ± 14	8 ± 7	Home-based wheelchair training	40	3	20 intervals of 30-60 s at RPE 8-10 (CR10)	6	MICT	$\dot{V}O_{2PEAK:}$ ↔
Graham et al. (2019)	7	C6-L1	51 ± 11	>3	ACE	2	2	4 x 30 s at 276% PPO	6	MICT	$\dot{V}O_{2PEAK:}$ ↑8% PPO: ↔ QUICKI: ↑7% BF%: ↔ BP: ↔ TC: ↔ HDL-C: ↔ LDL-C: ↔ TG: ↔ Glucose: ↔ Insulin: ↔ HOMA-IR: ↔
de Groot et al. (2003)	6	C5-L1	36 ± 13	<1	ACE	20	3	3 min bouts at 70-80% HRR	8	MICT	$\dot{V}O_{2PEAK:}$ ↑ 150% PPO: ↑159% IS: ↑ TG: ↓ TC: ↔ HDL-C: ↔ LDL-C: ↔ TC/HDL-C: ↓

n *sample size*, LOI *level of injury*, TSI *time since injury*, ACE *arm crank ergometry*, FES *functional electrical stimulation*, WCE *wheelchair ergometry*, MICT *moderate intensity continuous training*, PPO *peak power output*, HR_{PEAK} *peak heart rate*, HRR *heart rate reserve*, RPE *rating of perceived exertion*, $\dot{V}O_{2PEAK}$ *peak aerobic capacity*, BF% *body fat percentage*, TC *total cholesterol*, HDL-C *high-density lipoprotein cholesterol*, LDL-C *low-density lipoprotein cholesterol*, TG *triglycerides*, HOMA-IR *homeostatic model assessment of insulin resistance*, QUICKI *quantitative insulin sensitivity check index*, IS *insulin sensitivity*

2.11 Summary

Individuals with an SCI are at increased risk of developing CVD compared to the general population, and typically present with low CRF, and a multitude of CMS risk factors, including abdominal obesity, reduced HDL-C, and hyperglycaemia. Exercise is an effective countermeasure, although the optimal exercise intensity is relatively unknown for this population. In non-injured humans, there is extensive evidence suggesting HIIT can elicit similar of superior improvements in CRF, insulin resistance, body composition, and the lipid profile compared to MICT. However, the effect of upper-body HIIT for individuals with a SCI has not yet been determined in a RCT. Similarly, an acute bout of HIIE has a greater effect on glucose and lipid metabolism than MICE. In persons with SCI, there is preliminary evidence to suggest that upper-body HIIT is effective at improving CRF and fasting insulin sensitivity, whilst an acute bout of upper-body HIIE appears to improve postprandial glycaemic control.

2.12 Objectives of this Thesis

Accordingly, the aims of this thesis are:

1. To systematically review the evidence base and determine the effect of upper-body aerobic exercise training on individual markers of CMS risk factors in adults with chronic SCI (Chapter 4).
2. To determine the effect of a single bout of upper-body HIIE on postprandial metabolic responses in persons with chronic paraplegia, in comparison to MICE and a no-exercise CON condition (Chapter 5).
3. To determine if upper-body HIIE can reduce PPL when performed the evening prior to metabolic assessment, in comparison to MICE and a no-exercise CON condition (Chapter 6).
4. To determine the effect of upper-body HIIT on markers of CVD risk in persons with chronic paraplegia (Chapter 7).

The central hypothesis to this thesis is that upper-body high-intensity exercise will improve cardiometabolic health markers in individuals with chronic paraplegia. Specifically, it is hypothesised that an acute bout of upper-body HIIE will reduce

postprandial glycaemic and lipaemic responses, and a upper-body HIIT programme will improve fasting insulin sensitivity.

Chapter 3 - General Methods

This chapter describes some of the key methodologies common to more than one of the experimental studies presented in this thesis (i.e., Chapters 5, 6, and 7).

3.1 Ethical Approval

Each experimental study received ethical approval from the University of Bath Research Ethics Approval Committee for Health (REACH) and/or the Central Bristol NHS Health Research Authority Ethics Committee. All procedures were carried out in accordance with the Declaration of Helsinki, with written informed consent obtained from study participants. Each experimental study was registered at Clinicaltrials.gov.

3.2 Participants

Participants in Chapters 5 and 7 were recruited by email using the existing database of the DisAbility Sport & Health (DASH) research group, online and social media advertisements through national SCI charities (e.g., Spinal Injuries Association, Back Up, Aspire), and word of mouth. Participants were also recruited using the databases of local R&D offices (Salisbury NHS Foundation Trust and Cardiff and Vale University Health Board). Upon contact with the researcher, prospective participants were sent a participant information sheet describing the purpose of the study, an overview of the procedures involved, and the potential benefits and risks of participating. Participants were then fully briefed by the researcher and given the opportunity to ask questions. A signed statement of informed consent was then obtained, and participants completed a health screening questionnaire (Appendix A) to confirm study eligibility.

Participants with a SCI were asked to self-report their level of injury, TSI (years), and completeness of their injury based on the ASIA Impairment Scale (Roberts, Leonard and Cepela, 2017). Participants who self-reported an AIS classification of B to E where asked to confirm that they spent >75% of their waking day using a wheelchair. Participants were also asked to list any medications, vitamins, and

supplementations they were currently taking and confirm that they were weight stable (body mass not changed by >3% over the previous three months) (Stevens et al., 2006). Participants were also asked to complete a detailed health screening questionnaire (Appendix A) to identify any active medical issues (including pressure sores, urinary tract infections, and upper-body musculoskeletal issues) or contradictions to exercise testing.

3.3 Anthropometry

This section describes how body mass, supine height, and waist/hip circumferences were determined for individuals with an SCI.

Before body mass was measured, participants were asked to void (or empty their catheter bag) and remove all heavy clothing. Participant's body mass was determined (to the nearest 0.1 kg) using platform wheelchair scales (Detecto® BRW1000, Webb City, MO), with the participant's wheelchair and shoes weighed separately and subtracted from the total mass. Supine length was measured (to the nearest 0.5 cm) as an estimate of body stature, using a non-elastic tape measure whilst participant's laid flat on a scanning table (Froehlich-Grobe et al., 2011). A wooden board was pressed against the feet to achieve dorsal flexion, with the head placed in the Frankfurt plane. For participants who were unable to lay flat (e.g., due to joint contractures and/or spasticity), body length was measured in three segments (head to hip, hip to knee, knee to heel). Waist and hip measurements were taken in accordance with guidelines from the WHO (FerroLuzzi et al., 1995). Waist circumference was measured at the end of normal expiration, at the mid-way point between the lowest palpable rib and the iliac crest. Hip circumference was measured around the widest portion of the buttocks. Measurements were taken in duplicate using a non-metallic tape measure whilst the participant lay flat on the scanning table.

3.4 Indirect Calorimetry

Expired gas samples were collected into 100 – 150 L pre-evacuated Douglas Bags (Hans Rudolph, Kansas City, MO, USA) through a two-way mouthpiece (Model

2700, Hans Rudolph, Kansas City, MO, USA). The mouthpiece was connected to a three way stopcock valve by falconia tubing. A paramagnetic O_2 and infrared CO_2 analyser (miniMP 5200; Servomex, Crowborough, UK) was used to determine concentrations of expired gas samples and inspired gases. The sensors were calibrated on the morning of testing with two certified, gases of known concentrations: i) 100% N_2 and ii) 20% O_2 and 8% CO_2 (BOC Industrial Gases, Linde AG, Munich, Germany). The volume and temperature of expired gas samples were determined using a dry gas pump (Harvard Apparatus, Kent, UK) and thermometer (model C, Edale Instruments, Cambridge, UK) respectively. Ambient O_2 and CO_2 fractions were measured to account for changes in an enclosed laboratory environment (Betts and Thompson, 2012). Ambient temperature and atmospheric pressure were recorded using a weather station (WS-2080, Ambient Weather, Arizona, US) to standardise gas volumes. At rest, stochiometric equations (Frayn, 1983) were used to estimate substrate (carbohydrate and lipid) utilisation rates, assuming protein oxidation was negligible:

$$\text{Carbohydrate utilisation } (g \cdot min^{-1}) = (4.55 \times \dot{V}CO_2) - (3.21 \times \dot{V}O_2)$$

$$\text{Lipid oxidation } (g \cdot min^{-1}) = (1.67 \times \dot{V}O_2) - (1.67 \times \dot{V}O_2)$$

3.5 Peak Aerobic Capacity

In all experimental chapters, $\dot{V}O_{2PEAK}$ was assessed using a ramp-based protocol on an electronically braked arm crank ergometer (Lode Angio, Groningen, Netherlands). Participants were fitted with a rubber face mask (Hans Rudolf, Shawnee, USA) and HR monitor (Polar H10, Polar Electro, Vansbro, Sweden) prior to testing. The facemask was connected to a two-way breathing valve and a computerised metabolic system (TrueOne® 2400, ParvoMedics, Salt Lake City, UT). The system was calibrated with a known concentration of gas (20% O_2, 8% CO_2) and a 3-L calibration syringe within 1 h of testing.

The protocol included a two-minute warm-up at 10 W, before increasing by 1 W every 6 seconds (i.e., 10 W every minute) (Smith et al., 2004). Arm crank rate has been demonstrated to effect maximal physiological responses, and therefore participants were encouraged to maintain a cadence of ~75 rpm throughout the test (Smith, 2001), with the test being terminated at volitional fatigue or when cadence

dropped below 50 rpm. Participants were given strong encouragement to achieve their maximum effort. RPE (on a scale ranging from 6 = no exertion to 20 = maximal exertion) (Borg, 1982) and HR were recorded every minute throughout the test, and at the point of test termination. $\dot{V}O_{2PEAK}$ was defined as the highest 15-breath rolling average for $\dot{V}O_2$ (both relative and absolute), according to best-practice guidelines (Robergs, Dwyer and Astorino, 2010). PPO was defined as the highest power output achieved before termination of the test. The criteria used to determine whether a valid $\dot{V}O_{2PEAK}$ was achieved were; peak HR ≥ 95% age-predicted maximum for upper-body exercise (200 bpm – chronological age), RPE ≥ 19, and peak RER ≥ 1.10 (Goosey-Tolfrey, 2007).

3.6 HIIE and MICE Protocols

In Chapters 5 and 6, participants performed two experimental exercise conditions (MICE and HIIE) on an electronically braked arm crank ergometer. During all exercise conditions, participants wore a rubber face mask connected to a computerized metabolic system, and a HR monitor as previously described. The exact exercise protocols are detailed within each Chapter's methods. The HIIE conditions involved 60 s intervals at 70-80% PPO interspersed with 60 s recovery intervals at 10% PPO. This HIIE protocol was chosen as it has previously been shown to be feasible in individuals with SCI and elicited significantly different $\dot{V}O_2$ and HR profiles in comparison to a time-matched MICE condition (Astorino and Thum, 2018b). HR and RPE were recorded manually at set-intervals throughout each exercise protocol. EE (kcal) for each exercise bout was calculated using a published equation ($0.55*\dot{V}CO_2 + 4.471*\dot{V}O_2$) for high-intensity exercise (50-75% $\dot{V}O_{2MAX}$) (Jeukendrup and Wallis, 2005) across one minute intervals. At higher exercise intensities, this equation is inaccurate due to the buffering of hydrogen ions, violating one of the steady-state assumptions associated with indirect calorimetry. Therefore, when RER exceeded 1.0, EE was estimated assuming a relationship of 5 kcal utilised for each 1 L of O_2 consumed (Weir, 1949), as performed in previous HIIE studies (Williams et al., 2013; Skelly et al., 2014).

3.7 Sample Size and Randomisation

In Chapters 5 and 6, an a-priori sample size calculation was performed to determine the minimum number of participants required to detect a significant difference in total TGs between the HIIE and the no-exercise CON condition. A meta-analysis in non-injured individuals (Freese, Gist and Cureton, 2014) reported a large pooled effect size (*d*=0.97, n=91) towards a reduction in total TGs following HIIE. Therefore, based on an alpha of 5% and power of 80%, we aimed to recruited 11 participants (not including drop-outs) for both studies.

In Chapters 5 and 6, participants completed three conditions (HIIE, MICE, and a no-exercise condition) in a randomised order. The order of trials was determined for all participants prior to each study commencing using an online random number generator (https://www.randomizer.org/).

3.8 Physical Activity Levels

In Chapters 5 and 7, physical activity levels were assessed using a chest-worn monitor (Actiheart^{TM}, CamNtech Ltd, Cambridge Neurotechnology Ltd., Papworth, UK) that combined HR and tri-axial accelerometery. It has been demonstrated that this multi-sensor device is a valid measure of physical activity (Brage et al., 2005) and TDEE (Brage et al., 2015). The device has also been specifically validated for use in manual wheelchair users (Nightingale et al., 2017e). We were therefore able to determine the habitual physical activity levels of participants (Chapters 5 and 7) and detect any changes in these patterns during an exercise intervention (Chapter 7).

Participants were instructed how to fit and wear the activity monitor (using either ECG pads or a strap) and instructed to only remove the activity monitor when exposed to water or physical activity that involved high physical contact (e.g., wheelchair rugby). Data from the Actiheart^{TM} was downloaded and participant characteristics (gender, age, body mass, and height) were entered, in addition to sleeping and peak HR. Individual calibration of each participant's Actiheart^{TM} data was performed by adding the HR and corresponding EE from a sub-maximal exercise test as previously recommended (Nightingale et al., 2017e), in addition to

the individual's RMR. This incremental sub-maximal exercise test was performed on an electronically braked arm-crank ergometer, and consisted of four 3-min stages, starting at 5 W and increasing by 10 or 15 W (depending on self-reported fitness level). Participant's wore a rubber face mask connected to a two-way breathing apparatus as previously described. During the final minute of each stage, HR was recorded, and a one-minute expired gas sample was collected using the Douglas Bag method.

The data derived from the Actiheart™ were used to calculate TDEE, and the physical activity thresholds, expressed as METS: sedentary, <1.5 METs; light, ≥ 1.5 to <3 METs; moderate ≥ 3 to < 6 METs; and vigorous, ≥ 6 METs. PAL was calculated by dividing TDEE by RMR. In accordance with recommendations for the assessment of free-living EE for individuals with an SCI (Nightingale et al., 2017f), participant data from the Actiheart™ was included if at least four valid days (>80% of data for that 24 h period), including at least one weekend day were recorded.

3.9 Energy Intake

In Chapters 5 and 7, participants were provided with a set of digital weighing scales (Salter 1036 BKSSDR, FKA Brands Ltd, UK) and asked to record their habitual diet (other than water) for a continuous 7-day period. Participants were asked to not alter their typical food intake, and to provide as much information as possible about portion sizes when weighing food was not possible (e.g., when eating out). Despite its limitations (i.e., underreporting, participant burden), a weighed food diary provides a more valid estimate of free-living EI and macronutrient composition than recall diaries and interviews (Martin et al., 2002). Participants were given a choice to record their food diaries using a paper diary, or using an mobile application (LIBRO, Nutritics Ltd., Dublin, Ireland). Diet records were analysed using Nutritics software (Nutritics Ltd., Dublin, Ireland) to determine average total energy and macronutrient intakes (grams). In accordance with recommendations for the assessment of habitual EI for individuals with an SCI, participant's data were only included if at least four days, including at least one weekend day were recorded (Nightingale et al., 2017f).

3.10 Mixed Meal Tolerance Test

Participants in Chapters 5 and 6 consumed a mixed-macronutrient liquid drink, consisting of banana, peanut butter (Jif Creamy Peanut Butter, The J.M. Smucker Company, US), coconut oil (Vita Coco Extra Virgin Coconut Oil, All Market Europe Ltd, UK), unflavoured maltodextrin powder (MyProtein, Manchester, UK) and chocolate-flavoured whey protein powder (Optimum Gold Standard Double Rich Chocolate Whey, Optimum Nutrition, Ireland). The drink provided 45.2% calories from carbohydrate, 37.6% calories from fat, and 17.2% calories from protein. This macronutrient composition was chosen to reflect *ad libtum* diet for individuals with SCI (Groah et al., 2009). The energy content of the drink was provided relative to RMR to standardise EI for differences in body mass and composition between individuals. The total energy content of the drink was 65% of RMR, which reflects similar studies utilising MMTT's (Travers et al., 2017) and ensured participant's resting energy requirements were met for the study hours in which no other food was consumed. Participants were asked to consume the drink within 10 min on the first condition and replicate this consumption time for the following conditions.

3.11 Blood Sampling

In Chapter 5, a fasting venous blood sample was obtained from a dorsal hand or antecubital vein (standardised within participants) via venepuncture (BD Vacutainer Safety Lok, BD, USA). All other blood samples taken during the MMTT's and OGTT's were drawn through an indwelling cannula (Venflon, BD Becton Dickinson Ltd, Oxford, UK) inserted anterograde into the antecubital forearm vein. The cannula and connecting octopus were kept patent with 0.9% NaCl (B. Braun, Pennsylvania, USA) infusion, with the first 3 mL of each blood draw discarded. For all samples, blood was split into either a 10 mL serum/clotting activator tube (Serum Z/10 mL, Sarstedt, Germany) or a 5 mL ethylenediaminetetraacetic acid-coated tube (EDTA) tube (K3 EDTA, Sarstedt, Germany) for serum and plasma separation, respectively. Plasma samples were centrifuged immediately, whilst serum samples were left to clot for 15 min at room temperature prior to centrifugation. All serum and plasma samples were centrifuged (Heraeus Biofuge Primo R, Kendro Laboratory Products Plc., UK) at 4000 g for 10 min at 4ºC. The remaining supernatant was aspirated into

1.5 mL Eppendorf's, before being immediately placed on dry ice for the remainder of the day, and then stored at -80ºC for storage until analysis. For the 15 minutes prior to each blood sample, participants were asked to place their hand in a heated hand-box (55ºC). This ensured all samples were 'arterialised' and therefore more closely represented the exposure of the peripheral tissues to systemic hormones and substrates (Edinburgh et al., 2017).

3.12 Blood Analysis

All plasma and serum samples were defrosted at room temperature for ~1 hour before analysis. Insulin was measured using commercially available enzyme-linked immunosorbent assay's (ELISA's) (Mercodia AB, Uppsala, Sweden), according to the manufacturer instructions. Where samples were outside the standard curve, samples were re-analysed using a dilution factor. Absorption was determined using a microplate reader (SPECTROstar Nano, BMG LABTEACH, Ortenberg, Germany). Glucose, TG, NEFA, glycerol, HDL-C, LDL-C, and TC concentrations were determined using automated analysers (Randox RX Daytona and Randox RX Daytona+, Co. Antrim, UK) with commercially available immunoassays (Randox Laboratories, Co. Antrim, UK). Selected samples (for insulin) and quality controls (for all other analytes) were performed in duplicate to calculate the intra-assay and inter-assay precision (C3 Table 1). All analysis was performed in serum (except for plasma glucose in Chapter 7), and all samples for each participant were completed on the same ELISA plate or analyser run.

C3 Table 1 Reported sensitivity, intra and inter-assay precision for all analytes measured.

Analyte	Sensitivity	Intra-assay prevision (CV)	Inter-assay precision (CV)
Insulin	5.4 to 1320 pmol·L^{-1}	11.5%	12.9%
Glucose	0.45 to 34.4 mmol·L^{-1}	-	2.8%
HDL-C	0.517 to 3.37 mmol·L^{-1}	-	3.1%
LDL-C	0.5 to 24 mmol·L^{-1}	-	1.5%
TC	0.645 to 16.0 mmol·L^{-1}	-	1.3%
TG	0.14 to 11.3 mmol·L^{-1}	-	3.0%
NEFA	0.072 to 2.24 mmol·L^{-1}	-	6.7%
Glycerol	14.5 to 2545 µmol·L^{-1}	-	5.9%

In Chapters 5, 6, and 7, meal tolerance responses are characterised as total AUC and iAUC. These were calculated on a freely available Time Series Response Analyser (Narang et al., 2020) using denominations of the trapezoidal rule. Both total AUC and iAUC are presented due to the intra-individual variation in metabolites at baseline.

Chapter 4 - The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

This declaration concerns the article entitled:			
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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate contributed to / considerably contributed to / predominantly executed the… Formulation of ideas: MF and JB formulated the idea, with input from TN and DT. Design of methodology: MF designed the methodology, with input from TN, DT, CM, and JLJB. Experimental work: MF performed the literature search. MF and TN screened for eligible studies. MF and JM scored the articles. Presentation of data in journal format: MF wrote the manuscript. JM, TN, DT, CM, and JLJB all revised the manuscript and approved the final article.		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Matthew Farrow	**Date**	10/02/2022

Relevance of Chapter 4 to Thesis

The primary aim of this thesis is to determine the effect of upper-body high-intensity exercise on CVD risk markers in individuals with chronic SCI. To answer this question, it is firstly important to understand how traditional continuous upper-body aerobic exercise (i.e., at a moderate, or moderate-to-vigorous intensity) effects CVD risk markers in those with SCI. The latest systematic review of the available evidence concluded there was low to moderate confidence (using the Grading of Recommendations Assessment, Development and Evaluation [GRADE] tool) that 3-5 sessions per week of upper-body aerobic exercise at a moderate-to-vigorous intensity for 20-44 minutes can improve CRF, muscle strength, body composition, and cardiovascular risk (van der Scheer et al., 2017). This review grouped outcomes of body mass, BMI, FM and FFM as markers of 'body composition', and outcomes relating to the lipid profile, glucose homeostasis, inflammation, and cardiac/arterial function as markers of 'cardiovascular risk'. It is unclear which outcome measures respond positively to upper-body exercise training, and therefore the systematic review presented in this chapter will help determine the effect of upper-body aerobic exercise on individual markers of cardiometabolic health. It is important to systematically summarise the available evidence in this area to help overcome the lack of high-quality studies, which is a result of the large heterogeneity of the SCI population, use of single-group study designs, and small sample sizes. Therefore, the findings from this review pertaining to upper-body aerobic exercise training will act as a comparator when assessing the effect upper-body HIIT on markers of cardiometabolic health.

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The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

Abstract

Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI).

Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (January 1, 1970, to July 31, 2019)

Study Selection Articles were included if they met the following criteria: (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained ≥ 1-year ago, (3) exercise intervention duration ≥ 2 weeks, and (4) included any CMS risk factor as an outcome.

Data Extraction The methodological quality of articles was assessed using the Downs and Black score.

Data Synthesis Sixty-five studies were included for the final analysis, including nine studies classified as high quality (≥66.7%), 35 studies classified as fair quality (50-66.6%), and 21 studies classified as low quality (<50%). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES) cycling. Improvements in lipid profile (4/5 studies) were observed following upper body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES hybrid, FES rowing, and FES RT.

Conclusions Upper body aerobic exercise training (>75% maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper body aerobic exercise may elicit favourable changes in the

lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.

Key Words exercise therapy; metabolic diseases; rehabilitation; spinal cord injuries

Abbreviations

CMS cardiometabolic syndrome
DBP diastolic blood pressure
ES effect size
FES functional electrical stimulation
HDL-C high-density lipoprotein-cholesterol
HOMA-IR homeostatic model assessment insulin resistance
HRR heart rate reserve
ISI-matsuda insulin sensitivity index
LDL-C low-density lipoprotein-cholesterol
RT resistance training
RCT randomised controlled trial
SBP systolic blood pressure
SCI spinal cord injury
TC total cholesterol
TG triglycerides

Introduction

Persons with a spinal cord injury (SCI) are at an increased risk of cardiovascular disease and diabetes compared to able-bodied individuals [1, 2]. The risk of developing these chronic diseases is raised in individuals who present with a clustering of associated risk factors including obesity, insulin resistance, dyslipidaemia, and hypertension, commonly referred to as cardiometabolic syndrome (CMS) [3]. The International Diabetes Federation defines CMS as central obesity (indicated by waist circumference), plus the presence (or treatment) of two of more of the following: hypertriglyceridemia (≥ 1.7 mmol/L), reduced high-density lipoprotein-cholesterol (HDL-C) (< 1.03 mmol/L for men, < 1.29 mmol/L for women), hypertension (systolic blood pressure [SDP] ≥ 130 mmHg, or diastolic blood pressure [DBP] ≥ 85 mmHg), and raised fasting plasma glucose (≥ 5.6 mmol/L, or diagnosed with type 2 diabetes) [4]. A waist circumference >94 cm and/or a body mass index (calculated as weight in kilograms divided by heigh in meters squared)>22 have been suggested as suitable cut-points to define central obesity in SCI [5, 6]. The prevalence of CMS in chronic SCI appears to be high; with the largest study to date (n=473) reporting a prevalence rate of 57.5% [7].

There is strong evidence that exercise is an effective countermeasure for the prevention of chronic disease and the treatment of CMS risk factors in the able-bodied population [8]. This has allowed national and global health organisations to produce guidelines regarding the total volume and intensity of physical activity (minimum of 150 min/wk of moderate intensity, or 75 minutes/wk of vigorous intensity) required to improve cardiometabolic health [9, 10]. However, as the most recent systematic review of the effect of exercise on health in SCI concluded, the evidence base for persons with SCI “lags far behind” that for the general population [11](p744). This review formed the basis for the latest SCI-exercise guidelines, which recommend adults with a chronic SCI perform a minimum of 90 min/wk of moderate to vigorous-intensity aerobic exercise to improve cardiometabolic health [12]. Additional systematic reviews have also reported beneficial effects of exercise on specific CMS risk factors, including systemic inflammation (C-reactive protein) and obesity (fat mass and waist circumference) in persons with chronic SCI [13, 14].

Since the last systematic search of the literature by van der Scheer et al (search date: January 1, 2016), several randomised controlled trials (RCTs) assessing the effect of exercise training on CMS risk factors in SCI have been published. However, this systematic review did not address clinical thresholds for CMS risk factors at baseline, the magnitude of change following exercise training, and how different exercise modalities may impact specific individual CMS biomarkers. These questions are important for practitioners prescribing exercise to patients presenting with CMS risk factors, and researchers designing future studies in this field. A review which addresses these importance issues and focuses specifically on how different forms of exercise impacts on individual CMS risk factors in chronic SCI is therefore required. The aim of this systematic review is to determine the effect of different exercise modality interventions on CMS risk factors in adults with chronic SCI.

Methods

The study inclusion criteria and planned analysis were specified in advance (PROSPERO: CRD42018105110) and the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines were followed [15]. The databases of PubMed, Web of Science, EMBASE, and Scopus (Elsevier) were searched on August 22, 2018, using a search strategy formulated based on a similar previous systematic review [11]. The search was repeated on July 31, 2019, to identify any additional articles prior to publication. The search strategy was piloted to ensure known articles were included and reviewed by two authors (M.F, T.N.). The full search strategy for PubMed is presented in Supplement 1 (available online only at http://www.archives-pmr.org/) as an exemplar. Briefly, the search was performed by combining key words associated with SCI (eg, “paraplegia”, “spinal cord lesion”), exercise, (eg, “physical activity”, “resistance training”, “functional electrical stimulation”), and CMS risk factors (eg, “glucose”, “BMI”, “blood pressure”). The reference list of included items and previous systematic reviews were checked, and further articles identified. The final step involved hand-searching the journals which had returned the highest proportion of articles in the initial search, to identify any additional studies (eg, *Journal of Spinal Cord Medicine* [1982-2018] and *Archives of Physical Medicine and Rehabilitation* [1985-2018]).

Titles and abstracts of retrieved articles were independently screened for relevance by two reviewers (M.F, T.N.). The same two reviewers independently assessed the full text of relevant articles for eligibility. In the event of any disagreements in article selection, a third reviewer (J.B.) made the final decision. Articles were included if they met the criteria according to the PICOS structure: (1) participants: ≥50% of participants were aged 18 years or older and had a chronic SCI (≥1y post injury), (2) intervention: included an exercise training programme (any, or combination of: voluntary upper body exercise, lower-body functional electrical stimulation (FES), and assisted ambulation training) lasting ≥2 weeks, (3) comparison: studies comparing exercise intervention to a control group or preintervention data, (4) outcomes: study included ≥1 CMS risk factor as an outcome variable (Table 1) [4], and (5) study design: study used and reported quantitative statistical analysis to determine the impact of the exercise intervention on the relevant CMS risk outcome(s) (ie, case reports and case-series were excluded), and was published in an English-language peer-reviewed journal (ie, abstracts and conference proceedings were excluded) between January 1, 1970, and the final search date. Studies involving solely neuromuscular electrical stimulation with no functional movement and passive cycling were excluded on the basis that the skeletal muscle contractions produced during these activities do not directly produce a functional movement, and therefore cannot be classed as exercise, per se. Studies assessing the impact of exercise on solely blood pressure amongst tetraplegics were excluded on the basis that the aim of the exercise intervention was to increase resting blood pressure, and therefore was not reflective of a CMS risk factor (ie, hypertension). Two articles did not identify participants' time since injury [16, 17]. The corresponding authors were contacted by email and asked to provide clarification and given 2 weeks to respond. Both articles were excluded as the corresponding authors were unable to provide this information.

C4 Table 1 CMS outcome measures

CMS Category	CMS Outcome Measure
Central Adiposity/Obesity	Body mass index Body mass Waist circumference Hip circumference Waist-to-hip ratio Body fat percentage (assessed via DEXA/CT) Fat mass (assessed via DEXA/CT) Android fat mass Visceral adipose tissue Liver fat content Leptin
Glycaemic control	Fasting insulin and glucose Glucose to insulin ratio Fasting proinsulin Glycosylated haemoglobin Fasting/postprandial insulin sensitivity measures C-peptide
Dyslipidaemia	TGs LDL-C HDL-C TC TC: HDL-C Non-esterified fatty acids Free-fatty acids Apolipoprotein B
Inflammation	C-reactive protein Interleukin-6 Tumour necrosis factor α Adiponectin
Vascular dysregulation	SBP DBP Pulse wave velocity Flow-mediated dilation Microalbuminuria
Thrombotic State	Fibrinogen Plasminogen activator inhibitor 1

Abbreviations: CT, *computed tomography*, DEXA, *dual-energy x-ray absorptiometry*

Two reviewers (M.F., J.M.) independently evaluated the quality of included studies using a modified Downs and Black scale [18]. In the modified version, the scoring for question 27 (relating to statistical power) is simplified to “Yes” (1) or “No” (0). In the event of any discrepancies in scoring, discussion between the reviewers was used to reach a consensus. The total Downs & Black score for each article was expressed as a percentage of the maximum score possible (28) to allow

categorisation of study quality [19]. Articles were classified as high (≥66.7%), fair (between 50.0% and 66.6%), or low (<50.0%) quality [19].

A meta-analysis was not possible due to i) the low number of studies examining the same outcomes following similar exercise modalities, and ii) the wide range of exercise intensity descriptors used (e.g., $HR_{PEAK,}$ $\dot{V}O_{2PEAK}$, heart rate reserve, power output). Therefore, a coding system, as previously described by Batacan *et al* [19], was used to summarise the effect of different exercise training modalities on each CMS risk factor (Figure 2). If 0-33% of studies reported a statistically significant change in a specific CMS risk factor following exercise training, the result was categorised as “no effect”. If 34-59% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as “inconsistent”. If 60-100% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as “positive”. If 4 or more studies reported the same effect, the result was highlighted in bold to indicate a consistent finding. The findings from 1 particular study [20] were counted as non-significant for summary coding, due to the significance being set at *P*<.10, with actual *P* values not reported. Data extraction was performed by M.F., and later checked independently by T.N., J.M., and J.B.

To aid interpretation of results, group average values at baseline for body mass index (≥22) [6], waist circumference (>94 cm) [5], triglycerides (TGs) (≥1.7 mmol/L), total cholesterol (TC) (≥5 mmol/L), low-density lipoprotein (LDL-C) (>3 mmol/L), HDL-C (<1.03 mmol/L), fasting glucose (≥5.6 mmol/L), SBP (≥130 mmHg), and DBP (≥85 mmHg) [4] were highlighted to indicate that they can be classified as clinically high, according to the International Diabetes Federation and SCI-specific guidelines (Tables 2-8).

The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (eg, oral glucose tolerance test) and categorized using indices such as the Matsuda Insulin Sensitivity Index.

Results

The initial database search yielded a total of 2450 unique records, of which 2245 were excluded following title and abstract screening. An additional 10 articles were retrieved from hand-searching of relevant journals (n=1), relevant systematic reviews (n=2), the associated reference list of an included paper (n=4), and the updated search (n=3). Therefore, the full text of 215 studies were subsequently assessed, two articles [85,86] contained data presented in another article, and these were removed from all analysis, leaving 65 articles for final review. The study selection process is detailed in Figure 2.

There was substantial agreement between reviewers for title and abstract screening (*k*=0.635, 95% CI, 0.581-0.689), and almost perfect agreement for the full-text screening (*k*=0.880, 95% CI, 0.811-0.949) [87]. We identified studies as pre-post designs (n=47), RCTs (n=15), non-RCTs (n=2), and a retrospective cohort study (n=1). Numerous studies utilised arm-cranking (n=9), wheelchair ergometry (n=3), wheelchair treadmill propulsion (n=2), or hand-cycling (n=2). These 16 studies were grouped together for analysis as voluntary upper body aerobic exercise (see Table 2). Seven studies utilised upper body resistance training (RT) (with or without upper body aerobic exercise) (see Table 3). The most common exercise modality was FES cycling (n=17) (see Table 4). Six studies utilised FES RT exercise (in the form of non-isometric knee extensions), and 3 studies involved a combination of FES cycling and FES-RT (see Table 5). Studies which involved hybrid FES cycling (n=4) or FES rowing (n=4) were grouped together as they both involve lower body FES combined with voluntary upper body aerobic exercise (see Table 6). Several studies utilised solely body-weigh-supported treadmill training (n=6), FES walking, exoskeletal body-weight-supported treadmill training (n=1), or robotic body weight-supported-treadmill training (n=1). These 10 studies were grouped together for analysis (see Table 7). Studies that involved a combination of upper body aerobic, upper body RT and neuromuscular stimulation (n=1), or a combination of lower body FES RT, and body-weight-supported treadmill training(n=1), were not grouped for qualitative analysis (see Table 8)

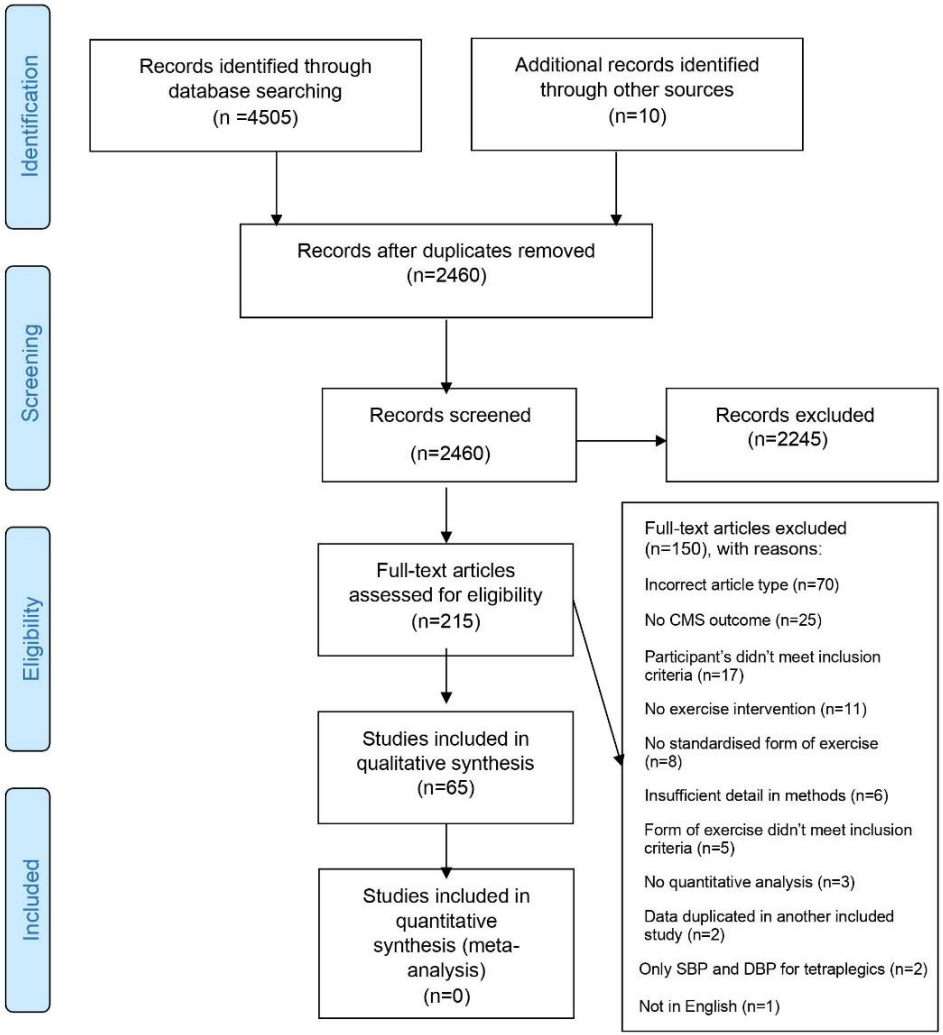
		Aerobic	Aerobic + RT	Ambulation	Hybrid and Rowing	FES-cycling	FES-RT/Combined
Central Adiposity/Obesity	BM	**1/8(13%)**	1/2 (50%)	1/3 (33%)	**0/5 (0%)**	1/4 (25%)	**0/4 (0%)**
	BMI	1/4 (25%)	1/4 (25%)	1/1 (100%)	0/1 (0%)	0/2 (0%)	1/3 (33%)*
	Waist	**4/6 (67%)**	2/3 (67%)	-	1/2 (50%)	-	-
	WHR	-	1/1 (100%)	-	-	-	-
	BF%	0/2 (0%)	-	1/2 (50%)	0/2 (0%)	1/2 (50%)	0/2 (0%)
	FM	0/3 (0%)	1/2 (50%)	0/2 (0%)	-	1/2 (50%)	0/2 (0%)
	Android FM	0/1 (0%)	-	-	0/1 (0%)	-	-
	Abdominal AT	-	-	-	--	0/1 (0%)	-
	VAT	0/1 (0%)	1/1 (100%)	-	--	-	0/2 (0%)
	Leptin	1/1 (100%)	0/1 (0%)	-	1/1 (100%)	-	-
Inflammation	CRP	0/1 (0%)	--	1/1 (100%)	0/1 (0%)	1/2 (50%)	0/1 (0%)
	IL-6	1/2 (50%)	0/1 (0%)	-	0/1 (0%)	1/2 (50%)	0/1 (0%)
	TNF-α	1/1 (100%)	0/1 (0%)	-	-	1/2 (50%)	0/1 (0%)
	Adiponectin	0/1 (0%)	0/1 (0%)	-	-	-	1/1 (100%)
Dyslipidaemia	TG	**1/7 (14%)**	2/4 (50%)	0/2 (0%)	1/1 (100%)	1/3 (33%)	1/3 (33%)
	FFA	-	-	-	-	0/1 (0%)	0/1 (0%)
	NEFA	0/1 (0%)	-	-	-	-	-
	TC	**1/7 (14%)**	2/5 (40%)	1/2 (50%)	0/1 (0%)	0/2 (0%)	1/3 (33%)
	HDL-C	**0/7 (0%)**	**1/5 (20%)**	0/2 (0%)	0/2 (0%)	1/3 (33%)	1/3 (33%)
	LDL-C	**0/6 (0%)**	2/5 (40%)	1/2 (50%)	0/1 (0%)	1/3 (33%)	0/3 (0%)
	TC: HDL-C	0/2 (0%)	1/2 (50%)	1/1 (100%)	-	1/1 (100%)	1/2 (50%)
Glycaemic Control	Fasting Glucose	**0/8 (0%)**	0/3 (0%)	0/1 (0%)	1/2 (50%)	0/1 (0%)	0/2 (0%)
	Fasting Insulin	**4/5 (80%)**	1/3 (33%)	-	0/2 (0%)	0/3 (0%)	0/1 (0%)
	HbA1c	0/1 (0%)	0/1 (0%)	-	-	-	-
	HOMA-IR	**4/4 (100%)**	2/2 (100%)	-	0/2 (0%)	-	0/2 (0%)
	HOMA-%S	1/1 (100%)	-	-	-	-	0/1 (0%)
	HOMA-%β	0/2 (0%)	-	-	-	-	0/1 (0%)
	ISI-Matsuda	0/2 (0%)	-	-	-	-	-
	Glucose OGTT	0/2 (0%)	-	1/1 (100%)	0/1 (0%)	2/3 (67%)	0/3 (0%)
	Insulin OGTT	0/2 (0%)	-	1/1 (100%)	-	1/3 (33%)	0/2 (0%)
	IVGTT Si	0/1 (0%)	-	-	-	0/1 (0%)	0/1 (0%)
	IVGTT Glucose	0/1 (0%)				0/1 (0%)	0/1 (0%)

	Cederholm Index	-	-	-	-	1/1 (100%)	-
	HEC Si	-	-	-	-	1/1 (100%)	-
	HEC Glucose	-	-	-	-	1/1 (100%)	-
Thrombotic State	PAI-1	1/2 (50%)	0/1 (0%)	-	-	-	-
	Fibrinogen	0/1 (0%)	-	-	-	0/1 (0%)	-
Vascular Dysregulation	SBP	**1/9 (11%)**	0/3 (0%)	0/3 (0%)	0/2 (0%)	1/4 (25%)	0/1 (0%)
	DBP	**0/9 (0%)**	0/3 (0%)	0/3 (0%)	1/2 (50%)	1/3 (33%)	0/1 (0%)
	FMD	-	0/1 (0%)	-	1/2 (50%)	-	1/1 (100%)
	PWV	-	0/1 (0%)	-	-	0/1 (0%)	-
	Albumin	-	-	-	-	-	0/1 (0%)

Black fill, white text: 0-33% of studies reported significant differences; grey fill, black text: 34-59% of studies reported significance differences; grey fill, white text: 60-100% of studies demonstrated positive significance differences, bold writing: ≥4 studies demonstrate the same effect. *one study reported a significant increase in BMI. NA; not applicable

HOMA-IR; *homeostatic model assessment insulin resistance*, HOMA-%S; *insulin sensitivity*; HOMA-%β; *beta cell function*, ISI-Matsuda*; insulin sensitivity index-Matsuda*. OGTT; *oral glucose tolerance test*, IVGTT Si; intravenous glucose tolerance test insulin sensitivity, IVGTT Glucose; intravenous glucose tolerance test glucose effectiveness, HEC Si; *hypereuglycaemic clamp insulin sensitivity*.

C4 Figure 1 Summary coding of studies examining the effect of exercise on CMS outcome measures



C4 Figure 2 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram

Intervention durations ranged from 4-52 weeks, with the most common length of 12 week (n=14). Training frequency ranged from 1-7 sessions per week, with 3 times per week the most common frequency of exercise performed (n=35). No serious adverse events were reported in any of the included studies.

Sample sizes ranged from 4-48. Only seven studies reported a priori sample size calculations, and 4 of these met their target sample size (Table 9). There was a total of 872 participants (658 men, 110 women, 104 not reported) (see Table 9). There were 9 studies classified as high quality, 35 studies classified as fair quality, and 21 studies classified as low quality. The most commonly assessed outcome measures for obesity, glycaemic control, dyslipidaemia, inflammation, vascular dysregulation, and thrombotic state were body mass (n=28), interleukin-6 (n=7), HDL-C (n=23), fasting glucose (n=18), plasminogen activator inhibitaror-1 (n=3), and SBP (n=22), respectively. No studies reported outcome measures of hip circumference, liver fat content, apolipoprotein B, or proinsulin.

Summary coding revealed consistent findings that upper-body aerobic training was effective at reducing waist circumference, fasting insulin, and HOMA-IR (Figure 2). There were consistent findings that upper-body aerobic training had no effect on body mass, TG, TC, HDL-C, LDL-C, fasting glucose, SBP and DBP (Figure 2). Additionally, there were consistent findings that upper-body aerobic exercise combined with RT had no effect on HDL-C (Figure 2). There were also consistent findings that hybrid or rowing exercise, and FES-RT had no effect on body mass (Figure 2). Summary coding revelated no other consistent findings, although a positive effect of FES-cycling was observed when outcomes relating to peripheral insulin sensitivity were grouped together (Figure 2).

C4 Table 2 Detailed findings from voluntary upper body aerobic exercise studies.

Author **Design** **D&B Quality**	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** Intervention (Control), Mean ± SD	**Change** *Intervention* (Control)	***P* value***	**ES**
Bakkum et al [21] Pre-post† 20 High	10	Hand-cycle 16 wk 2 sessions/wk 65-75% HRR 18-32 mins	**Waist (cm)**	**89.7 ± 3.5**	**-2.5**	**0.03**	**0.75**
			Android fat mass (kg)	2.6 ± 0.4	0.0	0.85	0.00
			Android fat (%)	38.6 ± 3.7	-1.3	0.26	0.40
			TG (mmol/L)	1.2 ± 0.2	-0.1	0.67	0.63
			HDL-C (mmol/L)	1.4 ± 0.2	0.0	0.94	0.00
			Fasting glucose (mmol/L)	5.3 ± 0.2	-0.2	0.30	1.00
			Fasting insulin (pmol/L)	**54.6 ± 8.5**	**-14.3**	**0.01**	**1.78**
			HOMA-IR	**1.9 ± 0.3**	**-0.5**	**0.02**	**2.35**
			SBP (mmHg)	119 ± 4	+4	0.30	1.13
			DBP (mmHg)	72 ± 3	-3	0.34	0.57
			CRP (mg/L)	2.86 ± 1.36	-0.39	0.23	0.28
			IL-6 (pg/mL)	2.40 ± 0.57	-0.64	0.10	0.56
Nightingale et al [22] RCT 19 High	21	ACE 6 wk 4 sessions/wk 60-65% $\dot{V}O_{2PEAK}$ 45 mins	Body mass (kg)	76.8 ± 13.3 (76.8 ± 11.3)	-1.1 (-0.7)	NS	-
			Fat mass (kg)	27.6 ± 10.0 (25.5 ± 6.6)	-0.6 (0.0)	NS	-
			VAT (cm^2)	181 ± 85 (186 ± 47)	-22 (-3)	NS	-
			TG (mmol/L)	1.2 ± 0.5 (1.3 ± 0.5)	-0.1 (+0.5)	NS	1.02
			TC (mmol/L)	4.9 ± 1.0 (5.1 ± 0.9)	-0.1 (+0.1)	NS	0.17
			HDL-C (mmol/L)	1.1 ± 0.3 (1.0 ± 0.2)	+0.1 (0.0)	NS	0.07
			LDL-C (mmol/L)	3.2 ± 0.9 (3.5 ± 0.8)	0.0 (-0.2)	NS	0.05
			NEFA (mmol/L)	0.6 ± 0.3 (0.7 ± 0.6)	+0.3 (-0.1)	NS	0.40
			Fasting glucose (mmol/L)	5.3 ± 0.5 (5.7 ± 1.3)	0.0 (0.0)	NS	-
			Fasting insulin (pmol/L)	**54.8 ± 30.1 (41.3 ± 18.1)**	**-12.7 (+3.1)**	**0.03**	**0.54**
			HOMA2-IR	**1.03 ± 0.57 (0.80 ± 0.35)**	**-0.24 (+0.06)**	**0.04**	**0.49**
			HOMA2-%ß (%)	87 ± 31 (66 ± 23)	-14 (+1)	NS	0.58
			Matsuda ISI	4.8 ± 2.2 (6.4 ± 3.1)	+0.3 (-0.7)	NS	-

			Glucose OGTT (%)	-	+8 (-9)	NS	-
			Insulin OGTT (%)	-	-8 (+6)	NS	-
			SBP (mmHg)	128 ± 23 (128 ± 15)	-3 (-2)	NS	-
			DBP (mmHg)	77 ± 15 (81 ± 13)	-1 (-4)	NS	-
Rosety-Rodriquez [23] RCT 19 High	17	ACE 12 wk 3 sessions/wk 50-65% HRR 20-30 mins	BMI (kg/m^2)	27.6 ± 4.1 (27.8 ± 4.4)	-0.2 (NR)	0.72	-
			Waist (cm)	**98.1 ± 6.6 (98.4 ± 6.7)**	**-3.7 (NR)**	**0.05**	**-**
			Leptin (ng/mL)	**9.6 ± 2.7 (9.8 ± 2.8)**	**-2.1 (+0.1)**	**<0.05**	**0.71**
			PAI-1 (ng/mL)	29.8 ± 6.2 (30.2 ± 6.1)	-0.7 (-0.1)	NS	0.09
			IL-6 (pg/mL)	**6.7 ± 2.2 (6.9 ± 2.3)**	**-2.6 (+0.1)**	**<0.05**	**1.08**
			TNF-α (pg/mL)	**23.3 ± 5.6 (23.6 ± 5.5)**	**-2.7 (-0.1)**	**<0.05**	**0.47**
			Adiponectin (ng/mL)	18.8 ± 4.1 (18.5 ± 4.2)	+0.6 (+0.1)	NS	0.11
Bresnahan et al [24] Pre-post 17 Fair	10	ACE 10 wk 3 sessions/wk 70% $\dot{V}O_{2PEAK}$ 30 mins	BF (%)	34.9 ± 34.9	0.0	0.35	0.01
			Fat mass (kg)	25.1 ± 11.9	-0.3	0.75	0.02
			TC (mmol/L)	4.50 ± 0.58	+0.04	0.75	0.08
			HDL-C (mmol/L)	0.94 ± 0.16	-0.06	0.07	0.22
			LDL-C (mmol/L)	2.71 ± 0.39	+0.31	0.12	0.72
			Fasting glucose (mmol/L)	5.54 ± 0.82	-0.05	0.92	0.06
			Fasting insulin (pmol/L)	**84.9 ± 38.8**	**-31.8**	**0.03**	**1.07**
			Glucose: insulin	**9.77 ± 4.49**	**+3.92**	**0.03**	**1.00**
			Glucose OGTT (AUC)	-	+6%	0.25	0.29
			Insulin OGTT (AUC)	-	+5%	0.92	0.13
			HOMA-IR	**1.6 ± 0.7**	**-0.6**	**0.05**	**1.11**
			HOMA-%ß (%)	111.4 ± 48.7	-29.0	0.12	0.78
			HOMA%S (%)	**73.3 ± 31.6**	**+32.3**	**0.05**	**1.10**
			Matsuda ISI	3.4 ± 1.6	+0.2	0.35	0.16
Han et al [25] Pre-post 17 Fair	5	ACE 12 wk 3 sessions/wk Anaerobic Threshold 30 mins	Body mass (kg)	65.6 ± 6.6	+2.3	0.18	0.33
			BMI (kg/m^2)	23.5 ± 3.4	+0.8	0.18	0.22
			SBP (mmHg)	110 ± 25	+1	0.13	0.04
			DBP (mmHg)	66 ± 12	+2	0.80	0.11

McLean et al [26] Pre-post 17 Fair	14	ACE 10 wk 3 sessions/wk 25-35 mins 60% W_{PEAK}	Body mass (kg)	69.2	-2	NS	-
Gorgey et al [27] Pre-post† 16 Fair	4	ACE 16 wk 5 sessions/wk 75% HR_{MAX} 40 mins	Body mass (kg) BMI (kg/m^2) BF (%) Fat mass (kg) Fasting glucose (mmol/L) Fasting insulin (pmol/L) IVGTT insulin sensitivity IVGTT glucose effectiveness SBP (mmHg) DBP (mmHg)	80 ± 12 28 ± 4 40 ± 3.7 31 ± 7 5.27 ± 0.50 76.4 ± 62.5 - - 119 ± 13 75 ± 5	0 0 -2 -2 -0.06 -23.6 +62.5% +35% -1 +2	NS NS NS NS 0.9 NS NS NS NS NS	0.00 0.00 0.52 0.31 0.08 0.41 0.64 0.70 0.08 0.36
Akkurt et al [28] RCT 16 Fair	33	ACE 12 wk 3 sessions/wk 50-70% $\dot{V}O_{2PEAK}$ 30 mins	Waist (cm) TGs (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting glucose (mmol/L) SBP (mmHg) DBP (mmHg)	86.5 (94.5) 1.50 (1.38) 4.57 (4.60) 0.96 (1.05) 2.87 (2.91) 4.44 (4.47) 100 (100) 60 (60)	+4.75 (+1.5) +0.06 (+0.29) +0.26 (+0.05) 0.0 (+0.14) 0.0 (0.09) -0.19 (+0.14) 0 (0) 0 (0)	NS NS NS NS NS NS NS NS	- - - - - - - -
Kim et al [29] RCT 15 Fair	16	Hand-cycle 6 wk 3 sessions/wk 70-80% HR_{PEAK} 44 mins	**BMI (kg/m^2)** **Waist (cm)** TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting glucose (mmol/L)	**22.0 ± 3.7 (20.8 ± 2.7)** **88.3 ± 13.1 (81.7 ± 9.0)** 1.16 ± 0.47 (1.09 ± 0.56) 4.56 ± 0.92 (4.73 ± 0.55) 1.10 ± 0.30 (1.17 ± 0.18) 2.93 ± 0.67 (3.07 ± 0.62) 4.36 ± 0.46 (4.92 ± 0.60)	**-0.2 (+0.3)** **-2.6 (+0.8)** -0.01 (-0.12) +0.03 (-0.09) +0.09 (-0.01) -0.06 (-0.03) -0.09 (+0.04)	**<0.01** **<0.01** 0.95 0.81 0.29 0.99 0.32	**1.58** **2.67** 0.25 0.25 0.82 0.09 0.39

			Fasting insulin (pmol/L)	**37.5 ± 16.7 (34.0 ± 20.1)**	**-13.9 (+11.8)**	**<0.01**	**1.57**
			HOMA-IR	**1.0 ± 0.6 (1.1 ± 0.8)**	**-0.4 (0.4)**	**<0.01**	**1.40**
Horiuchi et al [30] Pre-post 14 Fair	9	ACE 10 wk 4 sessions/wk 50-70% HRR 60 mins	**Body mass (kg)**	**61.0 ± 7.0**	**-1.9**	**<0.05**	**0.26**
			Waist (cm)	**85.5 ± 6.2**	**-1.9**	**<0.05**	**0.26**
			TG (mmol/L)	**1.74 ± 0.78**	**-0.43**	**<0.05**	**0.31**
			TC (mmol/L)	5.25 ± 0.88	-0.18	NS	0.14
			HDL-C (mmol/L)	1.45 ± 0.18	+0.05	NS	0.20
			LDL-C (mmol/L)	2.95 ± 0.62	-0.10	NS	0.15
			Fasting glucose (mmol/L)	5.66 ± 1.39	-0.17	NS	0.10
			HbA1c (%)	4.9 ± 0.6	-0.10	NS	0.14
			PAI-1 (g/L)	**5.2 ± 1.1**	**-1.4**	**<0.05**	**1.22**
			Fibrinogen (g/L)	2.97 ± 5.7	-0.7	NS	0.14
			SBP (mmHg)	**136 ± 5**	**-3**	**<0.05**	**0.66**
			DBP (mmHg)	75 ± 8	-2	NS	0.30
Midha et al [31] Pre-post 14 Fair	12	WCE 10 wk 2-3 sessions/wk Intensity NR 20-30 mins	Body mass (kg)	74 ± 10	+2.0	NS	0.20
			TG (mmol/L)	1.32 ± 0.59	-0.08	NS	0.12
			TC (mmol/L)	**4.78 ± 1.09**	**-0.39**	**0.04**	**0.40**
			HDL-C (mmol/L)	1.24 ± 0.26	0.0	NS	0.00
			TC: HDL-C	4 ± 1	-0.2	NS	0.20
			Fasting glucose (mmol/L)	4.77 ± 1.94	-1.0	NS	0.03
			SBP (mmHg)	124 ± 10	0	NS	0.00
			DBP (mmHg)	85 ± 7	-3	NS	0.35
Murherjee et al [32] Pre-post 14 Fair	12	WCT 12 wk 14 sessions/wk 60-70% HR_{PEAK}	Body mass (kg)	41.8 ± 5.8	0.0	NS	0.00
Gass et al [33]	9	WCT 7 wk	Body mass (kg)	82.1 ± 14.6	+1.2	NS	0.09
			Waist (cm)	109.6 ± 12.2	+4.1	NS	0.28

Pre-post 13 Low		5 sessions/wk Intensity NR Duration NR					
Yim et al [34] Pre-post 12 Low	11	WCE 5 wk 2 sessions/wk <80% HR_{PEAK} 30 mins	SBP (mmHg) DBP (mmHg)	126 ± 12 82 ± 6	-2 -2	NS NS	0.16 0.29
Davis et a [35] Non-RCT 11 Low	14	ACE 16 wk 3 sessions/wk 50 or 70% $\dot{V}O_{2PEAK}$ 20 or 40 mins	SBP (mmHg) DBP (mmHg)	122 ± 5 (114 ± 6) 78 ± 5 (81 ± 4)	+4 (+18) -2 (+6)	NS NS	- -
Hooker et al [20] Pre-post 11 Low	11	WCE 8 wk 3 sessions/wk 70-80% HRR (or 50-60% HRR) 20 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C	1.08 ± 0.32 (0.88 ± 0.26) 5.04 ± 0.91 (4.81 ± 0.70) 1.01 ± 0.28 (1.27 ± 0.28) 3.54 ± 0.67 (3.15 ± 0.44) 5 ± 0.9 (4 ± 0.7)	-0.20 (-0.04) -0.41 (+0.16) +0.21 (-0.18) -0.54 (0.16) -1 (+1)	<0.1 (NS) NS (NS) <0.1 (NS) <0.1 (NS) <0.1 (NS)	0.76 (0.15) 0.63 (0.28) 0.83 (0.46) 1.12 (0.37) 1.37 (0.67)

Abbreviations: ACE, *arm-crank ergometry*; AUC, *area under the curve*; BMI, *body mass index (calculated as weight in kilograms divided by height in meters squared*); CRP, *C-reactive protein*; HbA1c*, glycosylated hemoglobin*; HRmax, *age-predicted maximum heart rate*; HRpeak, *peak heart rate*; IL-6*, interleukin 6*; IVGTT, *intravenous glucose tolerance test*; NEFA*, nonesterified fatty acids*; NR, *not reported*; NS, *not significant*; OGTT, *oral glucose tolerance test*; PAI-1, *plasminogen activator inhibitor-1*;TNF-α, *tumour necrosis factor α*; VAT, *visceral adipose tissue*; VO_2peak, *peak oxygen uptake*; WCE, *wheelchair ergometer*; WCT, *wheelchair treadmill ergometry*; Wpeak, *peak power output*.

*Group x time interaction for RCT and non-RCT, or pre-post change for pre-post study designs.

† True study design is RCT, presented as pre-post because 2 different exercise modalities were tested.

C4 Table 3 Detailed findings from upper body RT (with or without aerobic training) studies included in this review.

Author **Design** **D&B** **Quality**	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** Intervention (Control), Mean ± SD	**Change** Intervention (Control)	***P* value***	**ES**
Giangregorio et al [36] Pre-post† 23 High	17	16 wk 3 sessions/wk RT: 20-25 mins, 2-3 sets at 12-15 repetition max resistance Aerobic: 20-25 mins, 3-5 RPE	Fat mass (kg)	23.2 ± 10.8	-0.2	NS	0.02
de Zepetnek et al [37] RCT 19 High	23	16 wk 2 sessions/wk RT: 3 x 10, 50-70% 1RM Aerobic: >20 mins, 3-6 RPE	**Body mass (kg)**	**83.4 ± 18.9 (78.6 ± 15.7)**	↓	**0.03**	**1.07**
			BMI (kg/m^2)	**27.3 ± 5.2 (25.7 ± 4.9)**	**-0.3 (+0.9)**	**0.02**	**1.14**
			Waist (cm)	**96.2 ± 14.9 (89.6 ± 11.7)**	**-1.0 (+3.5)**	**0.03**	**1.02**
			Fat mass (kg)	**- (-)**	↓	**0.04**	**1.00**
			VAT (kg)	**- (-)**	↓	**0.04**	**1.02**
			Leptin (ng/mL)	10.12 ± 13.25 (10.2 ± 12.8)	+1.0 (+4.1)	NS	-
			TG (mmol/L)	1.3 ± 0.6 (1.1 ± 0.7)	+0.1 (-0.1)	NS	-
			TC (mmol/L)	4.5 ± 0.9 (4.1 ± 0.9)	-0.2 (0.0)	NS	-
			HDL-C (mmol/L)	1.01 ± 0.2 (1.13 ± 0.2)	0.0 (+0.04)	NS	-
			LDL-C (mmol/L)	2.9 ± 0.9 (2.5 ± 0.7)	-0.2 (-0.1)	NS	-
			TC: HDL-C	4.6 ± 0.9 (3.8 ± 1.1)	-0.2 (-0.2)	NS	-
			Fasting insulin (pmol/L)	39.2 ± 29.5 (68.2 ± 77.9)	+9.5 (+10.3)	NS	-
			HbA1c (mmol/L)	1.01 ± 0.2 (1.13 ± 0.3)	+0.9 (-0.2)	NS	-
			PAI-1 (ng/mL)	30.4 ± 17.7 (31.1 ± 22.7)	+11.6	NS	-
			SBP (mmHg)	116 ± 18 (118 ± 18)	(+15.5)	NS	-
			DBP (mmHg)	68 ± 9 (74 ± 13)	0 (-2)	NS	-
			Brachial FMD	-	-1 (-2)	0.31	-
			Femoral FMD	-	-	0.66	-
			PWV – Central	-	-	0.53	-
			IL-6 (pg/mL)	2.5 ± 2.2 (3.7 ± 2.1)	-	NS	-

			TNF-α (pg/mL)	4.7 ± 1.8 (4.1 ± 2.2)	-1.0 (+1.8)	NS	-
			Adiponectin (µg/mL)	76.7 ± 64.0 (82.02 ± 38.28)	-0.3 (-0.1) +13.4 (+35.67)	NS	-
Mogharnasi [38] RCT 17 Fair	20	8 wk 3 sessions/wk RT: 60-80% 1RM, 5 exercises.	BMI (kg/m^2)	25.3 ± 1.4 (24.9 ± 1.0)	-0.6 (+0.2)	NS	-
			Waist: Hip	**0.83 ± 0.02 (0.83 ± 0.14)**	**-0.02 (+0.01)**	**0.03**	**-**
			TG (mmol/L)	**1.77 ± 0.07 (1.80 ± 0.11)**	**-0.27 (+0.02)**	**0.001**	**-**
			TC (mmol/L)	**4.66 ± 0.18 (4.78 ± 0.10)**	**-0.38 (+0.04)**	**0.001**	**-**
			HDL-C (mmol/L)	1.12 ± 0.06 (1.15 ± 0.11)	+0.12	NS	-
			LDL-C (mmol/L)	**2.81 ± 0.10 (2.82 ± 0.12)**	**(+0.01)**	**0.001**	**-**
			Fasting glucose (mmol/L)	5.46 ± 1.34 (5.45 ± 1.42)	-0.12 (+0.05)	NS	-
			Fasting insulin (pmol/L)	110.6 ± 19.5 (116.7 ± 24.9)	-0.38 (-0.01)	NS	-
			HOMA-IR	**6.92 ± 1.27 (7.27 ± 2.09)**	**-2.4 (-3.5)** -0.62 (-0.25)	**0.03**	**-**
Kim et al [39] RCT 17 Fair	17	6 wk 3 sessions/wk RT: 1-3 x 10-20 Aerobic: 10-20 mins, 4-8 RPE or 65-85% HR_{MAX}	BMI (kg/m^2)	21.8 ± 2.9 (20.8 ± 1.9)	-0.4 (-0.1)	0.08	1.17
			Waist (cm)	**84.1 ± 11.9 (79.4 ± 6.6)**	**-2.6 (-0.2)**	**0.02**	**1.94**
			TC (mmol/L)	4.20 ± 0.88 (1.96 ± 0.09)	-0.04 (+0.05)	0.46	0.40
			HDL-C (mmol/L)	**1.26 ± 0.55 (1.32 ± 0.27)**	**+0.14 (-0.04)**	**0.05**	**1.24**
			LDL-C (mmol/L)	2.42 ± 0.81 (3.25 ± 0.76)	-0.12 (+0.36)	0.12	0.85
			Fasting glucose (mmol/L)	4.50 ± 0.30 (4.20 ± 0.20)	-0.09 (+0.10)	0.23	0.62
			Fasting insulin (pmol/L)	**52.1 ± 32.6 (20.1 ± 7.6)**	**-20.1 (+2.1)**	**0.05**	**1.24**
			HOMA-IR	**1.5 ± 1.0 (0.5 ± 0.2)**	**-0.6 (+0.06)**	**0.05**	**1.33**
Cugusi et al [40] Pre-post 15 Fair	16	12 wk 3 sessions/wk RT: 2 x 8 to 3 x 12. Aerobic: 60-75% HRR 20-60 mins	Body mass (kg)	74.9 ± 7.2	-2.9	NS	1.19
			BMI (kg/m^2)	26.0 ± 2.6	-1.0	NS	0.33
			Waist (cm)	104.1 ± 7.9	+1.3	NS	0.17
			TG (mmol/L)	**1.41 ± 0.93**	**-0.30**	**<0.05**	**0.35**
			TC (mmol/L)	**5.66 ± 1.32**	**-0.68**	**<0.05**	**0.54**
			HDL-C (mmol/L)	1.26 ± 0.40	+0.02	NS	0.05
			LDL-C (mmol/L)	4.20 ± 1.15	-0.19	NS	0.17
			Fasting glucose (mmol/L)	5.81 ± 0.05	-0.74	NS	1.64

		SBP (mmHg)	118 ± 20	-5	NS	0.26
		DBP (mmHg)	80 ± 11	-3	NS	0.27
Hicks et al 34 [41] RCT 15 Fair	36 wk 2 sessions/wk RT: 70-80% 1RM, Aerobic: 15-30 mins, 70% HR_{MAX} or 3-4 RPE.	SBP (mmHg)[$]	125 ± 23 (133 ± 20)	+2 (-2)	NS	-
		DBP (mmHg)[$]	72 ± 16 (85 ± 14)	+3 (-4)	NS	-
Nash et al 5 [42] Pre-post 12 Low	12 wk 3 sessions/wk Circuit Training: 50-60% 1RM 40-45 mins	TGs (mmol/L)	2.29 ± 1.35	-0.14	0.63	0.12
		TC (mmol/L)	4.73 ± 0.67	-0.42	0.20	0.56
		HDL-C (mmol/L)	1.05 ± 0.14	+0.11	0.10	0.49
		LDL-C (mmol/L)	**3.06 ± 0.57**	**-0.79**	**0.05**	**1.17**
		TC: HDL-C	**5.0 ± 1.1**	**-1.1**	**0.05**	**1.19**

Abbreviations: BMI, *body mass index (calculated as weight in kilograms divided by height in meters squared)*; D&B, *Downs and Black score*; FMD, *flow-mediated dilation*; HbA1c, *glycosylated hemoglobin*; HRmax, *age-predicted maximum heart rate*; IL-6, *interleukin 6*; NS, *not significant*; 1RM, *1-repetition maximum*; PAI-1, *plasminogen activator inhibitor-1*; PWV, *pulse wave velocity*; RPE*, rating of perceived exertion*; TNF-α*, tumour necrosis factor α*.

*Group x time interaction for RCT and non-RCT, or pre-post change for pre-post study designs.
†True study design is RCT, presented as pre-post because 2 different exercise modalities were tested.
[$] Only persons with paraplegia.

C4 Table 4 Detailed findings of FES cycling studies included in this review.

Author **Design** **D&B** **Quality**	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)*, Mean ± SD	**Change** *Intervention (Control)*	***P* value***	**ES**
Allsion et al [43]	10	FES-cycling	TG (mmol/L)	0.37 ± 0.19	-0.01	NS	0.06
Pre-post		12 wk	TC (mmol/L)	1.99 ± 0.46	+0.07	NS	0.15
16		3 sessions/wk	HDL-C (mmol/L)	0.48 ± 0.13	0.0	NS	0.00
Fair		90-95% of max tolerance	LDL-C (mmol/L)	1.13 ± 0.33	+0.07	NS	0.22
			CRP (pg/mL)	12.59 ± 14.06	-5.81	NS	0.55
		1-45 mins	IL-6 (pg/mL)	6.29 ± 4.65	+0.61	NS	0.13
			TNF-α (pg/mL)	25.62 ± 49.64	+4.27	NS	0.07
Sadowsky et al [44]	45	FES-cycling	**TG**	**NR**	**-**	**<0.05**	**-**
		3-168 wk	HDL-C	NR	-	NS	-
Retrospective cohort study		3 sessions/wk	**LDL-C**	**NR**	**-**	**<0.05**	**-**
		Intensity NR	**TC: HDL-C**	**4.1 ± 1.0 (5.3 ± 1.9)**	**-**	**0.03**	**0.79**
16		45-60 mins					
Fair							
Gorgey et al [27]†	9	FES-cycling	Body mass (kg)	79 ± 12	+6	NS	0.59
		16 wk	BMI (kg/m^2)	26 ± 5	+3	NS	0.82
Pre-post		5 sessions/wk	BF (%)	38 ± 5.7	0	NS	0.00
16		75% HR_{MAX}	Fat mass (kg)	29 ± 8.6	0	NS	0.00
Fair		40 mins	Fasting glucose (mmol/L)	5.00 ± 0.11	+0.33	0.4	0.65
			Fasting insulin (pmol/L)	97.2 ± 118.1	-59.0	0.8	0.70
			IVGTT insulin sensitivity (%)	-	+129	NS	0.69
			IVGTT glucose effectiveness (%)	-	+4	NS	0.19
			SBP (mmHg)	123 ± 8	+4	>0.5	0.44
			DBP (mmHg)	79 ± 5	+4	>0.5	0.36
Jeon et al [45]	7	FES-cycling	**2-h glucose OGTT (mmol/L)**	**7.77 ± 0.89**	**-0.98**	**0.01**	**2.13**

Pre-post 14 Fair		8 wk 3 sessions/wk Max load to finish 30 min 30 min	2-h insulin OGTT (pmol/L)	822 ± 296	-215	NS	1.00
Gerrits et al [46] Pre-post 14 Fair	9	FES-cycling 6 wk 3 sessions/wk Max load to finish 30 min 30 min	SBP (mmHg)	131 ± 20	+6	NS	0.40
Liu et al [47] Pre-post 14 Fair	18	FES-cycling 8 wk 3 sessions/wk Intensity NR 30 mins	Body mass (kg) BMI (kg/m^2)	73.8 ± 13.9 25.4 ± 3.9	+1.2 +0.3	0.06 NS	0.09 0.08
Faghri et al [48] Pre-post 13 Low	13	FES-cycling 12 wk 3 sessions/wk Max load to finish 30 min 30 min	**SBP (mmHg)$^{\$}$** **DBP (mmHg)$^{\$}$**	**-** **-**	↓ ↓	**<0.05** **<0.05**	**-** **-**
Griffin et al [49] Pre-post 13 Low	18	FES-cycling 10 wk 2-3 sessions/wk Max load to finish 30 min or fatigue	**Body mass (kg)** **Fat mass (kg)** TG (mmol/L) TC (mmol/L) **HDL-C (mmol/L)** LDL-C (mmol/L) **2-h glucose OGTT**	**69.6 ± 4.2** **22.9 ± 2.3** 1.18 ± 0.30 4.08 ± 0.16 **0.88 ± 0.05** 2.65 ± 0.16 **-**	**-2.1** **+0.6** -0.04 -0.04 **-0.10** +0.07 ↓	**<0.05** **<0.05** NS NS **<0.05** NS **<0.05**	**0.12** **0.06** 0.04 0.06 **0.43** 0.12 **-**

			2-h insulin OGTT	**-**	↓	**<0.05**	**-**
			CRP	**15.92 ± 1.57**	**-2.98**	**<0.05**	**0.57**
			IL-6	**4.91 ± 1.10**	**-1.12**	**<0.05**	**0.31**
			TNF-α	**11.82 ± 0.63**	**-0.51**	**<0.05**	**0.19**
Robergs et al [50] Pre-post 13 Low	8	FES-cycling 6 wk 3 sessions/wk Intensity NR 30 mins	SBP (mmHg) DBP (mmHg)	112 ± 6 77 ± 4	-3 -4	NS NS	0.63 1.00
Hjeltnes et al [52] Pre-post 12 Low	5	FES-cycling 8 wk 7 sessions/wk Max load to finish 30 min 30 mins	**BF (%)** Fasting insulin	**29.7 ± 2.6** NR	**-1.9** NR	**<0.05** NS	**0.80** -
Kahn et al [52] Pre-post 12 Low	12	FES-cycling 4 wk 2 sessions/wk Intensity NR 30 mins	Fibrinogen (mg/dL)	410 ± 78	+29	NS	0.17
Hjeltnes et al [53] Pre-post 11 Low	5	FES-cycling 8 wk 7 sessions/wk Max load to finish 30 min 30 mins	**HEC glucose uptake (%)**	**-**	**+33**	**<0.05**	**0.95**
Lammers et al [54]	8	FES-cycling 8 wk	Hyperaemic flow	-	↔	NS	-

Pre-post 11 Low		2-3 sessions/wk Max load to finish 30 min 30 mins					
Mohr et al [55] Pre-post 11 Low	10	FES-cycling 52 wk 3 sessions/wk Intensity NR 30 mins	FFA (mmol/L) Fasting insulin (pmol/L) Glucose OGTT (AUC) Insulin OGTT (AUC) **HEC SSGIR step 1 (%)** HEC SSGIR step 2 (%)	0.68 ± 0.08 83 ± 35 - - **-** -	-0.03 -28 ↔ ↔ **+28** +17	NS NS NS NS **<0.05** NS	0.13 0.33 - - **0.74** 0.63
Sköld et al [56] Pre-post 10 Low	15	FES-cycling 26 wk 3 sessions/wk Max load to finish 30 min 30 mins	Body mass Abdominal adipose tissue	NR NR	↔ ↔	NS NS	- -
Chilibeck et al [57] Pre-post 9 Low	5	FES-cycling 8 wk 3 sessions/wk Intensity NR 30 mins	**Cederholm index**	**-**	↑	**<0.05**	**-**

Abbreviations: AUC, *area under the curve*; BF, *body fat*; BMI, *body mass index (calculated as weight in kilograms divided by height in meters squared)*; CRP, *C-reactive protein*; D & B, *Downs and Black score*; FFA, *free-fatty acids*; HEC, *hydroxyethylcellulose*; HRmax, *age-predicted maximum heart rate*; IL-6, *interleukin 6*; IVGTT, *intravenous glucose tolerance test*; NR, *not reported*; NS, *not significant*; OGTT, *oral glucose tolerance test*; SSGIR, *steady-state glucose infusion rate*; TNF-α, *tumour necrosis factor α*

* Group x time interaction for RCT and non-RCT or pre-post change for pre-post study designs.
† True study design is RCT, presented as pre-post because of 2 different interventions (vs high-protein diet).
[$]Only persons with paraplegia.

C4 Table 5 Detailed findings of FES RT and combined (FES cycling and FES RT) studies included in this review.

Author Design D&B Quality	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***P* value***	**ES**
Gorgey et al [58]	22	FES knee extensions (with testosterone replacement therapy)	Body mass (kg)	80.5 ± 16 (77.5 ± 9.0)	+2.6 (+0.2)	NS	-
			BMI (kg/m^2)	**25 ± 4.5 (24.4 ± 3.6)**	**+1.6 (-0.4)**	**0.004**	**-**
RCT			BF (%)	32 ± 11 (33.4 ± 9)	-1.3 (-1.4)	NS	-
21		16 wk	Fat mass (kg)	26.7 ± 12.5 (26.1 ± 8.0)	0.0 (-1.0)	NS	-
High		2 sessions/wk	VAT (cm^2)	101 ± 71 (91.5 ± 49.5)	-13 (-7.0)	NS	-
		4 x 10	TG	NR	↔	NS	-
		~1 kg increments every 2 sessions	FFA	NR	↔	NS	-
			TC	NR	↔	NS	-
			HDL-C	NR	↔	NS	-
			LDL-C	NR	↔	NS	-
			IVGTT insulin sensitivity (%)	-	0.0 (0.0)	NS	-
			IVGTT glucose effectiveness (%)	-	31.5 (28.6)	NS	-
			CRP	NR	↔	NS	-
			IL-6 (pg/mL)	5.5 ± 5.6 (5.9 ± 6.0)	-2.6 (-2.0)	NS	-
			TNF-α	NR	↔	NS	-
			Adiponectin (ng/mL)	**4323 ± 1856 (3516 ± 1205)**	**-624 (+1291)**	**<0.05**	**-**
Gorgey et al [59]	9	FES knee extensions	Body mass (kg)	74 ± 14 (76 ± 8)	+1 (-1)	NS	-
		12 wk	BMI (kg/m^2)	21 ± 5 (23 ± 3)	0 (0)	NS	-
RCT		2 sessions/wk	BF (%)	30 ± 8 (29 ± 3)	-1 (-1)	NS	-
16		4 x 10	Fat mass (kg)	23.3 ± 9 (22 ± 2)	-0.7 (1)	NS	-
Fair		Increased by ~1kg every 2 sessions	Trunk VAT CSA (cm^2)	103 ± 80 (106 ± 32)	-9 (-14)	NS	-
			TG (mmol/L)	**1.58 ± 1.38 (1.25 ± 0.28)**	**-0.60 (+0.16)**	**0.05**	**-**
			FFA (mmol/L)	0.58 ± 0.1 (0.53 ± 0.1)	-0.14 (-0.11)	0.3	-
			TC (mmol/L)	4.19 ± 1.27 (3.93 ± 0.70)	+0.05 (+0.2)	0.1	-
			HDL-C (mmol/L)	0.78 ± 0.08 (0.83 ± 0.16)	+0.08 (-0.03)	0.07	-
			LDL-C (mmol/L)	2.72 ± 0.93 (2.53 ± 0.67)	+0.21 (+0.16)	0.5	-

			TC: HDL-C	**5.6 ± 2 (5 ± 1)**	**-0.8 (+0.2)**	**0.02**	-
			HOMA-IR (Log_{10})	0.44 ± 0.27 (0.33 ± 0.17)	-0.03 (+0.06)	NS	-
			Glucose OGTT (AUC) (%)	-	-6.5 (-8.5)	NS	-
			Insulin OGTT (AUC) (%)	-	-33.9 (+22.0)	NS	-
Rodgers et al [60] Pre-post 14 Fair	12	FES knee extensions 12 wk 3 sessions/wk 2 x 30 (25% Max), 1 x 60 (12.5% Max) Increased by 0.5 kg per session	Body Mass (kg)	67.6	-0.7	NS	-
Ryan et al [61] Pre-post 14 Fair	14	FES knee extensions 16 wk 2 sessions/wk 4 x 10 Increased by 0.9 kg evert 2 successful sessions	BMI (kg/m^2)	26.7 ± 4.7	-0.3	0.70	0.07
			TG (mmol/L)	1.55 ± 0.94	-0.13	0.36	0.16
			TC (mmol/L)	**4.76 ± 1.03**	**-0.18**	**0.05**	**0.16**
			HDL-C (mmol/L)	**1.09 ± 0.40**	**+0.09**	**0.02**	**0.24**
			LDL-C (mmol/L)	2.95 ± 0.94	-0.21	0.11	0.21
			TC: HDL-C	4.8 ± 1.8	-0.6	0.43	0.33
			Fasting glucose (mmol/L)	4.94 ± 1.05	+0.22	0.16	0.07
			2-h glucose OGTT (mmol/L)	6.62 ± 4.30	+0.85	0.41	0.19
			HOMA-IR	1.6 ± 1.4	-0.1	0.73	0.06
			HOMA%S	136.0 ± 112.0	+7.0	0.65	0.07
			HOMA%β	125.0 ± 68.0	-14.0	0.17	0.19
Stoner et al [62] Pre-post 14 Fair	5	FES knee extensions 18 wk 2 sessions/wk 4 x 10 Increased by 0.9-1.8 kg every 2 sessions	**Posterior tibial FMD (when adjusted for resting diameter)**	-	**+3.9%**	**0.03**	**-**

Ragnarsson et al [63] Pre-post 13 Low	19	Combined 10-32 wk 3 sessions/wk Max load to fatigue or 45 reps (FES knee extensions) 30 mins (FES cycling)	Albumin	NR	↔	NS	-
Pollack et al [64] Pre-post 12 Low	11	Combined 13-28 wk 3 sessions/wk Max load to fatigue or 45 reps (FES knee extensions) Duration NR	SBP (mmHg) DBP (mmHg)	114 ± 4 71 ± 3	-16 -4	NS NS	1.21 0.40
Mahoney et al [65] Pre-post 11 Low	5	FES knee extensions 12 wk 2 sessions/wk 4 x 10 Increased by 0.9-1.8 kg every 2 sessions	Fasting glucose (mmol/L) Fasting insulin (mmol/L) 2-h glucose OGTT (mmol/L) 2-h insulin OGTT	4.87 ± 0.58 NR 5.98 ± 1.44 NR	0.0 ↔ -0.47 ↔	NS NS NS NS	0.00 - 0.24 -
Pacy et al [66] Pre-post 9 Low	4	Combined 4-12 wk 5 sessions/wk Intensity NR 15 mins each	Body mass (kg)	67.9 ± 5.2	+4.9	NS	0.65

Abbreviations: AUC, *area under the curve*; BF, *body fat*; BMI*, body mass index (calculated as weight in kilograms divided by height in meters squared);* CRP, *C-reactive protein*; CSA, *cross sectional area*; D&B, *Downs and Black score*; FFA, *free-fatty acids*; FMD, *flow-mediated dilation*; IL-6*, interleukin 6*; IVGTT, *intravenous glucose tolerance test*; NR, *not reported*; NS, *not significant*; OGTT, *oral glucose tolerance test*; TNF-α, *tumour necrosis factor α*; VAT, *visceral adipose tissue*.

* Group x time interaction for RCT and non-RCT or pre-post change for pre-post study designs

C4 Table 6 Hybrid and FES rowing studies included in this review

Author **Design** **D&B** **Quality**	***n***	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control),* Mean ± SD	**Change** *Intervention (Control)*	***P* value***	**ES**
Bakkum et al [21]	9	Hybrid	**Waist (cm)**	**91.8 ± 4.7**	**-3.9**	**0.02**	**0.92**
20		16 wk	Android fat mass (kg)	2.0 ± 0.4	-0.1	0.34	0.25
Pre-post†		2 sessions/wk	**Android fat (%)**	**33.4 ± 2.9**	**-2.1**	**0.02**	**0.76**
High		65-75% HRR	**TG (mmol/L)**	**1.7 ± 0.2**	**-0.3**	**0.01**	**1.50**
		18-32 mins	HDL-C (mmol/L)	1.1 ± 0.1	+0.1	0.22	1.00
			Fasting glucose (mmol/L)	5.7 ± 0.3	+0.1	0.38	0.28
			Fasting insulin (pmol/L)	72.7 ± 10.6	-18.9	0.11	1.66
			HOMA-IR	2.8 ± 0.5	-0.6	0.16	1.09
			SBP (mmHg)	112 ± 6	+5	0.39	0.65
			DBP (mmHg)	**69 ± 3**	**-6**	**0.04**	**1.70**
			CRP (mg/L)	3.91 ± 1.75	-0.71	0.08	0.41
			IL-6 (pg/mL)	2.51 ± 0.91	-0.63	0.20	0.83
Thijssen et al [67]	9	Hybrid	Body mass (kg)	74 ± 18	+1	0.52	0.06
Pre-post		6 wk	Relative brachial FMD (%)	-	-	0.28	-
16		2 sessions/wk	**Relative femoral FMD (%)**	**-**	**-**	**<0.01**	**-**
Fair		Intensity NR					
		30 mins					
Kim et al [68]	12	FES rowing	BMI (kg/m^2)	23.4 ± 3.7	-0.4	0.06	0.11
Pre-post		6 wk	Waist (cm)	84.1 ± 10.3	-2.1	0.06	0.21
15		5 sessions/wk					
Fair		>70% HR_{MAX}					
		42.5 mins					

Qiu et al [69] Pre-post 14 Fair	12	FES rowing 26 wk 1.8 ± 2 sessions/wk 75-85% HR_{PEAK} 30 mins	Body mass (kg)	72.5 ± 3.9	+0.8	NS	0.20
Thijssen et al [70] Pre-post 14 Fair	10	Hybrid 4 wk 2-3 sessions/wk Intensity NR 30 mins	Body mass (kg) SBP (mmHg) DBP (mmHg) Absolute brachial FMD (mm) Relative brachial FMD (%) Absolute femoral FMD (mm) Relative femoral FMD (%)	73 ± 10 123 ± 18 73 ± 14	0 -4 -5	0.77 0.17 0.23 0.48 0.68 0.06 0.10	0.00 0.23 0.38 - - - -
Wilbanks et al [71] Pre-post 14 Fair	10	FES rowing 6 wk 3 sessions/wk 86 ± 8% HR_{PEAK} 30 mins	Body mass (kg) BF (%)	85.1 ± 19.6 36.9 ± 5.9	0.0 -0.2	0.18 0.64	0.00 0.03
Jeon et al [72] Pre-post 14 Fair	7	FES rowing 12 wk 3-4 sessions/wk 80% $\dot{V}O_{2PEAK}$ 200 kcal/session	Body mass (kg) BF (%) **Leptin (ng/mL)** **Fasting glucose (mmol/L)** Fasting insulin (pmol/L) HOMA-IR	72.1 ± 3.6 25.5 ± 1.8 **6.9 ± 1.7** **5.73 ± 0.09** 95.1 ± 14.6 3.6 ± 0.8	-1.1 -1.1 **-2.2** **-0.12** -16.7 -0.8	NS 0.07 **0.05** **<0.05** NS NS	0.14 0.26 **0.60** **0.73** 0.49 0.65
Hasnan et al [73] Pre-post 7 Low	8	Hybrid 6 wk 2 or 3 sessions/wk 80-90% HR_{MAX}	TC HDL-C LDL-C Glucose OGTT	NR NR NR NR	NR NR NR NR	NS NS NS NS	- - - -

Abbreviations: BF, *body fat*; BMI, *body mass index (calculated as weight in kilograms divided by height in meters squared)*; CRP, *C-reactive protein*; D & B, *Downs and Black score*; FMD, *flow-mediated dilation*, HRmax, *age-predicted maximum heart rate*; HRpeak*, peak heart rate*; IL-6, *interleukin 6*; NR, *not reported*; NS, *not significant*; OGTT, *oral glucose tolerance test*; VO_2peak, *peak oxygen uptake.*

†True study design is RCT, presented as pre-post because 2 different exercise modalities were tested.

C4 Table 7 Ambulation studies included in this review.

Author **Design** **D&B** **Quality**	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***P* value***	**ES**
Giangregorio et al [36] Pre-post† 23 High	17	FES walking 16 wk 3 sessions/wk Max load without knee buckling 45 mins	Fat mass (kg)	25.4	-1.1	NS	0.12
Gorman et al [74] RCT 19 High	18	Robotic BWSTT 12 wk 3 sessions/wk 80-85% HRR 20-45 mins	Body mass (kg) BF (%)	80.8 ± 14.6 (94.3 ± 25.0) 33.6 ± 7.9 (34.2 ± 6.9)	-1.0 (-2) -1.2 (-0.9)	0.72 0.20	- -
Ditor et al [75] Pre-post 19 High	10	BWSTT 16 wk 3 sessions/wk Max speed without loss of gait 60 mins	SBP (mmHg) DBP (mmHg)	114 ±19 66 ± 11	-1 -2	0.90 0.62	0.05 0.19
Ditor et al [76] Pre-post 18 Fair	8	BWSTT 26 wk 3 sessions/wk Max load and speed without knee bucking or loss of gait 60 mins	SBP (mmHg) DBP (mmHg)	117 ± 20 73 ± 11	-2 -1	NS NS	0.12 0.15
Turiel et al [77]	14	BWSTT	TG (mmol/L)	1.36 ± 0.17	-0.20	NS	0.33

Pre-post 17 Fair		6 wk 5 sessions/wk Intensity NR 45 mins	TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) **Fasting glucose (mmol/L)** CRP (NR) SBP (mmHg) DBP (mmHg)	4.67 ± 0.54 1.46 ± 0.31 2.61 ± 0.37 5.12 ± 0.67 **NR** 127 ± 10 75 ± 5	-0.14 +0.07 -2.9 -0.19 **-0.15** -3 -3	NS NS NS NS **<0.01** NS NS	0.28 0.26 0.21 0.54 **-** 0.21 0.49
Giangregorio et al [78] Pre-post 16 Fair	13	BWSTT 52 wk 3 sessions/wk Minimal load and max speed without knee buckling, losing proper weight shifting, and upright torso Up to 3 x 5-15 min bouts	**Fat mass (kg)**	**23.6 ± 11.0**	**+0.4**	**NS**	**0.04**
Karelis et al [79] Pre-post 16 Fair	5	Robotic exoskeleton walking 60-70% HRR 6 wk 3 sessions/wk Up to 60 mins	**Body mass (kg)** **BMI (kg/m^2)** **BF (%)**	**79.7 ± 12.5** **24.5 ± 1.7** **35.4 ± 7.1**	**+2.0** **+0.6** **-1.3**	**0.04** **0.04** **0.04**	**0.15** **0.32** **0.23**
Stewart et al [80] Pre-post 15 Fair	9	BWSTT 26 wk 3 sessions/wk Intensity NR Until self-reported fatigue	TG (mmol/L) **TC (mmol/L)** HDL-C (mmol/L) **LDL-C (mmol/L)** **TC: HDL**	1.51 ± 0.20 **4.91 ± 0.19** 1.29 ± 0.19 **3.25 ± 0.22** **3.83 ±0.33**	-0.19 **-0.55** +0.14 **-0.42** **-0.76**	0.17 **0.02** 0.19 **0.05** **0.04**	0.33 **1.15** 0.20 **0.54** **0.95**
Phillips et al [81] Pre-post 14	9	BWSTT 24 wk 3 sessions/wk Based on self-reported fatigue	**Glucose OGTT (AUC)** **Insulin OGTT (AUC)**	**-** **-**	**-15%** **-33%**	**<0.05** **<0.05**	**-** **-**

Fair		Until self-reported fatigue					
Klose et al [82] Pre-post 13 Low	16	FES walking 11 wk 3 sessions/wk Comfortable intensity Up to 3 sets	Body mass (kg)	66.0	+1.3	0.06	-

Abbreviations: AUC, *area under the curve*; BF, *body fat*; BMI, *body mass index (calculated as weight in kilograms divided by height in meters squared)*; BSWTT, *body-weight-supported treadmill training*; CRP, *C-reactive protein*; D&B, *Downs and Black score*; NR, *not reported*; NS, *not significant*; OGTT, *oral glucose tolerance test.*

* Group x time interaction for RCT and non-RCT or pre-post change for pre-post study designs.
† True study design is RCT, presented as pre-post because 2 different exercise modalities were tested.

C4 Table 8 Overview of other exercise studies included in review but not grouped for qualitative analysis.

Author **Design** **D&B** **Quality**	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention* *(Control)*	***P* value***	**ES**
Jones et al [83] RCT 19 High	48	Lower body RT and BSWTT or FES 24 wk 3 sessions Intensity NR Up to 180 mins	Body mass (kg) BMI (kg/m^2) QUICKI	89.4 ± 20.3 (75.7 ± 21.0) 27.1 ± 6.4 (24.8 ± 6.6) 0.35 ± 0.04 (0.38 ± 0.06)	-0.20 (+5.03) 0.0 (+0.7) -0.002 (-0.012)	0.31 0.29 0.92	0.45 0.41 0.06
Li et al [84] Pre-post† 18 Fair	6	Combined RT, ACE, and FES 8 weeks 3 sessions/wk ACE: 80-90% $\dot{V}O_{2PEAK}$, 15 x 1 mins Upper-body RT: 3 x 12 FES-knee extensions: 40 reps, increased by ~0.5-1 kg every 2 weeks	Body mass (kg) Fat mass (kg) Android fat mass (kg) TGs (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) **Fasting glucose (mmol/L)** Fasting insulin (pmol/L) Glucose OGTT (AUC) Insulin OGTT (AUC) HOMA-IR Matsuda ISI IL-6 (pg/mL) TNF-α (pg/mL)	87.7 ± 15.0 - - 1.36 ± 0.66 4.44 ± 0.99 1.09 ± 0.16 2.73 ± 0.80 **6.12 ± 1.14** 115.3 ± 127.1 - - 4.6 ± 5.1 3.3 ± 2.0 1.7 ± 1.0 2.2 ± 0.4	↔ ↔ ↔ +0.39 -0.21 -0.05 -0.34 **-0.54** -25.7 +4% -27% -1.3 +1.3 -0.7 -0.8	NS NS NS 0.47 0.94 0.96 0.75 **0.04** 0.91 0.87 0.34 0.83 0.98 0.20 0.27	- - - 0.45 0.25 0.27 0.48 **0.56** 0.24 0.14 0.28 0.31 0.43 0.95 0.97

Abbreviation: ACE, *arm-crank ergometry*; AUC, *area under the curve*; BMI, *body mass index (calculated as weight in kilograms divided by height in meters squared)*; BSWTT, *body-weight-supported treadmill training*; D&B, *Downs and Black score*; IL-6, *interleukin 6*; ISI, *Insulin Sensitivity Index*; NR, *not reported*; NS, *not significant*; OGTT, *oral glucose tolerance test*; QUICKI, *Quantitative Insulin-Sensitivity Check Index*; TNF-α, *tumour necrosis factor α*; VO_2peak, *peak oxygen uptake*.

* Group x time interaction for RCT and non-RCT or pre-post change for pre-post study design.

† True study design is RCT, presented as pre-post because 2 different exercise modalities were tested.

C4 Table 9 Participant characteristics, statistical power, and control group (if applicable) of included studies.

Authors	Control Type	Statistical Power	N (M/F)	Age (y)	TSI (y)	LOI	ASIA
Akkurt et al [28]	General exercises	NR	33 (29/4)	I: 15-42, C:19-62	I:0.2-12, C:0.3-10)	C7-L3	A-D
Allison et al [43]	N/A	NR	10 (9/1)	39±10 (26-55)	9±9	C4-T11	A-C
Bakkum et al [21]	N/A	No	19 (18/1)	Hybrid: 49±3, Handcycle: 47±3	Hybrid: 21±3, Handcycle: 16±2	C2-L2	A-D
Bresnahan et al [24]	N/A	NR	10 (8/2)	37±13 (23-55)	12±14 (1-34)	C7-T5	A-B
Chilibeck et al [57]	N/A	NR	5 (4/1)	31-50	3-25	C5-T8	A
Cugusi et al [40]	N/A	NR	16 (16/0)	45±12	12±10	Thoracic	A-C
Davis et al [35]	No exercise	NR	14 (14/0)	I: 30±3, C: 29±3	I: 19±3, C: 9±3	NR	NR
de Zepetnek et al [37]	Habitual lifestyle	NR	23 (21/2)	I: 39±11, C: 42±13	I: 15±10, C: 9±10	C1-T11	A-D
Ditor et al [76]	N/A	NR	8 (6/2)	28±5 (20-34)	10±8 (2-24)	C4-C5	B-C
Ditor et al [75]	N/A	NR	6 (4/2)	38±15	8±9	C4-T12	A-B
Faghri et al [48]	N/A	NR	13 (12/1)	31±5 (21-41)	8±4 (3-16)	C4-T10	A-D
Gass et al [33]	N/A	NR	9 (NR)	35±11 (25-50)	12±5 (5-18)	C5-T4	NR
Gerrits et al [46]	N/A	NR	9 (9/0)	39±11 (28-44)	11±10 (1-27)	C5-T8	A-C
Giangregorio et al [36]	N/A	NR	34 (26/8)	FES: 57±14, RT: 54±17	FES: 9±10, RT: 10±11	C2-T12	C-D
Giangregorio et al [78]	N/A	NR	14 (11/3)	29±8 (20-53)	8±7 (1-24)	C4-T12	NR
Gorgey et al [58]	TRT	Yes	22 (22/0)	I: 37±12, C: 35±8	I: 10±9; C: 7±6	C5-T11	A-B*
Gorgey et al [27]	N/A	NR	9 (9/0)	ACE: 41±13; FES: 37±7	ACE: 11±9; FES: 7±5	C8-T10	A-B
Gorgey et al [59]	Standardised diet	NR	9 (9/0)	35±9 (21-47)	13±9 (2-26)	C5-T11	A-B
Gorman et al [74]	Stretching	NR	18 (NR)	I: 52±12, C: 52±15	NR	NR	C-D
Griffin et al [49]	N/A	NR	18 (13/5)	40±2 (25-57)	11±3	C4-T7	NR
Han et al [25]	N/A	NR	5 (5/0)	40±7	13.9±5.0	C4-L1	A-D
Hasnan et al [73]	N/A	NR	8 (NR)	NR	NR	NR	NR
Hicks et al [41]	No exercise	NR	34 (NR)	I: 37±11; C: 43±9	I: 8±6 (1-22); C: 12±7 (3-24)	C4-S1	A-D
Hjeltnes et al [51]	N/A	NR	5 (5/0)	35±3 (28-44)	10±3 (4-23)	C5-C7	A-B
Hjeltnes et al [53]	N/A	NR	5 (5/0)	35±3 (28-44)	10±3 (4-23)	C5-C7	A-B
Hooker et al [20]	N/A	NR	11 (6/5)	31±4 (23-36)	12±7 (2-19)	C5-T9	NR
Horiuchi et al [30]	N/A	NR	9 (9/0)	38±10	16±7	T8-L1	A-B
Jeon et al [72]	N/A	NR	6 (6/0)	46±5 (24-56)	NR	T4-T10	A-B
Jeon et al [45]	N/A	NR	7 (5/2)	45±8 (30-53)	20±14 (3-40)	C5-T10	NR
Jones et al [83]	No exercise	Yes	48 (30/11)	I: 42±13; C: 34±12	I: 7±10; C: 6±7	NR	C-D
Kahn et al [52]	N/A	NR	12 (NR)	NR	>1	C4-C8;T1-T10	NR
Karelis et al [57]	N/A	NR	5 (4/1)	60±6	8±5	C7-T10	NR

Kim et al [39]	No exercise	NR	15 (9/6)	33±6 (22-46)	7±4 (2-16)	C5-T11	A-B
Kim et al [39]	Standard Care	NR	17 (11/6)	37±7 (23-53)	10±7 (2-27)	C4-L1	A-C
Kim et al [68]	N/A	NR	12 (10/2)	36±12 (16-45)	11±6 (5-24)	C6-L1	A-C
Klose et al [82]	N/A	NR	16 (13/3)	28±7 (21-45)	4±3 (0.7-9)	T4-T11	NR
Lammers et al [54]	N/A	NR	8 (8/0)	39±3	>4	C5-T11	A-B
Liu et al [47]	N/A	NR	18 (16/2)	40±11 (26-61)	3±2 (1-9)	C3-L1	B-D
Li et al [84]	N/A	NR	6 (6/0)	50±8 (36-58)	24±8 (10-30)	C6-T6	A-B
Mahoney et al [65]	N/A	NR	5 (5/0)	36±5	13±7	C5-T10	A
McLean et al [26]	N/A	NR	14 (NR)	Supine: 34±12; Sitting: 33±7	Supine: 9±13; Sitting: 14±6	CT-T1	NR
Midha et al [31]	N/A	NR	12 (11/1)	38±10 (22-58)	15±7 (4-29)	C6-L3	NR
Mogharnasi et al [38]	No exercise	NR	20 (20/0)	I: 25±3; C: 26±3	I: 10±4; C: 9±4	T9-T12	A
Mohr et al [55]	N/A	NR	10 (8/2)	35 (27-45)	12 (3-23)	C6 and T4	NR
Mukherjee et al [32]	N/A	NR	12 (12/0)	31±9 (19-45)	2±1 (1-3)	<T10	NR
Nash et al [42]	N/A	NR	5 (5/0)	38±4 (34-43)	5±1 (1-7)	T6-T12	NR
Nightingale et al [22]	No exercise	Yes	21 (15/6)	I: 46±6, C: 48±10	I: 20±10; C: 14±11	T4-L3	A-D
Pacy et al [66]	N/A	NR	4 (4/0)	20-35	4±3 (1-8)	T4-T6	NR
Phillips et al [81]	N/A	NR	9 (8/1)	31±3	8±3	C4-T12	C
Pollack et al [64]	N/A	NR	11 (7/4)	29±15 (18-54)	6±3 (0.5-11)	C4-T6	NR
Ragnarsson et al [63]	N/A	NR	19 (16/3)	19-47	2-17	C4-T10	NR
Robergs et al [50]	N/A	NR	8 (7/1)	32±2 (23-41)	12±2 (5-24)	C7-L1	NR
Robergs et al [60]	N/A	No	12 (9/3)	38±13 (19-63)	6±6 (1-17)	C4-T10	NR
Rosety-Rodriguez et al [23]	No exercise	NR	17 (17/0)	30±4 (I & C)	5±0	≤T5	NR
Ryan et al [61]	N/A	No	14 (11/3)	27±5 (28-57)	8±7 (2-22)	C4-T7	A-B
Sadowsky et al [44]	Standard Care	NR	45 (38/7)	I: 37±12; C: 35±12	I: 8 (1.5-43), C: 6 (1-27)	C1-L5	A-C
Qiu et al [69]	N/A	Yes	12 (11/1)	33±4 (22-60)	8±3 (0-33)	C4-T2	NR
Sköld et al [56]	No exercise	NR	15 (15/0)	33 (21-48)	9 (1-21)	NR	A-B
Stewart et al [80]	N/A	NR	9 (8/1)	31±3	8±3	C4-T12	C
Stoner et al [62]	N/A	NR	5 (5/0)	36±5	13±7	C5-T10	A
Thijssen et al [67]	N/A	NR	9 (8/1)	39±3 (25-52)	11±3 (1-25)	C5-T12	A, C
Thijssen et al [70]	N/A	NR	10 (9/1)	39±9 (23-53)	11±6 (1-20)	T1-T12	A, C
Turiel et al [77]	N/A	NR	14 (10/4)	51±17	2-10	NR	MI
Wilbanks et al [71]	N/A	NR	10 (8/2)	47±18	18±14 (2-39)	T4-T12	A-C
Yim et al [34]	N/A	NR	11 (11/0)	31±8 (20-49)	2±1 (0.5-4)	T8-T12	A

Abbreviations: ASIA, *American Spinal Injury Association Impairment Scale*; C, *control*; LOI, *level of injury*; NA, *not applicable*; NR, *not reported*; I, i*ntervention*; PA, *physical activity*; TSI, *time since injury*; MC *motor complete*, TRT *testosterone replacement therapy*
*ISNCSCI, *International Standards for Neurological Classification of Spinal Cord Injury*

Discussion

There are consistent findings that voluntary upper body aerobic exercise (>75% maximum heart rate) is effective in reducing waist circumference, and improving hepatic insulin sensitivity (ie, fasting insulin concentration and HOMA-IR); however, it does not appear to improve fasting glucose concentrations, lipid profile or resting blood pressure in persons with chronic SCI. The addition of upper body RT appears to have an inconsistent effect on lipid profiles but given the limited number of high-quality studies on combined exercise modalities, more research is needed in this area. FES cycling may improve outcomes relating to peripheral insulin sensitivity (ie, ability of the skeletal muscle to dispose of glucose), but more high-quality studies are required to strengthen the available evidence. There is insufficient evidence to conclude if FES resistance training, FES hybrid, FES rowing, or assisted ambulation training improves any of these CMS risk factors.

Four [21, 23, 29, 30] of the six studies utilising upper body aerobic exercise reported a reduction in supine waist circumference (-1.9 to -3.7 cm, effect size [ES]: 0.26-2.67), indicating that this form of exercise is effective for reducing central obesity. A reduction in waist circumference (-2.5 cm) was achieved with as few as 64 min/wk of exercise at 65-75% HRR, though this reduction did not translate to any change in android fat mass [21]. There was also no change in visceral adipose tissue [22] following 180 min/wk at 60-65% peak oxygen consumption of upper body aerobic exercise. Future studies should combine both surrogate and gold-standard measures (ie. dual-energy x-ray absorptiometry/computed tomography-derived) of central obesity/adiposity to further elucidate changes in body composition. Given the relatively small skeletal muscle mass involved in upper body aerobic exercise, it is perhaps unsurprising that there were consistent findings that body mass and body mass index were unchanged, as reported in a previous systematic review [14]. Whilst not part of the search strategy, only 1 study in this category measured free-living energy intake and expenditure during the exercise intervention [22]. To better understand the isolated impact of prescribed exercise interventions on energy balance and body composition, future studies should also attempt to estimate total energy intake and total energy expenditure. This would account for any compensatory changes in diet or exercise behaviours, providing a better understanding of the overall impact of exercise interventions on energy balance in

SCI [88]. Guidelines for measuring these variables in persons with chronic SCI have been published elsewhere [89].

Four [21,22,24,29] of the five studies that measured fasting insulin resistance by HOMA-IR and/or fasting insulin concentrations reported a reduction (22-40%, ES, 1.07-1.78) following upper body aerobic exercise, suggesting that this form of exercise is effective at improving hepatic insulin sensitivity (ie, ability of the liver to dispose of glucose). The single study [27] to find no statistically significant change in fasting insulin concentration following upper body aerobic exercise, reported that all 5 participants had a lower insulin concentration (22-76%, ES, 0.41) post-training, indicating that the study simply lacked the statistical power to demonstrate an effect. Despite the improvement in hepatic insulin sensitivity [90] observed following upper body aerobic exercise, the three studies [30,32,35] that measured outcomes relating to peripheral insulin sensitivity [91] found no changes following training. This is likely as a result of the limited skeletal muscle mass involved (ie, limited sink for glucose disposal). Furthermore, the upper body skeletal musculature is usually already well conditioned from habitual wheelchair propulsion, meaning that moderate-intensity upper body exercise is likely an insufficient stimulus to substantially promote molecular adaptations (eg, glucose transport 4 translocation, mitochondrial biogenesis) associated with improved peripheral insulin sensitivity [27]. A high-quality study reported no improvement in glucose or insulin area under the curve despite 180 min/wk of exercise at 60-65% peak oxygen consumption [22]. This suggests that even large volumes of upper body aerobic exercise above the recommended guidelines of 90 min/wk [12] may be insufficient to improve markers of peripheral insulin sensitivity.

There are also numerous studies indicating that upper body aerobic exercise alone does not improve fasting glucose, resting blood pressure (SBP, DBP), or lipid profiles (TC, HDL-C, LDL-C, and TGs). All eight studies [21,22,24,27,28,29,30,31] measuring fasting glucose reported no change following upper body aerobic exercise. However, only 1 study [30] reported a clinically elevated group mean glucose concentration at baseline (≥5.6 mmol/L). Nine studies [21,22,25,27,28,30,31,34,35] measured changes in resting blood pressure following upper body aerobic exercise. The only study [30] where participants presented with clinically elevated SBP (≥130 mmHg) at baseline reported a reduction (3 mmHg, ES, 0.66) following 10 weeks of exercise training (4 sessions/wk 50-70% HRR, 60

min). Thus, a basement effect may explain the lack of significant changes in fasting glucose and resting blood pressure in participants presenting with healthy values at baseline. Eight studies measured TGs, TC, HDL-C, or LDL-C [20,21,22,24,28,29,30,31] following upper body aerobic exercise, including four with clinically high mean concentrations at baseline. Only 2 studies reported a significant reduction in any variable. One study [30] reported a 25% reduction (ES, 0.31) in TGs in participants with a clinically elevated mean concentrations at baseline (≥1.7 mmol/L). One study reported improvements in HDL-C, LDL-C, TC: HDL-C and TGs following 60 mins/wk at 70-80% HRR, however the threshold for significance was set at *P*<.10 [20]. It therefore appears that upper body aerobic exercise may not be an adequate stimulus to improve blood lipid profile irrespective of baseline values. This is likely due to the low energy expenditure achieved through upper body exercise, which appears to drive changes in the lipid profile [92].

Upper body RT (with or without aerobic exercise) appears to reduce central obesity, with 3 of 4 studies [37,38,39] reporting a reduction in waist circumference (-1.0 to -2.6 cm) or waist-to-hip ratio (-0.02). These changes were accompanied by a decrease in whole-body fat mass and visceral adipose tissue following 120 min/wk of training (3 x 10 of 50-70% single repetition maximum lift, 20 min at 3-6 rating of perceived exertion) [37]. Upper body RT (with or without aerobic exercise) may elicit improvements in lipid profile, with 4 of 5 retrieved studies [20,38,39,40] reporting a beneficial effect of at least one marker (TC, HDL-C, LDL-C, TC: HDL-C, and TGs). However, more studies are needed to determine this, particularly given the high-quality study reporting no change in the lipid profile following 16-weeks of twice-weekly combined training [37].

Five of the 6 studies [45,49,53,55,57] to measure outcomes relating to peripheral insulin sensitivity reported a significant improvement following FES cycling. The largest of these studies (n=18) [49] reported a significant reduction in glucose and insulin at multiple time-points during a 2-h oral glucose tolerance test following 10 weeks of exercise (2-3 sessions/wk, 30 min). However, 4 of these studies were rated as low quality, and therefore more high-quality studies are needed to confirm if FES cycling can improve peripheral insulin sensitivity, which upper body exercise appears unable to achieve. We identified no RCTs assessing the efficacy of FES cycling compared to a true control group (ie, passive cycling or stretching), which should be addressed in future research. Four studies reported no change in body

mass following FES-hybrid or FES-rowing training. There was a distinct lack of training studies with sufficient breadth of outcomes to make any other meaningful conclusions on the effect of FES RT, FES hybrid, FES rowing and assisted ambulation on CMS risk factors. Nonetheless, given that hybrid training (2 sessions/wk, 18-32 min, 65-75% HRR) [21] improved a multitude of CMS risk factors (waist circumference, android fat percentage, TGs, DBP), and that different exercise modalities appear to offer specific benefits to CMS risk factors, other rigorously conducted prospective studies assessing multimodal (eg, FES cycling combined with upper body aerobic and resistance exercise) interventions should be conducted in this area of promise.

This review has highlighted the lack of research assessing novel markers of CMS risk, including outcomes relating to inflammation, dual-energy x-ray absorptiometry/computed tomography–derived measures of central adiposity, and endothelial function. It is clear that many studies in the area recruit a convenience sample of relatively active and lean individuals, who are not reflective of the wider, chronic SCI population (ie, poor metabolic health), which should be considered when interpreting results. For example, individuals with SCI have a significantly lower HDL-C compared to able-bodied controls (1.06 vs 1.28 mmol/L) [93], however only 5 of the 23 studies to measure HDL-C had a clinically low mean concentration at baseline (<1.03 mmol/L). As is widely acknowledged, this review has also confirmed the existing evidence base of exercise and CMS risk in SCI lacks sufficiently powered (4 in total identified), high-quality studies (8 in total identified). However, this review identified 16 additional studies, published since the previous systematic review by van der Scheer and colleagues [11] that were all categorised as fair or high quality, including 8 RCT’s.

Study Limitations

The main limitation of this systematic review is the use of summary coding to draw conclusions regarding the effect of each exercise modality on specific CMS risk factors. Due to the variability in CMS risk factors measured, exercise modes and training parameters (ie. exercise intensity and volume), and participant characteristics (ie. paraplegic vs. tetraplegic), a meta-analysis was not possible. Whilst the coding system provides a useful assessment of the consistency of findings in the field, it uses arbitrary classifications and does not distinguish studies

of differing quality. However, when studies rated as low-quality were removed from this analysis (Supplement 2, available online only at http://www.archives-pmr.org/), the conclusions remained unchanged, with the exception of potential of FES cycling to improve peripheral insulin sensitivity. Further, given that the vast majority of included studies lacked sufficient statistical power, there is a risk of a type II error in the conclusions formed. Finally, this review did not include acute SCI as van der Scheer et al determined there was an "absence of high-quality, consistent evidence" in this area, a view which still appears to be true [11](p742).

Conclusions

In summary, this systematic review has provided evidence that in adults with chronic SCI, upper body aerobic exercise improves outcomes relating to central obesity and hepatic insulin sensitivity, but is not sufficient to improve fasting glucose, lipid profiles, or resting blood pressure. Practitioners should consider prescribing moderate to vigorous-intensity (>75% maximum heart rate) upper body aerobic exercise to improve fasting glycaemic control and central obesity. To elicit improvements in lipid profile, this should be combined with upper body resistance training. More high-quality RCTs assessing novel markers of CMS and responses to combined exercise interventions (eg, aerobic exercise with resistance training), high-intensity exercise interventions, and FES-based exercise are needed to inform and refine evidence-based exercise guidelines for the prevention and management of CMS in this population.

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C4 Supplemental 1 PubMed Search Strategy

#1 spinal cord injur* OR spinal cord injury OR paraplegia OR tetraplegia OR quadriplegia OR spinal cord lesion* OR spinal lesion* OR spinal injury OR spinal transection OR spinal impairm* OR spine injur* OR spine injury OR spine transection OR spine impairm* OR brown-sequard's syndrome OR brown-sequard OR brown-sequard syndrome OR brown-sequard's OR cauda equina syndrome OR central cord syndrome OR anterior cord syndrome OR posterior cord syndrome OR myelitis OR spinal cord disease* OR spinal cord injury [Mesh] OR myelitis [Mesh]

#2 exercise OR exercis* OR strength training OR resistance training OR aerobic training OR endurance training OR circuit training OR physical activit* OR functional electrical stimulation OR functional electric stimulation OR functional stimulation OR FES OR exercise [Mesh] OR resistance training [Mesh]

#3 glucose OR HOMA-IR OR QUICKI OR ISI-Matsuda OR Cederholm OR homeostatic model assessment of insulin resistance OR quantitative insulin sensitivity check index OR QUICKI OR Matsuda OR HOMA OR homeostatic model assessment OR HOMA-S OR HOMA-B OR HOMA-β OR C-peptide OR hyperinsulinemic euglycaemic clamp OR cholesterol OR HDL-C OR LDL-C OR TC OR total cholesterol OR HDL cholesterol OR HDL-cholesterol OR LDL cholesterol OR LDL-cholesterol OR triglyceride OR triglyceride* OR TAG OR triacylglycerol OR TG OR glycosylated haemoglobin OR HbA1c OR glycated hemoglobin OR glycosylated hemoglobin OR glycated haemoglobin OR Hb1c OR HBGA1C OR interleukin 6 OR interleukin-6 OR IL-6 or IL6 OR c-reactive protein OR CRP OR tumour necrosis factor alpha OR TNF-α OR TNFα OR TNFa OR body mass index OR BMI OR body mass OR body weight OR bodyweight OR total body mass OR total bodyweight OR total bodyweight OR waist circumference OR hip circumference OR waist to hip ratio OR waist-to-hip ratio OR blood pressure OR BP OR SBP OR DBP OR central adiposity OR obesity OR fat mass OR adipose tissue OR visceral adipose tissue OR visceral adipos* OR fat free mass OR lean mass OR fat-free mass OR FFM OR LBM OR lean body mass OR lean mass OR muscle mass OR lean tissue mass OR body fat percentage OR fat percentage OR M value OR proinsulin OR apolipoprotein B OR ApoB OR free fatty acids OR FFA OR NEFA OR non-esterified fatty acids OR adiponectin OR leptin OR fibrinogen OR PAI-1 OR plasminogen activator inhibitor-1 OR flow-mediated dilation OR FMD OR pulse wave velocity OR PWV OR albumin OR liver fat content OR hepatic fat fraction OR liver fat fraction OR liver fat-fraction OR hepatic fat-fraction OR hepatic fat percentage OR liver fat percentage OR flow-mediated dilation OR FMD OR pulse wave velocity OR PWV

#5 NOT animal

#6 NOT rat

#7 NOT mice

Filter to English and Humans, 1/1/1970 to 22/08/2018

C4 Supplemental 2 Summary coding of studies ('high' and 'fair' quality only) examining the effect of exercise on CMS outcome measures.

		Aerobic	Aerobic + RT	Ambulation	Hybrid and Rowing	FES cycling	FES RT/Combined
Central Adiposity/Obesity	BM	**1/8 (13%)**	1/2 (50%)	1/2 (50%)	**0/5 (0%)**	0/2 (0%)	0/3 (0%)
	BMI	1/4 (25%)	1/4 (25%)	1/1 (100%)	0/1 (0%)	0/2 (0%)	1/3 (33%)*
	Waist	**4/5 (80%)**	2/3 (67%)	-	1/2 (50%)	-	-
	WHR	-	1/1 (100%)	-	-	-	-
	BF%	0/2 (0%)	-	2/2 (100%)	0/2 (0%)	0/1 (0%)	0/2 (0%)
	FM	0/3 (0%)	1/2 (50%)	0/2 (0%)	-	0/1 (0%)	0/2 (0%)
	Android FM	0/1 (0%)	-	-	0/1 (0%)	-	-
	Abdominal AT	-	-	-	--	-	-
	VAT	0/1 (0%)	1/1 (100%)	-	--	-	0/2 (0%)
	Leptin	1/1 (100%)	0/1 (0%)	-	1/1 (100%)	-	-
Inflammation	CRP	0/1 (0%)	--	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
	IL-6	1/2 (50%)	0/1 (0%)	-	0/1 (0%)	0/1 (0%)	0/1 (0%)
	TNF-α	1/1 (100%)	0/1 (0%)	-	-	0/1 (0%)	0/1 (0%)
	Adiponectin	0/1 (0%)	0/1 (0%)	-	-	-	1/1 (100%)
Dyslipidaemia	TG	**1/6 (17%)**	2/3 (67%)	0/2 (0%)	1/1 (100%)	1/2 (50%)	1/3 (33%)
	FFA	-	-	-	-	-	0/1 (0%)
	NEFA	0/1 (0%)	-	-	-	-	-
	TC	**1/6 (17%)**	2/4 (50%)	1/2 (50%)	-	0/1 (0%)	1/3 (33%)
	HDL-C	**0/7 (0%)**	1/4 (25%)	0/2 (0%)	0/1 (0%)	0/2 (0%)	1/3 (33%)
	LDL-C	**0/5 (0%)**	2/4 (50%)	1/2 (50%)	-	1/2 (50%)	0/3 (0%)
	TC: HDL-C	0/1 (0%)	1/1 (100%)	1/1 (100%)	-	1/1 (100%)	1/2 (50%)
Glycaemic Control	Fasting Glucose	**0/8 (0%)**	0/3 (0%)	0/1 (0%)	1/2 (50%)	0/1 (0%)	0/1 (0%)
	Fasting Insulin	**4/5 (80%)**	1/3 (33%)	-	0/2 (0%)	0/1 (0%)	-
	HbA1c	0/1 (0%)	0/1 (0%)	-	-	-	-
	HOMA-IR	**4/4 (100%)**	2/2 (100%)	-	0/2 (0%)	-	0/2 (0%)
	HOMA-%S	1/1 (100%)	-	-	-	-	0/1 (0%)
	HOMA-%β	0/2 (0%)	-	-	-	-	0/1 (0%)
	ISI-Matsuda	0/2 (0%)	-	-	-	-	-

	Glucose OGTT	0/2 (0%)	-	1/1 (100%)	-	1/1 (100%)	0/3 (0%)
	Insulin OGTT	0/2 (0%)	-	1/1 (100%)	-	0/1 (0%)	0/1 (0%)
	IVGTT Si	0/1 (0%)	-	-	-	0/1 (0%)	0/1 (0%)
	Cederholm Index	-	-	-	-	-	-
	HEC Si	-	-	-	-	-	-
	HEC Glucose	-	-	-	-	-	-
Thrombotic State	PAI-1	1/2 (50%)	0/1 (0%)	-	-	-	-
	Fibrinogen	0/1 (0%)	-	-	-	-	-
Vascular Dysregulation	SBP	**1/7 (14%)**	0/3 (0%)	0/3 (0%)	0/2 (0%)	0/2 (0%)	-
	DBP	**0/7 (0%)**	0/3 (0%)	0/3 (0%)	1/2 (50%)	0/1 (0%)	-
	FMD	-	0/1 (0%)	-	1/2 (50%)	-	1/1 (100%)
	PWV	-	0/1 (0%)	-	-	-	-
	Albumin	-	-	-	-	-	0/1 (0%)

Red: 0-33% of studies reported significant differences; yellow: 34-59% of studies reported significance differences; green: 60-100% of studies demonstrated positive significance differences, bold writing: ≥4 studies demonstrate the same effect. *one study reported a significant increase in BMI, NA; not applicable

Relevance of the Findings from Chapter 4 to Thesis

This systematic review of the available evidence in people with chronic SCI has revealed that upper body aerobic exercise training (>75% HR_{PEAK}), which is the focus of this thesis, improves waist circumference and hepatic insulin sensitivity (fasting insulin and HOMA-IR), but is insufficient for improving fasting glucose, lipid profile, or resting BP. The reduction in waist circumference, and improvement in hepatic insulin sensitivity appear to occur with a relatively low exercise volume (40 min per week) (Bakkum et al., 2015), with no further changes to CMS biomarkers with a high exercise volume (180 min per week) (Nightingale et al., 2017d). This supports the view that to elicit substantial changes in CMS biomarkers for this population, either i) a greater exercise volume well-beyond that of general population exercise guidelines (i.e. >150 min per week), or ii) a higher intensity of upper-body exercise may be required (Nightingale et al., 2017a).

A final search of PubMed for any additional eligibility studies (upper-body aerobic exercise only) was performed on 11th February 2022. This search revealed three recent studies that assessed the effect of upper-body aerobic exercise training on biomarkers of CMS in chronic SCI (Alrashidi et al., 2021; Farkas et al., 2021b; Jansen et al., 2021). Jansen et al. (2021) reported no change in arterial health following 16 weeks of handcycling (two sessions per week, 18-32 min per session, 65-65% HRR) in five adults with chronic SCI. Despite an improvement in CRF, Alrashidi et al. (2021) reported no other changes in the fasting lipid profile, fasting glucose, or arterial health following 24 weeks of arm crank exercise (three sessions per week, 30 min per session, RPE 11-16) in 14 adults with chronic SCI. Unfortunately, this study did not report fasting insulin concentrations and therefore, it is not possible to compare this study against the relatively consistent findings of improvements in fasting insulin and HOMA-IR reported in this chapter.

Finally, in addition to an increase in CRF, Farkas et al. (2021) reported a significant reduction in FM, fasting insulin, and systolic BP, following 16 weeks of arm crank exercise in seven physically inactive adults with chronic paraplegia (five sessions per week, 40 min per session, 75% HR_{PEAK}). This volume of exercise (200 min per week) is the largest reported in the literature, with participants expending 237 ± 63 kcal during the final exercise training session. This study did not measure EI; however, it is likely that this substantial exercise EE (~1,200 kcal during final week) performed for a prolonged period explains the reduction in FM. Although no changes

in the lipid profile were reported, or assessment of peripheral insulin sensitivity performed, this study provides a preliminary indication that a very high exercise volume can elicit profound changes to cardiometabolic health for those with chronic SCI.

Chapter 5 - A single bout of upper-body exercise has no effect on postprandial metabolism in persons with chronic paraplegia

<table>
<tr><td colspan="4">This declaration concerns the article entitled:</td></tr>
<tr><td colspan="4">Chapter 5 - A single bout of upper-body exercise has no effect on postprandial metabolism in persons with chronic paraplegia</td></tr>
<tr><td colspan="4">Publication status (tick one)
Draft manuscript ☐ Submitted ☐ In review ☐ Accepted ☐ Published ✓</td></tr>
<tr><td>Publication details (reference)</td><td colspan="3">Farrow, M., Maher, J., Nightingale, T., Thompson, D. & Bilzon, J. L. J. (2021). A single bout of upper-body exercise has no effect on postprandial metabolism in persons with chronic paraplegia. Medicine & Science in Sports & Exercise, 53(5), 1041-1049.</td></tr>
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<tr><td>Candidate's contribution to the paper (provide details, and also indicate as a percentage)</td><td colspan="3">The candidate contributed to / considerably contributed to / predominantly executed the…

Formulation of ideas:
MF formulated the idea, with input from TN, DT, and JLJB.

Design of methodology:
MF designed the methodology, with input from TN, DT, and JLJB.

Experimental work:
MF recruited all participants, was present on all trial days and led the experimental work. JM and JLJB provided assistance on trial days.

Presentation of data in journal format:
MF wrote the manuscript. JM, TN, DT, and JLJB all revised the manuscript and approved the final article.</td></tr>
<tr><td>Statement from Candidate</td><td colspan="3">This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.</td></tr>
<tr><td>Signed</td><td>Matthew Farrow</td><td>Date</td><td>18/01/2022</td></tr>
</table>

Relevance of Chapter 5 to Thesis

The primary aim of this thesis is to determine the effect of upper-body high-intensity exercise on CVD risk markers in individuals with chronic SCI. To understand the effect of exercise on CVD risk, it is important to not only determine chronic adaptations to prolonged training, but to also understand the effect of a single bout of exercise, given that these chronic adaptations are the cumulative result of multiple single exercise bouts. It is well-established in the general population that a single bout of aerobic exercise can reduce postprandial glucose and TG responses and improve insulin sensitivity in the 24 h post-exercise (Freese, Gist and Cureton, 2014; Sylow and Richter, 2019). These outcomes are important due to their strong relationship with increased CVD risk (O'Keefe and Bell, 2007; Gast et al., 2012). Furthermore, in persons with SCI, there is evidence of impaired ability to dispose of ingested lipids, and high levels of insulin resistance, in comparison to the general population (Gordon, Farkas and Gater, 2021; McMillan et al., 2021a). Therefore, it is particularly important to identify if a single bout of upper-body high-intensity exercise can improve postprandial metabolism in individuals with chronic SCI.

A single bout of upper-body exercise has no effect on postprandial metabolism in persons with chronic paraplegia

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Abstract

Purpose: The acute effects of a single bout of upper-body exercise on postprandial metabolism in persons with spinal cord injury is currently not well understood. The primary aim of this study was to evaluate the effects of a single bout of upper-body high-intensity interval exercise (HIIE) and moderate-intensity continuous exercise (MICE), in comparison to a no-exercise control (REST) condition on postprandial metabolic responses in persons with chronic paraplegia.

Methods: 10 participants (eight males, two females, age: 49 ± 10 yrs, time since injury: 22 ± 13 yrs) with chronic paraplegia took part in a randomised cross-over study, consisting of three conditions: HIIE (8 x 60 s at 70% peak power output (P_{PEAK})), MICE (25 min at 45% P_{PEAK}), and REST, at least 3 days apart. Exercise was performed in the fasted state, and participants consumed a mixed-macronutrient liquid meal 1-h post-exercise. Venous blood and expired gas samples were collected at regular intervals for 6-h post-meal consumption.

Results: There were no significant differences in postprandial iAUC for triglycerides (p=0.59) or glucose (p=0.56) between conditions. Insulin iAUC tended to be lower following MICE (135 ± 85 nmol/L· 360 min^{-1}) compared to REST (162 ± 93 nmol/L · 360 min^{-1}), but this did not reach statistical significance (P=0.06, *d*=0.30). Participants reported a greater fondness (P=0.04) and preference for HIIE over MICE.

Conclusions: Following an overnight fast, a single bout of upper-body exercise before eating, has no effect on postprandial metabolism in persons with chronic paraplegia, irrespective of exercise intensity. This suggests that alternative exercise strategies may be required to stimulate postprandial substrate oxidation for this population.

Key Words: EXERCISE INTENSITY, SPINAL CORD INJURY, INSULIN, GLUCOSE, TRIGLYCERIDES

Introduction

Individuals with a spinal cord injury (SCI) are at an increased risk of developing cardiovascular disease (CVD) in comparison to the non-disabled population (1). As expected, this population present a high prevalence of risk factors associated with CVD, including central adiposity (2), dyslipidaemia (3), and impaired glucose tolerance (4). The role of regular exercise training in the prevention of these CVD risk factors is well-established in non-injured humans, and current SCI-specific exercise guidelines recommend that people with chronic SCI engage in at least 30 minutes of moderate-to-vigorous intensity aerobic exercise three times per week to improve cardiometabolic health (5). Specifically, there is consistent evidence that upper-body moderate-intensity continuous training improves fasting insulin sensitivity and reduces waist circumference in persons with chronic SCI (6). These chronic adaptations are a result of numerous individual bouts of exercise, but the metabolic responses to a single-bout of upper-body exercise in this population are not well understood.

In particular, the effect of a single-bout of upper-body exercise on postprandial metabolism is important to determine as humans spend most of the waking-day in a fed state, with elevated postprandial glucose and triglyceride responses, both independent risk factors for CVD (7, 8). In addition, persons with SCI may have exaggerated postprandial lipaemic and glycaemic responses compared to the non-disabled population, which may partially explain their increased risk of developing CVD (9, 10). A single-bout of moderate-intensity continuous exercise (MICE) (90 min at 50% maximal oxygen update) can decrease the postprandial triglyceride response to a high-fat meal consumed ~12-18 h post-exercise in healthy non-disabled individuals (11). In people with type-2 diabetes, a single bout of MICE performed in the postprandial state can reduce short-term glucose area under the curve and the prevalence of 24-h hyperglycaemia (12). However, it is unclear how a single-bout of upper-body MICE affects subsequent postprandial responses in persons with SCI.

There has been growing interest in high-intensity interval exercise (HIIE) as an alternative solution to MICE to improve cardiometabolic health outcomes in persons with SCI (13). HIIE can be generally characterised as repeated short intervals eliciting ≥80% (but often 85-95%) of maximum heart rate (14). This interest stems

from a randomised controlled trial demonstrating that 180 min/week of MICE is sufficient to improve cardiorespiratory fitness and fasting insulin sensitivity, but not fasting glucose, peripheral insulin sensitivity, or the lipid profile, suggesting a higher exercise intensity is required (15). Training programmes involving HIIE and MICE elicit comparable improvements, in insulin sensitivity, blood pressure, and body composition, in non-disabled overweight and obese individuals (16). Pilot work in individuals with SCI also indicate similar improvements in insulin sensitivity following training programmes involving HIIE and MICE (17). HIIE is particularly appealing given the reduced time commitment and is often cited as more enjoyable than MICE (18). This finding has recently been replicated during upper-body exercise in persons with chronic SCI (19). It also appears that a single bout of HIIE can attenuate the postprandial glucose and triglyceride to meal, to a similar extent as MICE in non-injured humans (20, 21).

Bailey et al. (22) recently reported that postprandial glucose responses were attenuated by regularly breaking up sedentary time with short bouts of moderate-intensity arm crank ergometry in persons with chronic paraplegia. However, to our knowledge, there are no published studies assessing the effect of a single bout of upper-body exercise on subsequent metabolic responses to a mixed-macronutrient test in this population. Therefore, the aim of this study was to evaluate the effects of both an acute bout of upper-body HIIE and MICE, in comparison to a no-exercise control condition (REST) on postprandial metabolic responses to a mixed-macronutrient meal in persons with chronic paraplegia. We hypothesised that HIIE and MICE would be equally and more effective at reducing the total serum triglyceride response in comparison to the no-exercise condition.

Methods

This study was approved by South West (Bristol) National Research Ethics Committee (REC reference number 19/SW/0021). All participants provided written informed consent and the study conformed to the principles of the Declaration of Helsinki. The study was registered as a clinical trial at ClinicalTrials.gov (https://clinicaltrials.gov/) under the identifier NCT04011137.

Participants

We aimed to recruit 11 participants, based on an *a*-priori sample size calculation (Cohen's *d*=0.97, α=0.05, ß=0.80) to detect a significant difference in the total postprandial triglyceride response between HIIE and the no-exercise control condition (20). A total of 13 individuals with chronic paraplegia agreed to take part in this randomised cross-over study, two participants were withdrawn due to difficulties with venous cannulation, and one participant withdrew due to a lack of time, leaving a total of ten participants (eight males, two females) completing all components of the study. Participant descriptive characteristics are presented in Table 1.

C5 Table 1 Participant characteristics (n=10)

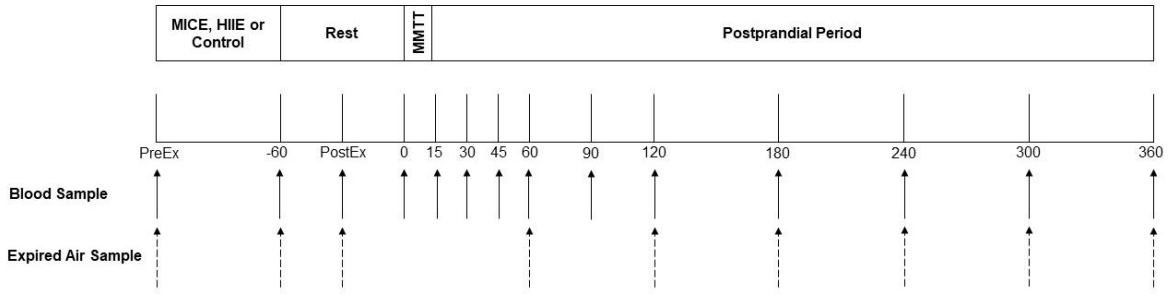
Age (yrs)	49 ± 10
AIS Classification	A: 7, B: 3
LOI	T3-T11 (T3:1, T4:1, T5:1, T6:2, T10:1, T12:4)
TSI (yrs)	22 ± 13
BMI ($kg \cdot m^{-2}$)	28.1 ± 6.2
Waist: Hip	0.94 ± 0.08
PAL	1.50 ± 0.17
$\dot{V}O_2$peak ($mL \cdot min^{-1} \cdot kg^{-1}$)	20.3 ± 5.32
HOMA2-IR	1.29 ± 0.74
Fasting Glucose ($mmol \cdot L^{-1}$)	6.53 ± 1.54
Fasting Triglycerides ($mmol \cdot L^{-1}$)	1.73 ± 1.00

Data presented as Mean ± SD. AIS *American Spinal Injury Association Impairment Scale*, LOI *level of injury*, *TSI time since injury*, BMI *body mass index*, PAL *physical activity level*, $\dot{V}O_{2PEAK}$ *peak oxygen uptake*, HOMA2-IR *homeostatic model assessment for insulin resistance*

Participants were eligible to participate if they met all the following criteria: aged between 18 and 65 years, chronic (>1 yr post-injury) spinal cord lesion at or below the second thoracic level, self-reported wheelchair use of >75% of waking day in individuals with motor-incomplete injuries, and body mass not changed by >3% over the previous three months. Individuals who self-reported the use of lipid lowering agents and/or anti-hyperglycaemic drugs, type 2 diabetes *mellitus* medication, active medial issues (including pressure sores, urinary tract infection, and upper-body musculoskeletal issues) or contraindications to exercise testing were excluded.

Study Design

Participants visited the laboratory on four separate occasions (one pre-experimental visit, three experimental conditions). The pre-experimental procedures included basic anthropometric measurements, an assessment of resting metabolic rate (RMR) and peak aerobic capacity ($\dot{V}O_{2PEAK}$), and HIIE familiarisation session. A sub-maximal exercise test was also performed to allow the individual calibration of a physical activity monitor, which participants wore for a 7-day period commencing immediately following this initial visit. The three experimental conditions (MICE, HIIE, and REST) were then performed in a randomised order, at least 3 days apart. Participants arrived in a fasted state and performed one of the three conditions, which was followed by a 6-h mixed meal tolerance test (MMTT) (Figure 1).



C5 Figure 1 Schematic of experimental conditions (laboratory visits 2-4).

Pre-experimental visit

Participants arrived at the laboratory following an overnight fast (>10 h), having refrained from caffeine and alcohol (24-h prior) and strenuous physical activity (48-h prior). Body mass was measured using platform wheelchair scales (Decto ® BRW1000, Missouri, USA). Supine length, waist and hip circumferences were measured with participant's lying flat on a medical bed. Resting metabolic rate (RMR) was estimated via indirect calorimetry from four 5-minute expired gas samples collected into Douglas Bags (Hans Rudolph, MO, USA) through a mouthpiece. Ambient O_2 and CO_2 fractions, in addition to atmospheric pressure and temperature were measured at close proximity to the participants to account for changes in an enclosed laboratory environment (23). Fractions of expired O_2 and CO_2 were measured using a paramagnetic O_2 and infrared CO_2 analyser (miniMP 5200, Servomex, Crowborough, UK), calibrated with known concentrations of gas on the morning of testing. RMR was calculated using stoichiometric equations (24) and was recorded as the mean of three samples differing by ≤100 kcal · day^{-1}.

A sub-maximal incremental exercise test was then performed on an electronically braked arm-crank ergometer (Lode Angio, Groningen, Netherlands), consisting of four 3-minute stages, starting at 5 W, and increasing by either 10 or 15 W (depending on self-reported fitness). Energy expenditure (using the Douglas Bag method) and heart rate for each stage were used to perform an individual calibration of a chest-worn physical activity monitor (Actiheart^{TM}, Cambridge Neurotechnology Ltd, Papworth, UK) (25). Participants were instructed to wear the device for 7 days to monitor habitual physical activity patterns. Subsequently, physical activity energy expenditure, and physical activity level (PAL) were estimated (26).

Following an adequate rest, participants then performed a $\dot{V}O_{2PEAK}$ test on an electronically braked arm-crank ergometer. The ramp-based protocol included a two-minute warm-up at 10 W before increasing by 1 W every 6 seconds. Before the test, participants were fitted with a rubber-face mask connected to two-way breathing valve, this was connected to a computerised metabolic system (TrueOne® 2400, ParvoMedics, Salt Lake City, UT). The system was calibrated with a known concentration of gas (20% O_2, 8% CO_2) and a 3-L calibration syringe, on the morning of testing. Heart rate and single-breath data were recorded simultaneously on the software throughout the entire test. A cadence of ~75 rpm

was encouraged throughout, and the test was terminated at volitional fatigue or when cadence dropped below 50 rpm. $\dot{V}O_{2PEAK}$ was defined as the highest 15-breath rolling average for $\dot{V}O_2$. Peak power output (P_{PEAK}) was defined as the highest power output achieved before termination of the test. All participants achieved a valid $\dot{V}O_{2PEAK}$ according to the following criteria: peak HR ≥ 95% age-predicted maximum for upper-body exercise (200 b · min^{-1} - Age), rating of perceived exertion (RPE) ≥ 19, and a peak respiratory exchange ratio (RER) ≥ 1.10. Participants then performed a shortened HIIE protocol on the electronically braked arm-crank ergometer, consisting of a one-minute warm-up at 10% P_{PEAK}, followed by four 60-s intervals at 70% P_{PEAK}, interspersed by 60-s recovery intervals at 10% P_{PEAK}. The purpose of this was to familiarise participants with the HIIE protocol. Participants were encouraged to reach a cadence of at least 75 rpm prior to the start of each high-intensity bout.

Experimental conditions

Before all three conditions, participants refrained from strenuous physical activity in the 48-h prior, and consuming alcohol or caffeine in the 24 h prior. Participants arrived at the laboratory at the same time each morning (between 08:00 and 10:00) to minimise diurnal variation, following an overnight fast (>10 h) and having consumed ~1 pint of water on waking. In the two days before the first experimental condition, participants completed a non-weighed food diary, and asked to replicate this before each experimental condition. Each condition was completed within the follicular phase of the menstrual cycle (3-10 days after onset of menses) for the eumenorrheic females taking part in the study.

Upon arrival, body mass was measured, a resting expired gas sample obtained, and a fasting blood sample taken via venepuncture (‘PreEx’) from the antecubital vein. One of three conditions was then performed in a randomised order (≥3 days apart): i) REST - a no-exercise control condition, ii) MICE - 25-min at 45% P_{PEAK}, and iii) HIIE - eight 60-s intervals at 70% P_{PEAK}, interspersed with 60-s recovery intervals at 10% P_{PEAK}. Both exercise protocols began with a 5-min warm-up at 10% P_{PEAK}, and the HIIE condition included a 5-min cool-down at the same intensity. Participants wore a rubber face mask connected to a computerised metabolic system as

previously described. Heart rate, RPE (global, local, and central), and affective valence were recorded at the end of the warm-up (0), 25, 50, 75, and 100% through each exercise condition. Affective valence was measured using the Feeling Scale, whereby participants are asked how they feel at the current moment using an 11-point scale, ranging from, “Very Bad” (-5) to “Very Good” (+5) (27). Expired gases were averaged across 1-minute intervals and total exercise energy expenditure was calculated using published equations for high-intensity exercise (28). When RER exceeded 1.0, energy expenditure was calculated assuming a relationship of 5 kcal utilised for each 1 L of O_2 consumed (29).

Within 30-min of exercise completion, participants completed a modified Physical Activity Enjoyment Scale (PACES) (30). Participants also completed a 5-item questionnaire relating to exercise self-efficacy (31). This measure asked participants to consider how confident they were to be able to perform the exercise protocol (once to five times per week) over the next 4 weeks, with responses ranging from “Not at all” (0%) to “Extremely confident” (100%), in increments of 10%. After completion of both exercise conditions, participants were asked which type of exercise they preferred, and their fondness of each, on a 7-point Likert scale ranging from “Very much dislike” (1) to “Extremely like” (7).

At 30-min post-exercise, expired gas and blood samples were obtained (‘PostEx’), after a cannula was inserted into an antecubital vein. At 60-min post-exercise, participants then consumed a mixed-macronutrient liquid meal that provided a total energy content of 65% RMR, chosen to meet resting energy requirements for the study hours in which no other food was consumed (i.e., ~17 hours). The macronutrient composition (45% calories from carbohydrate, 37% calories from fat, and 18% calories from protein) was designed to reflect that of a typical meal in persons with SCI (32). Participants were given 10-min to consume the meal. Expired gas samples were taken at 60, 120, 180, 240, 300, and 360-min post drink consumption. Blood samples were drawn at 0, 15, 30, 45, 60, 90, 120-, 180-, 240-, and 360-min post meal consumption. All blood samples were taken with the participant’s hand in a heated hand-box (55ºC) (33).

All arterialised blood samples collected (10 mL) were dispensed into treated serum collection tubes, and then centrifuged at 4000 g for 10 min at 4°C. The serum was then apportioned into aliquots, cooled immediately on dry-ice and then stored in a -

80°C freezer for long-term storage before analysis. Serum triglyceride, glucose, NEFA, and glycerol concentrations were determined using an automated analyser (Randox RX Daytona, Co., Antrim, UK). Serum insulin concentrations were determined by commercially available enzyme-linked immunosorbent assay (Mercodia AB, Uppsala, Sweden). Expired gas samples were used to estimate carbohydrate and fat oxidation rates, using previously published equations (24).

Statistical Analysis

Paired t-tests were performed to compare total exercise energy expenditure, exercise enjoyment, exercise self-efficacy, and fondness between MICE and HIIE. The normality of the paired differences was checked using a Shapiro-Wilk test, and if significant, Wilcoxon tests were performed instead. Mixed-model ANOVA's (condition x time) were performed to analyse serum blood analytes (glucose, insulin, triglycerides, non-esterified fatty acids (NEFA), and glycerol) and indirect calorimetry derivates (carbohydrate and fat oxidation rates, and RER) over time. Two-way ANOVA's were used to compare $\%HR_{PEAK}$, RPE, and affective valence over time between MICE and HIIE. One-way repeated ANOVA's were performed to compare the total (TAUC) and incremental area under the curve (iAUC) in the postprandial period (0 to 360 min) for glucose, insulin, and triglycerides, NEFA, and glycerol. Where significant interaction effects were found, Bonferroni comparisons were performed to identify the source of variation. Sphericity was determined with Greenhouse-Geisser epsilon; all values <0.75 were corrected with Greenhouse-Geisser corrections. Statistical significance was accepted at $P \leq 0.05$. All data are presented as mean (lower 95% CI, upper 95% CI) unless otherwise noted. In addition, effect sizes (Cohen's *d*) were calculated, and interpreted as: small effect = 0.20-0.49, medium effect = 0.50-0.79, and large effect ≥0.80.

Results

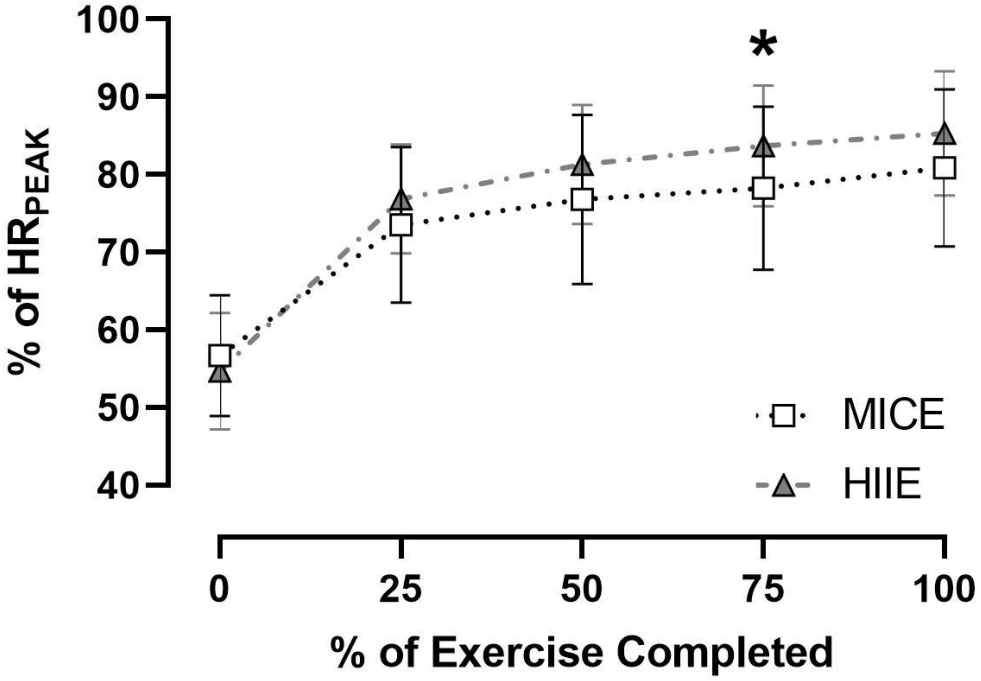
Participant Characteristics

The mean (±SD) $\dot{V}O_{2PEAK}$ of the male (n=8) and female (n=2) participants was 21.4 ± 5.4 $ml \cdot min^{-1} \cdot kg^{-1}$ and 15.8 ± 0.6 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively. Therefore, the fitness classifications of the male participants were poor (n=1), average (n=2), good (n=3), and excellent (n=2) (34). Eight participants (80%) could be classified as a living a sedentary lifestyle (PAL ≤1.60). Nine participants (90%) had a raised fasting glucose concentration (≥5.6 $mmol \cdot L^{-1}$), and four participants (40%) could be classified as having hypertriglyceridemia (fasting triglycerides ≥ 1.7 $mmol \cdot L^{-1}$) (35). Mean (±SD) RMR was 1595 ± 227 $kcal \cdot day^{-1}$, therefore participants consumed a total 1037 ± 148 kcal for the MMTT, consisting of 129 ± 18 g of carbohydrate, 41 ± 6 g of fat, and 42 ± 6 g of protein.

Exercise characteristics

Mean (±SD) P_{PEAK} was 100 ± 28 W. Participants exercised at 45 ± 13 W for the MICE condition which corresponded to an overall exercise intensity of 58 ± 7% $\dot{V}O_{2PEAK}$. During the HIIE condition, participants exercised at 70 ± 20 W and 10 ± 3 W for the 'high' and 'recovery' phases respectively. This corresponded to an overall exercise intensity of 58 ± 8% $\dot{V}O_{2PEAK}$ for the HIIE condition; 57 ± 10% $\dot{V}O_{2PEAK}$ for the 'high' intervals and 59 ± 8% $\dot{V}O_{2PEAK}$ for the 'recovery' intervals.

The mean (±SD) total exercise energy expenditure was greater during MICE (128 ± 24 kcal) compared to HIIE (98 ± 15 kcal, P<0.01). The $\%HR_{PEAK}$ was greater in HIIE compared to MICE at 75% (P=0.02, *d*=0.42) of exercise completion, and tended to be greater at 50% (P=0.08, *d*=0.34) and 100% (P=0.09, *d*=0.35) of exercise completion (Figure 2).



C5 Figure 2 Heart rate (expressed as a % of HR_{PEAK}) at 0, 25, 50, 75, and 100% of exercise completion during MICE and HIIE.

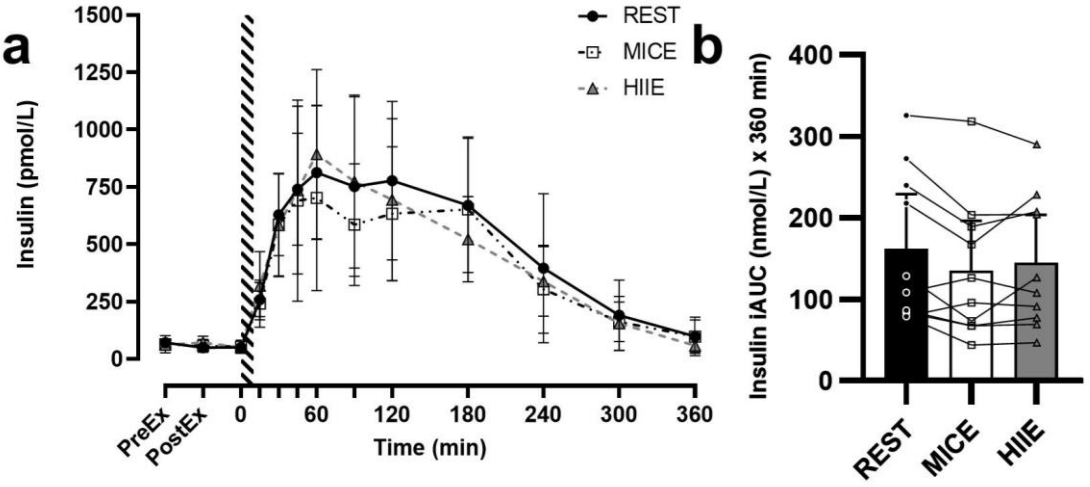
*****indicates significant difference (P≤0.05) between conditions

There were no significant interaction effects between conditions at any time-point for global (P=0.75), local (P=0.94), and central (P=0.73) RPE, or affective valence (P=0.97). There was not a significant difference in enjoyment (mean ± SD) between HIIE (93 ± 14) and MICE (82 ± 23) (P=0.13). However, participants reported a greater fondness (mean ± SD) for HIIE (5.5 ± 1.0) compared to MICE (4.1 ± 1.5) (P=0.04; *d*=1.15). Participant's also reported a higher exercise self-efficacy at being able to perform four (P=0.03; *d*=0.54) and five (P=0.04; *d*=0.33) bouts per week of HIIE compared to MICE. Eight participants stated a preference for the HIIE, and two participants for MICE.

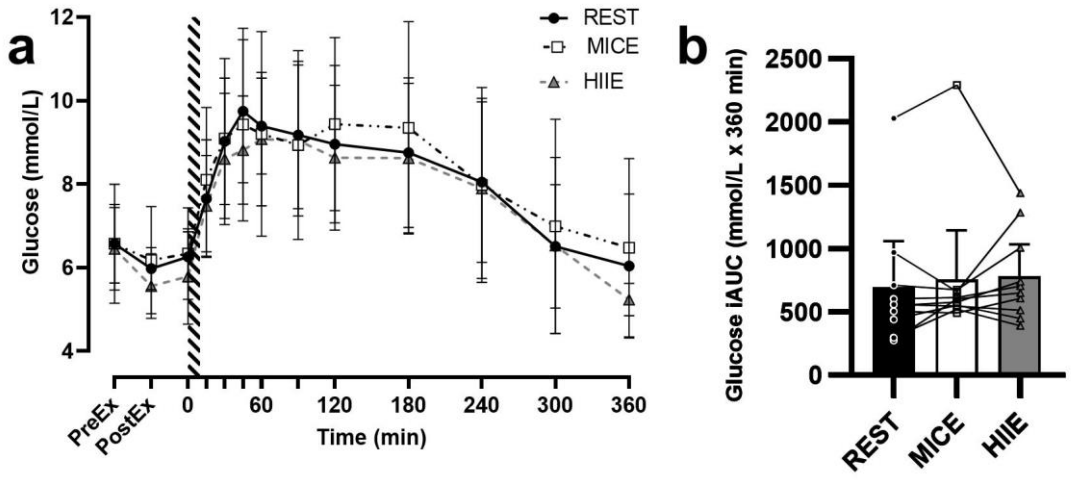
Serum blood analytes

There were no significant interaction effects between conditions at any time-point for serum insulin (P=0.77; Figure 3), glucose (P=0.98; Figure 4), or triglycerides (P>0.99; Figure 5). However, there was a significant effect of condition for glucose (P<0.01; Figure 4), with the mean blood glucose concentration lower for the HIIE

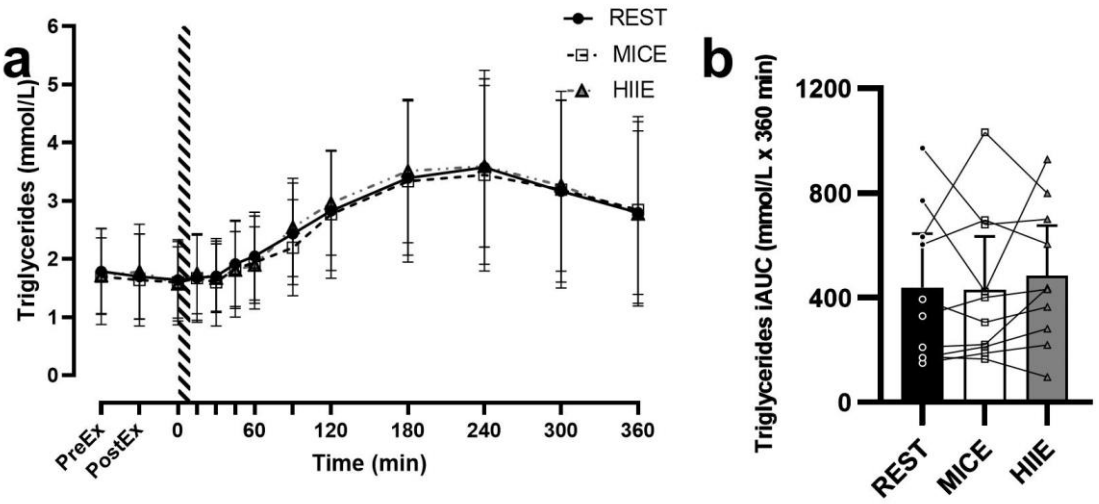
condition, in comparison to the MICE and REST (both P<0.01). Serum insulin TAUC (data not shown, *d*=0.27) and iAUC (*d*=0.30) tended to be lower following MICE compared to REST (both P=0.06) (Figure 3). There were no significant differences between conditions for TAUC (data not shown) or iAUC for glucose (P=0.27 and P=0.56 respectively; Figure 4) and triglycerides (P=0.74 and P=0.59 respectively; Figure 5).



C5 Figure 3 Serum concentrations of insulin (a) across each condition and iAUC (individual responses also denoted) for serum insulin (b) across the 6-h postprandial period following consumption of the MMTT (dashed line).



C5 Figure 4 Serum concentrations of glucose (a) across each condition and iAUC (individual responses are also denoted) for serum glucose (b) across the 6-h postprandial period following consumption of the MMTT (dashed line).



C5 Figure 5 Serum concentrations of triglycerides (a) across each condition and iAUC (individual responses are also denoted) for serum triglycerides (b) across the 6-h postprandial period following consumption of the MMTT (dashed line).

There were no significant interaction effects between conditions at any time-point for serum NEFA or glycerol, although there was a significant effect of condition for glycerol (P=0.01), with mean glycerol concentration higher in the HIIE condition compared to the resting control condition (P=0.02) (data not shown). Additionally, serum NEFA (P=0.20) and glycerol TAUC (P=0.37) did not differ between conditions (data not shown).

Indirect calorimetry

There were no significant interaction effects between conditions at any time-point for fat (P=0.84) and carbohydrate (P=0.71) oxidation rates, or RER (P=0.85). However, there was a significant effect of condition for both fat and carbohydrate oxidation, and RER across the whole condition (all P<0.01). RER was significantly lower in the MICE condition compared to both the HIIE (P=0.02) and resting control condition (P<0.01).

Discussion

The purpose of this study was to determine the effect of prior upper-body exercise (MICE and HIIE) on postprandial responses to a mixed-macronutrient meal in individuals with chronic paraplegia. Contrary to our hypothesis, a single bout of upper-body exercise was insufficient to reduce the subsequent postprandial triglyceride responses in comparison to the no-exercise condition. Despite no differences in postprandial glucose responses, the insulin response tended to be lower following MICE in comparison to the no-exercise REST condition. Participants reported a preference, and a greater fondness and self-efficacy for HIIE compared to MICE.

Upper-body MICE and HIIE had no effect on the subsequent postprandial triglyceride response in comparison to the no-exercise REST condition. This contrasts findings from non-injured populations that a single acute bout of MICE or HIIE performed 12-18 h prior to a standardised meal attenuates the postprandial triglyceride response (11, 36). Although studied less extensively, prior research indicates that this effect appears to still hold true when exercise is performed immediately (≤1-h) prior to the tolerance test (37, 38). However, it appears that the magnitude of this effect is partially dependent on the energy expended during exercise and there may be an exercise energy expenditure threshold needed to elicit changes in postprandial triglycerides (20, 39). Therefore, an insufficient exercise energy expenditure (~100-130 kcal), which is a result of the limited active muscle mass involved in upper-body exercise, may partially explain the lack of change observed in the postprandial triglyceride response in the present study. It is also important to note that following consumption of the liquid meal, participants were initially in a positive energy balance, which appears to diminish the lowering effect of exercise on postprandial triglycerides (20).

There was also no effect of either exercise condition on postprandial glucose responses in comparison to the no-exercise condition. This is perhaps unsurprising, given that studies have demonstrated that 60-min of treadmill walking in the fasted state has no effect on glucose responses to a mixed-macronutrient meal in persons with obesity (37) and hyperglycaemia (40). An increased rate of appearance of glucose from the liquid meal during the initial 3-h post-exercise period is likely to be the reason for the lack of difference in postprandial glucose, offsetting the increased

clearance rate (41). However, it is important to note that Short et al. (42) found that glucose clearance was increased following 35-min moderate-to-vigorous handcycle exercise in adolescents with spina bifida or cerebral palsy. The reasons for this discrepancy with the present study are not immediately clear but may be related to the basal glucose tolerance of participants, and/or differences in the quantity and macronutrient content of the oral tolerance test.

Despite the lack of differences in postprandial glucose following either exercise condition, the insulin iAUC tended (20%, P=0.06) to be lower following MICE compared to the no-exercise REST condition, with eight participants displaying a reduction. Comparatively, Farah & Gill (37) observed a 19% reduction in insulin AUC, but no change in glucose response, when 60-min of walking at 50% maximal O_2 uptake was performed in the fasted state, prior to an 8.5 h postprandial period, in overweight men. It is well-established that even in individuals with insulin-resistance, a single acute bout of aerobic exercise increases insulin sensitivity for up to 24-h (43). Given the curvilinear relationship between exercise energy expenditure and ensuing improvements in insulin sensitivity, it is possible that MICE (128 ± 24 kcal) but not HIIE (98 ± 15 kcal) may be sufficient to induce a change in insulin sensitivity (44).

Whilst there was no significant difference in exercise enjoyment between MICE and HIIE, participants did report a preference for HIIE, in addition to a greater fondness and exercise self-efficacy. Further, despite the higher $\%HR_{PEAK}$ achieved during the HIIE, levels of affective valence during exercise were similar compared to MICE. These findings largely support previous research in habitually active persons with chronic SCI who reported a greater preference and higher enjoyment for HIIE compared to MICE, and no differences in affective valence (19). Given that individuals are more likely to adhere to exercise that they enjoy and are confident they can perform (45), HIIE appears to be a viable training modality for persons with chronic SCI.

A significant strength of this study is that our sample of participants was representative of people with chronic paraplegia (i.e., physically inactive with poor metabolic health). It has been conservatively estimated that almost two thirds of individuals with chronic SCI have cardiometabolic syndrome (46), and in the current study, nine out of the ten participants would be classified as having this condition.

Additionally, the macronutrient content of the MMTT reflected the habitual diet of persons with SCI (21) and allowed for triglyceride concentrations to peak at 4-5 h post-meal consumption without participant's being in a large energy deficit across the day. Finally, the exercise protocols were matched for total time commitment, and represented realistic and achievable exercise sessions for this population, that closely match the SCI-exercise guidelines (5, 19). For example, in a free-living environment, persons with chronic paraplegia perform an average of just 17 min per day of moderate-to-vigorous physical activity (47), which is less than both MICE and HIIE conditions. Therefore, we believe our findings have considerable real-world relevance.

The main limitation of this study is that despite the exercise protocols matching those previously characterised is this population (19), there was no difference in $\%\dot{V}O_{2PEAK}$ between MICE and HIIE, and the $\%HR_{PEAK}$ achieved was only marginally higher for HIIE. It is possible that a more vigorous exercise intensity during the HIIE condition may have elicited changes in postprandial metabolism. Additionally, we did not match the MICE and HIIE conditions for energy expenditure, and therefore the total energy expenditure of MICE was ~30 kcal greater than HIIE. Thirdly, due to participant drop-out, we failed to reach our target sample size of 11, however based on the observed effect size (d=0.04) for our primary outcome (triglyceride TAUC) between HIIE and REST, one extra participant would not have meaningfully changed our findings regarding postprandial triglyceride responses. Finally, the MMTT contained a large bolus of calories (1037 ± 148 kcal), which isn't typically consumed in a habitual diet. Whilst a more ecologically valid approach would have been to study responses to a typical breakfast and lunch meal, the total energy consumed ensured participants resting energy requirements were met.

There remain large knowledge gaps with regards to the effect of a single-bout of upper-body exercise on postprandial metabolism in persons with chronic SCI. To address this, future studies should assess the effect of exercise performed the evening prior to a MMTT, as the activity of the enzyme (lipoprotein lipase) believed to be primarily responsible for exercise-induced reductions in postprandial triglycerides peaks at 8-h post-exercise in skeletal muscle (48). However, we speculate that any localised activation of lipoprotein lipase, is unlikely to result in a reduction in the postprandial triglyceride response, given the limited active muscle

mass involved in upper-body exercise. Additionally, both HIIE and MICE performed in the postprandial state appear to improve 24-h glucose profiles in a free-living environment in non-injured populations (49, 50), and it would be useful to understand if this effect is still present in persons with chronic SCI. Finally, we only recruited individuals with paraplegia, but this work should also be expanded to individuals with tetraplegia, who experience an early onset of exercise fatigue due to cardiovascular impairments.

Conclusions

Following an overnight fast, acute upper-body exercise is not sufficient to improve subsequent postprandial responses to a large mixed-macronutrient meal in persons with SCI, irrespective of exercise intensity. This is likely due to the substantially lower active muscle mass and consequently reduced energy expenditure that can be achieved during upper-body exercise compared to whole and/or lower-body exercise. These findings highlight the need to identify alternative strategies to stimulate postprandial substrate oxidation in this population, including maximising exercise energy expenditure (e.g., combining upper-body exercise with functional electrical stimulation cycling and/or resistance training), combining exercise with dietary restriction, or performing regular bouts of activity throughout the day.

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Conflicts of Interest

All authors have no conflicts of interest to declare and acknowledge that the results of the present study do not constitute endorsement by the American College of Sports Medicine, and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Relevance of the Findings from Chapter 5 to Thesis

This study found that a single-bout of upper-body HIIE in the fasted state had no effect on postprandial metabolism following the ingestion of a MMTT in individuals with chronic paraplegia. These findings are noteworthy and relevant to the focus of this thesis, as unlike consistent findings from the general population (Freese, Gist and Cureton, 2014; Cassidy et al., 2017) upper-body HIIE was not effective at ameliorating important CVD risk factors, namely postprandial glycaemic and lipaemia (O'Keefe and Bell, 2007). Similarly, in contrary to well-controlled studies in the general population, upper-body HIIE also offered no acute insulin-sensitising effect (Fisher et al., 2019; Ryan et al., 2020), which is significant due to the link between insulin resistance and CVD risk (Gast et al., 2012).

Importantly, these findings have been replicated in a recent study employing similar methods to the study presented in this chapter (McMillan et al., 2021c). McMillan et al. (2021c) reported no differences in glucose, insulin, or TG iAUC across the 2.5 h postprandial period following arm crank exercise (both MICE and HIIE) and circuit resistance exercise, in comparison to a resting control condition. Despite differences in the total energy content (1037 ± 148 kcal vs 600 kcal), the macronutrient composition of the MMTT was identical to the study presented in this chapter. Therefore, it can be concluded with relative confidence that upper-body high-intensity exercise has no effect on metabolic responses when performed immediately prior to a MMTT in individuals with chronic SCI.

Chapter 6 - Prior arm crank exercise has no effect on postprandial lipaemia in non-disabled adults

This declaration concerns the article entitled:			
Chapter 6 - Prior arm crank exercise has no effect on postprandial lipaemia in non-disabled adults			
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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate contributed to / considerably contributed to / predominantly executed the… Formulation of ideas: MF formulated the idea with input from JLJB. Design of methodology: MF designed the methodology. Experimental work: MF recruited the majority of participants, was present on all trial days and led the experimental work. JM, JO, and SK provided assistance on trial days. Presentation of data in journal format: MF wrote the manuscript. JM, JO, SK, DT, and JLJB all revised the manuscript and approved the final article.		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	Matthew Farrow	**Date**	9/03/2022

Relevance of Chapter 6 to Thesis

In Chapter 5, we demonstrated that upper-body HIIE and MICE had no effect on postprandial metabolism when performed 1 h prior to a MMTT in persons with chronic paraplegia. However, studies reporting a reduction in PPL following an acute bout of exercise have typically employed a study design whereby exercise is performed 12-18 h prior (e.g. the evening prior) to the test meal (Freese, Gist and Cureton, 2014). This is due to the mechanisms linked to reductions in PPL (i.e., LPL expression/activation) following exercise, which appear to peak >8 hours following exercise (Seip et al., 1997). Furthermore, exercise performed 12 h before the assessment of PPL has been shown to reduce TG concentrations to a greater extent than exercise performed 1 h prior (Zhang, Thomas and Ball, 1998). Therefore, in this Chapter we sought to determine if upper-body HIIE performed the evening prior to the MMTT was effective at reducing PPL. We decided to test this hypothesis in non-injured individuals to reduce the heterogeneity in responses we observed in Chapter 5, which were likely a result of injury characteristics (i.e., level and completeness of injury). By recruiting a sample of healthy, non-injured adults we were also able to carefully control for other potential confounding variables, including exercise EE and pre-condition diet.

In Chapter 5, the exercise EE of the HIIE and MICE conditions were not matched (MICE was ~30 kcal greater than HIIE), as this would have required an additional participant visit. This is a potential confounding variable as the magnitude of the PPL lowering effect of exercise appears to partially dependent on the energy expended during exercise (Maraki and Sidossis, 2013; Freese, Gist and Cureton, 2014). In Chapter 6, we were able to include an additional pre-experimental condition, and therefore were able to calculate the expected EE of HIIE and consequently calculate the duration of MICE required to elicit the same total exercise EE.

In Chapter 5, we were not able to carefully standardise pre-condition diet which may have increased the heterogeneity of postprandial responses. For example, the ratio of carbohydrate to fat in an evening meal has been shown to effect PPL responses the following morning (Robertson et al., 2002). In Chapter 6, we provided participants with weighing scales to record their pre-condition food for the first main visit so that this could be replicated exactly for the remaining two visits. We also

provided a standardised evening meal to participants to ensure the final meal had no effect on consequent MMTT responses between participants.

Finally, in Chapter 5 the $\%HR_{PEAK}$ elicited by the HIIE was lower than expected and did not exceed 80% HR_{PEAK} until 50% of the protocol was completed. Therefore, in Chapter 6, we increased the intensity of the high-intensity work intervals from 70% to 80% PPO. We performed pilot work to determine a challenging but achievable workload for the HIIE condition, with the aim of increasing the $\%HR_{PEAK}$ elicited.

Prior arm crank exercise has no effect on postprandial lipaemia in non-disabled adults

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Abstract

A single bout of cycling or running performed in the evening can reduce postprandial lipaemia (PPL) the following morning, although this is currently unknown for upper-body exercise. The aim of this study was to determine if a bout of arm crank exercise (high-intensity interval [HIIE] or moderate-intensity continuous [MICE]), can attenuate PPL in non-injured individuals. Eleven healthy and recreationally active participants (eight males, three females; age: 27 ± 7 yr; body mass index: 23.5 ± 2.5 kg · m^{-2}) volunteered to participate in three conditions: HIIE (10 x 60 s at 80% peak power output), MICE (50% peak power output of isocaloric duration), and a no-exercise control condition. Each exercise bout was performed at 18:00, and participants consumed a standardized evening meal at 20:00. Following an overnight fast, a 5-h mixed-macronutrient tolerance test was performed at 08:00. There were no significant differences in triglyceride incremental area under the curve between HIIE (192 ± 94 mmol. L^{-1} per 300 min), MICE (184 ± 111 mmol. L^{-1} per 300 min), and the no-exercise condition (175 ± 90 mmol. L^{-1} per 300 min) (P=0.46). There were no significant differences in incremental area under the curve for glucose (P=0.91) or insulin (P=0.59) between conditions. Upper-body MICE and HIIE performed in the evening do not influence PPL the following morning, in normotriglyceridemic individuals.

Clinical Trials Registration: NCT04277091

Novelty:

- Arm crank exercise has no effect on PPL when performed the evening prior to a mixed-macronutrient meal test
- Upper-body sprint interval exercise should be investigated as a potential solution to reduce PPL

Keywords: exercise intensity, arm crank ergometry, postprandial metabolism, triglycerides, glucose, insulin

Introduction

Individuals presenting with elevated non-fasting triglycerides or exaggerated postprandial lipaemia (PPL) have an increased risk of cardiovascular disease and mortality (Nordestgaard et al., 2007). Whilst the exact mechanism for this is unknown, the increased circulation of triglyceride-rich lipoproteins following the ingestion of a high-fat meal, results in a cascade of events that leads to plaque build-up within the vascular endothelium, causing atherosclerosis (Nordestgaard et al., 2007; Zilversmit, 1979). The modern-day Western diet features a large volume of processed foods, high in saturated fats, and individuals can spend ~18 hours per day in a postprandial state (Ruge et al., 2009). Therefore, it is pertinent to identify strategies to reduce PPL, and consequently reduce an individual's cardiovascular disease risk.

It has been consistently demonstrated that a single bout of aerobic exercise of low to moderate intensity (commonly defined as 45-70% HR_{MAX}) performed within 24 h of a high-fat meal is effective at reducing PPL (Freese et al., 2014; Peddie et al., 2012). The magnitude of this effect is moderated by sex, exercise intensity, and energy deficit following exercise (Freese et al., 2014). Exercise performed immediately before eating is likely to reduce PPL via a reduction in hepatic secretion of very-low density lipoproteins (Gill & Hardman, 2003). Exercise performed 12-18 h prior to a meal is likely to reduce PPL due to, at least in part, an increase in triglyceride hydrolysis, stimulated by an upregulation in muscle lipoprotein lipase (LPL) activity (Gill & Hardman, 2003). A meta-analysis revealed that high-intensity interval exercise (HIIE; >90% HR_{MAX}) (*d*=1.49) induced a greater attenuation of PPL than MICE (*d*=0.58) (Freese et al., 2014), and this finding has been confirmed with direct observations (Kruger et al., 2016). Given the emergence of HIIE as a viable and efficacious alternative to moderate-intensity continuous exercise (MICE) for protecting cardiometabolic health (Campbell et al., 2019), several studies have also indicated that HIIE may be more effective than MICE for improving postprandial lipid metabolism (Lee et al., 2018; Trombold et al., 2013).

To date, studies that have assessed the effect of an acute bout of exercise on PPL have been largely limited to whole- and lower-body exercise modalities (e.g., running and cycling). These modalities may not be possible for a wide range of individuals who are non-ambulatory, and who have a heightened risk of developing

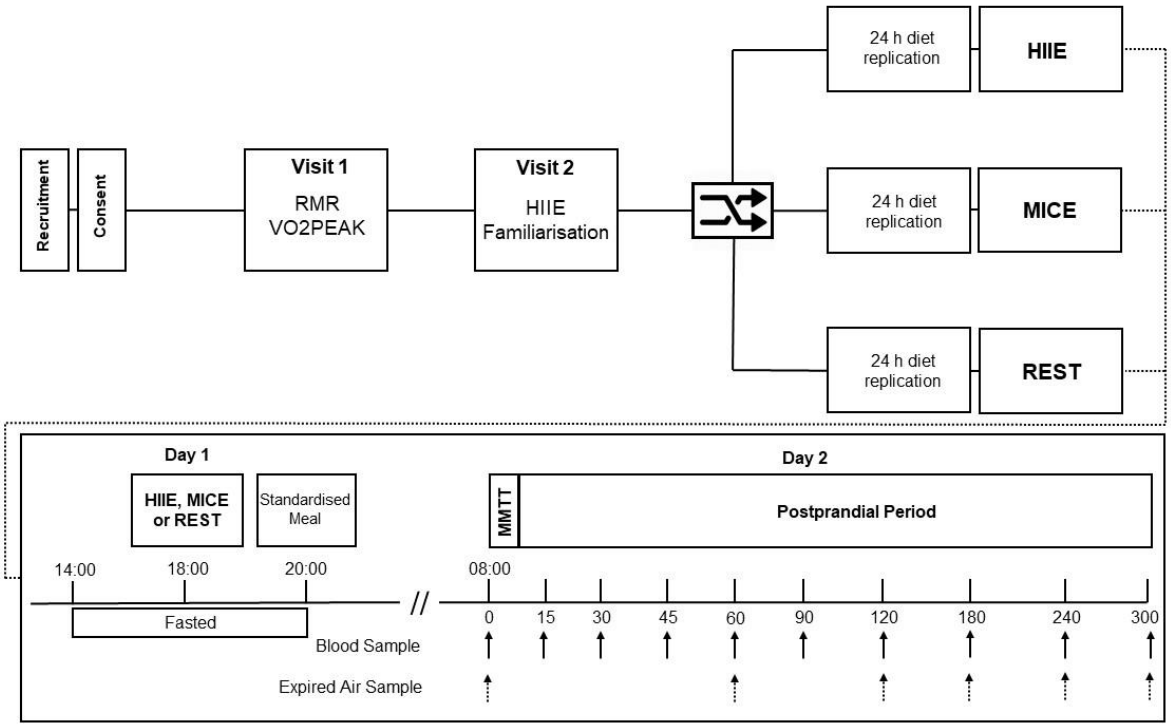
cardiovascular disease, including those with spinal cord injuries (SCI, Cragg et al., 2013), lower-limb amputations (Malyar et al., 2016), osteoarthrosis (Turkiewicz et al., 2019), and cerebral palsy (Ryan et al., 2019). The limited evidence suggests that upper-body exercise is not sufficient to reduce PPL if the meal tolerance test is performed within 1-h of exercise completion. In persons with a chronic SCI, two studies have demonstrated that arm-crank ergometry based MICE and HIIE prior to consuming a mixed-macronutrient meal have no effect on PPL (Farrow et al., 2021; McMillan et al., 2021). Furthermore, regularly breaking up sitting time with shorts bouts of moderate-intensity arm crank ergometry across a 5.5 h period in the same population has no effect on PPL assessed concurrently (Bailey et al., 2020). However, to date, there are no studies that have assessed the effect of upper-body exercise performed 12-18 h prior to a test meal. Seminal work by Zhang et al. (1998) on the role of exercise timing revealed that exercising 12 h before PPL assessment may have a better overall effect on triglyceride concentrations compared to exercise performed 1 h before. Furthermore, the expression of LPL, believed to be a primary mechanism for PPL reductions, peaks >8 hours following exercise completion (Seip et al., 1997). Therefore, it is important to determine the effect of upper-body exercise performed the evening prior to an assessment of PPL.

The primary aim of this study was to determine if a single bout of arm crank ergometry (MICE or HIIE) performed the evening prior to a mixed-macronutrient meal test can attenuate PPL in comparison to a no-exercise control condition (REST). We hypothesized that upper-body HIIE would significantly reduce the PPL in comparison to REST. This study was performed in healthy non-injured individuals to minimize heterogeneity in participant characteristics (e.g., type of injury, level of injury, time since injury, age) that are likely to influence PPL responses.

Methods

Study Design

This randomized cross-over design study was approved by the University of Bath's Research Ethics Approval Committee for Health and registered on ClinicalTrials.gov (https://clinicaltrials.gov/) under the identifier NCT04277091. All participants provided written informed consent, and the study conformed to the principles of the Declaration of Helsinki. Participants attended the laboratory for pre-experimental procedures on two separate occasions and all took part in three main experimental conditions. The first pre-experimental visit involved an assessment of resting metabolic rate (RMR) and peak aerobic capacity ($\dot{V}O_{2PEAK}$). On the second occasion, participants performed a HIIE bout to calculate the isocaloric duration of MICE. The three experimental conditions (HIIE, MICE, and REST) were then performed in a randomized order, at least 3 d apart. Exercise was performed the evening prior to a 5-h mixed macronutrient tolerance tests (MMTT) the following morning (Figure 1).



C6 Figure 1 Study overview

RMR; *resting metabolic rate*, VO2PEAK; *peak aerobic capacity*, HIIE; *high-intensity interval exercise*, MICE; *moderate-intensity continuous exercise*; MMTT; *mixed macronutrient tolerance test*

Participants

Eleven recreationally active individuals (eight males, three females) completed all components of the study. Participant descriptive characteristics are presented in Table 1. Participants were eligible to take part if they were between 18 and 65 yr old, a non-smoker, and had no history of cardiovascular, metabolic, or neuromuscular disease, and self-reported no contraindications to exercise testing. Participants completed an International Physical Activity Questionnaire (IPAQ) to determine habitual physical activity levels. An *a priori* sample size calculation revealed a total of 11 participants were needed to detect a significant difference in the total postprandial triglyceride responses between HIIE and REST conditions (Freese et al., 2014).

C6 Table 1 Participant characteristics

	Males (*n* = 8)	**Females (*n* = 3)**	**All (*n* = 11)**
Age (y)	28 ± 11	23 ± 2	27 ± 7
BMI (kg·m^{-2})	23.4 ± 2.9	23.7 ± 2.9	23.5 ± 2.5
$\dot{V}O_{2PEAK}$ (mL^{-1}·kg^{-1}·min^{-1})	33.6 ± 5.52	24.0 ± 3.45	31.0 ± 6.62
P_{PEAK} (W)	134 ± 16	85 ± 5	120 ± 27
RMR (kcal·day^{-1})	1896 ± 159	1862 ± 230	1887 ± 168
Total METs (min·week^{-1})	2759 ± 1172	5147 ± 1048	3410 ± 1557

Data presented as mean ± SD. BMI, *body mass index*; $\dot{V}O_{2PEAK}$, *peak oxygen uptake*; P_{PEAK}, *peak power output*; RMR, *resting metabolic rate*; METs, *metabolic equivalents*

Pre-experimental visits

On the first visit, participants arrived at the laboratory after an overnight fast (>10 h), having refrained from caffeine and alcohol ingestion (24 h prior), and strenuous physical activity (48 h prior). Height was measured using a stadiometer (Seca 214, Leicester Height Measure; Seca GmbH & Co, Hamburg, Germany) and body mass measured using electronic scales (BC-543, Tanita, Tokyo, Japan). Resting metabolic rate (RMR) was estimated via indirect calorimetry from three 5-min

expired gas samples collected into Douglas Bags (Hans Rudolph, Kansas City, MO, USA) through a mouthpiece. Participants rested in a recumbent position, with ambient O_2 and CO_2 fractions recorded, in addition to atmospheric pressure and temperature. A paramagnetic O_2 and infrared CO_2 analyzer (miniMP 5200; Servomex, Crowborough, UK), calibrated with known concentrations of gas, was used to measure fractions of ambient and expired O_2 and CO_2. RMR was calculated using stoichiometric equations (Frayn, 1983) and recorded as the mean of three samples differing by ≤100 kcal·d^{-1}.

Participants then performed a ramp-based protocol on an electronically braked arm-crank ergometer (Lode Angio, Groningen, Netherlands) to determine peak oxygen uptake ($\dot{V}O_{2PEAK}$). The test involved a 2-min warm-up at 10 W before increasing by 1 W every 6 s. Single-breath data were recorded throughout using a two-way mouthpiece connected to a computerized metabolic system (TrueOne® 2400; ParvoMedics, Salt Lake City, UT, USA). The system was calibrated with a known concentration of gas (20% O_2, 8% CO_2) and a 3-L calibration syringe. Participants were encouraged to maintain a cadence of ~75 rpm, and the test was terminated at volitional fatigue or when cadence dropped below 50 rpm. Peak power output (P_{PEAK}) was defined as the highest power output reached before termination of the test. $\dot{V}O_{2PEAK}$ was defined as the highest 15-breath rolling average for $\dot{V}O_2$. All participants achieved a valid $\dot{V}O_{2PEAK}$ according to the following criteria: peak HR ≥ 95% age-predicted maximum for upper-body exercise (200 b · min^{-1} - Age), rating of perceived exertion (RPE) ≥ 19, and a peak respiratory exchange ratio (RER) ≥ 1.10.

On the second visit, participants arrived at the laboratory having refrained from any food (>4 h), caffeine and alcohol ingestion (24 h prior). Participants completed a HIIE familiarization bout consisting of 10 x 60-s intervals at 80% P_{PEAK}, interspersed with 60-s recovery intervals at 10% P_{PEAK}, and including a 5-min warm-up and cool-down at the 10% P_{PEAK}. Participants wore a rubber face-mask connected to the same computerized metabolic system as described above throughout the entire exercise protocol. Energy expenditure (kcal) was calculated across 1-min intervals using a published equation ($0.55*VCO_2 + 4.471*VO_2$) for high-intensity exercise (Jeukendrup & Wallis, 2005). When RER exceeded 1.0, energy expenditure was calculated using an assumed relationship of 5 kcal used for each 1 L of O_2

consumed (Williams et al., 2013). A linear regression was performed between workload and VO_2 during the $\dot{V}O_{2PEAK}$ test and used to calculate the duration of MICE required to elicit a comparable total exercise energy expenditure as HIIE.

Experimental conditions

Participants refrained from performing strenuous exercise in the 48-h prior (i.e., day 0 and 1), or consuming alcohol and caffeine in the 24-h prior (i.e., day 1) for all three conditions. Conditions were completed within the follicular phase on the menstrual cycle (3-10 d after onset of menses) for eumenorrheic females. Participants completed a weighed food diary on day 1 which was replicated for each subsequent condition.

At 18:00 on day 1, and having fasted for 4-h, participants completed one of three experimental conditions in a randomized order: (i) REST – a no-exercise control condition, (ii) HIIE – ten 60-s intervals at 80% P_{PEAK}, interspersed with 60-s recovery intervals at 10% P_{PEAK}, and (iii) MICE – 50% P_{PEAK} at isocaloric duration. Both exercise protocols consisted of a 5-min warm-up and cool-down at 10% P_{PEAK}, with participants instructed to maintain a constant cadence at each workload. Heart rate was recorded at the end of the warm-up (0), 20, 40, 60, 80 and 100% through each exercise condition. Participants were asked to refrain from ingesting any food that evening, other than a standardised meal (Tesco® Spinach & Ricotta Cannelloni, Trek Protein Cocoa Coconut Flapjack; 697 kcal: 77 g carbohydrate, 28 g fat and 33 g protein) at 20:00.

Participants arrived at the laboratory the following morning (i.e., day 2) at 08:00 having refrained from any additional food intake (i.e., 12-h fast). Body mass was measured, and a cannula was inserted into an antecubital vein. Participants consumed a mixed-macronutrient liquid meal that provided a total energy content of 65% RMR, with 45% of calories from carbohydrate, 37% of calories from fat, and 18% of calories from protein. The meal consisted of banana, peanut butter (Jif Creamy Peanut Butter, The J.M. Smucker Company, US), coconut oil (Vita Coco Extra Virgin Coconut Oil, All Market Europe Ltd, UK), unflavoured maltodextrin powder (MyProtein, Manchester, UK) and chocolate-flavoured whey protein powder (Optimum Gold Standard Double Rich Chocolate Whey, Optimum Nutrition,

Ireland). Expired gas samples were collected immediately prior (“Pre”) and 60, 120, 180, 240, and 300 min after drink consumption, using the Douglas Bag technique. Blood samples were collected immediately prior (0), and 15, 30, 45, 60, 90, 120, 180, 240, and 300 min after drink consumption. All blood samples were arterialized with the participant’s hand placed in a heated box (55°C) (Edinburgh et al., 2017).

All arterialized blood samples (5 mL) were dispensed into treated serum collection tubes, left to clot at room temperature for 15 min, and then centrifuged at 4000g for 10 min at 4°C. The serum was then apportioned into aliquots, cooled immediately on dry ice, and then stored in a -80°C freezer for long-term storage before analysis. An automated analyzer (Randox RX Daytona, Co. Antrim, UK) was used to determine serum triglyceride and glucose concentrations. An enzyme-linked immunosorbent assay (Mercodia AB, Uppsala, Sweden) was used to determine serum insulin concentrations. Carbohydrate and fat oxidation rates were estimated from expired gas samples, using previously published equations (Frayn, 1983).

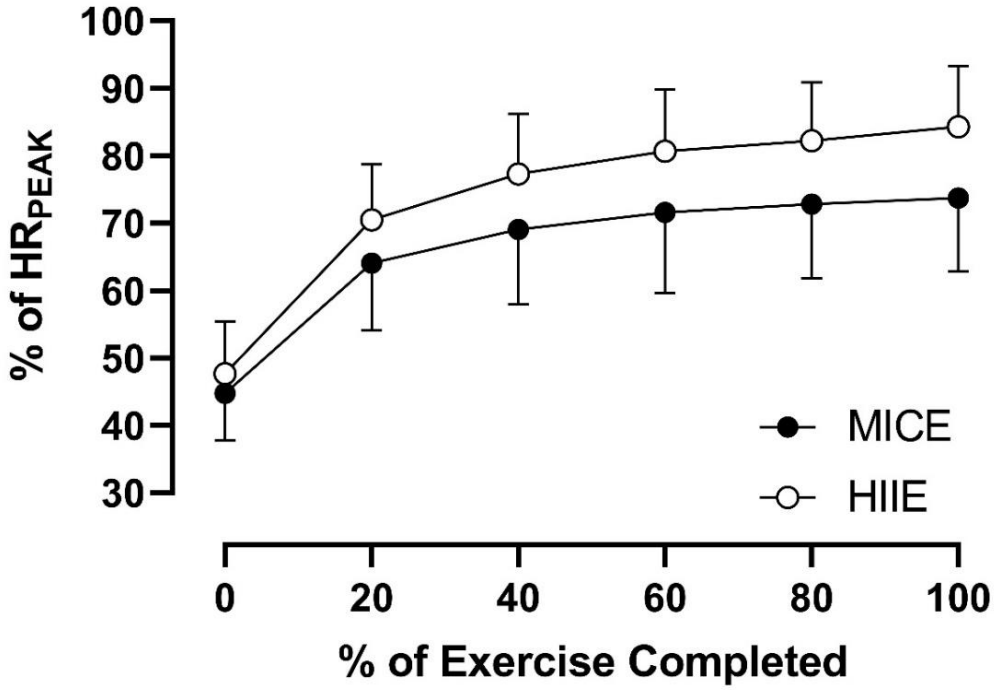
Statistical analyses

A series of mixed-model two-way Analysis of Variance (ANOVA) tests (condition x time) were performed to analyze serum blood analytes (triglycerides, glucose, and insulin) and indirect calorimetry derivatives (carbohydrate and fat oxidation rates) over time. One-way repeated measures ANOVAs were performed to compare the total and incremental area under the curve for serum triglycerides, glucose, and insulin, and carbohydrate and fat oxidation (Narang et al., 2020). Statistical significance was accepted at $P \leq 0.05$. All data are presented as mean ± SD unless otherwise stated.

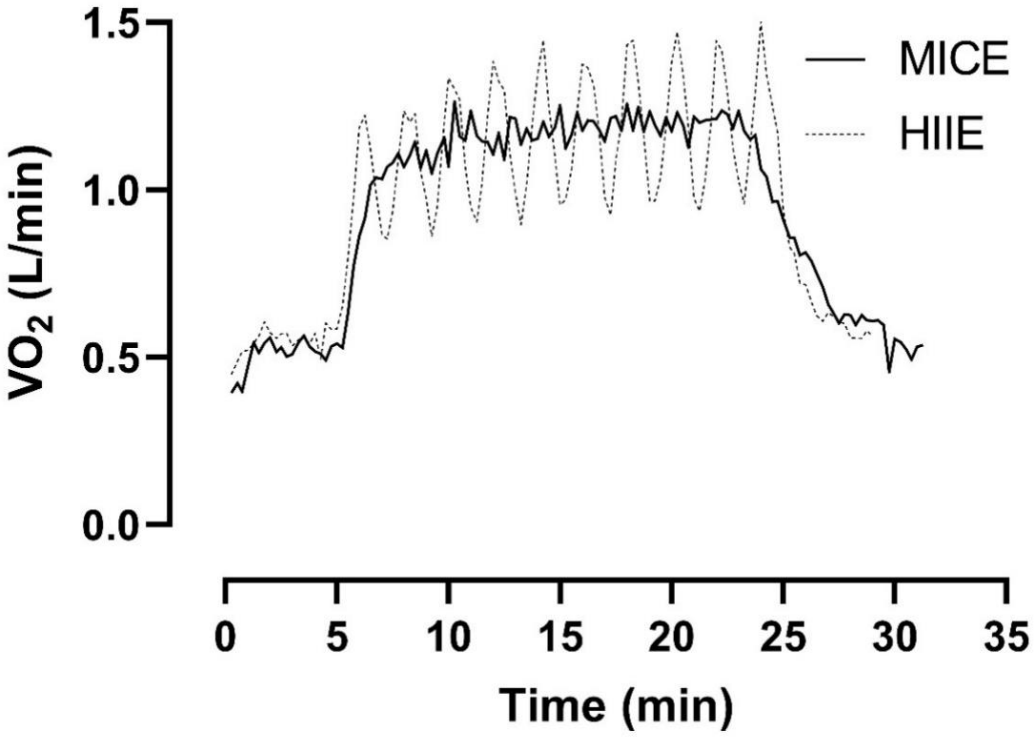
Results

Exercise characteristics

The mean P_{PEAK} was 134 ± 16 W, and participants exercised at 96 ± 21 W and 67 ± 8 W for the HIIE ('high' bouts) and MICE bouts respectively. Participants expended 141 ± 21 and 141 ± 28 kcal during the HIIE and MICE bouts (P=0.96), respectively. Participants exercised at a higher $\%HR_{PEAK}$ during HIIE compared to MICE (P=0.05; Figure 2). Mean $\dot{V}O_2$ was 0.97 ± 0.15 L · min^{-1} and 0.96 ± 0.02 L · min^{-1} for HIIE and MICE respectively (Figure 3).



C6 Figure 2 Heart rate (expressed as a % of HR_{PEAK}) at 0%, 20%, 40%, 60%, 80%, and 100% of exercise completion during MICE and HIIE



C6 Figure 3 Oxygen uptake (averaged across all participants) for MICE and HIIE conditions

Energy intake

On day 1, participants consumed an average of 2352 ± 600 kcal (including the standardised meal), consisting of 453 ± 619 g of carbohydrate, 92 ± 27 g of fat, and 99 ± 33 g of protein. For the MMTT, participants consumed an average of 1221 ± 103 kcal, consisting of 151 ± 13 g of carbohydrate, 48 ± 4 g of fat, and 49 ± 4 g of protein.

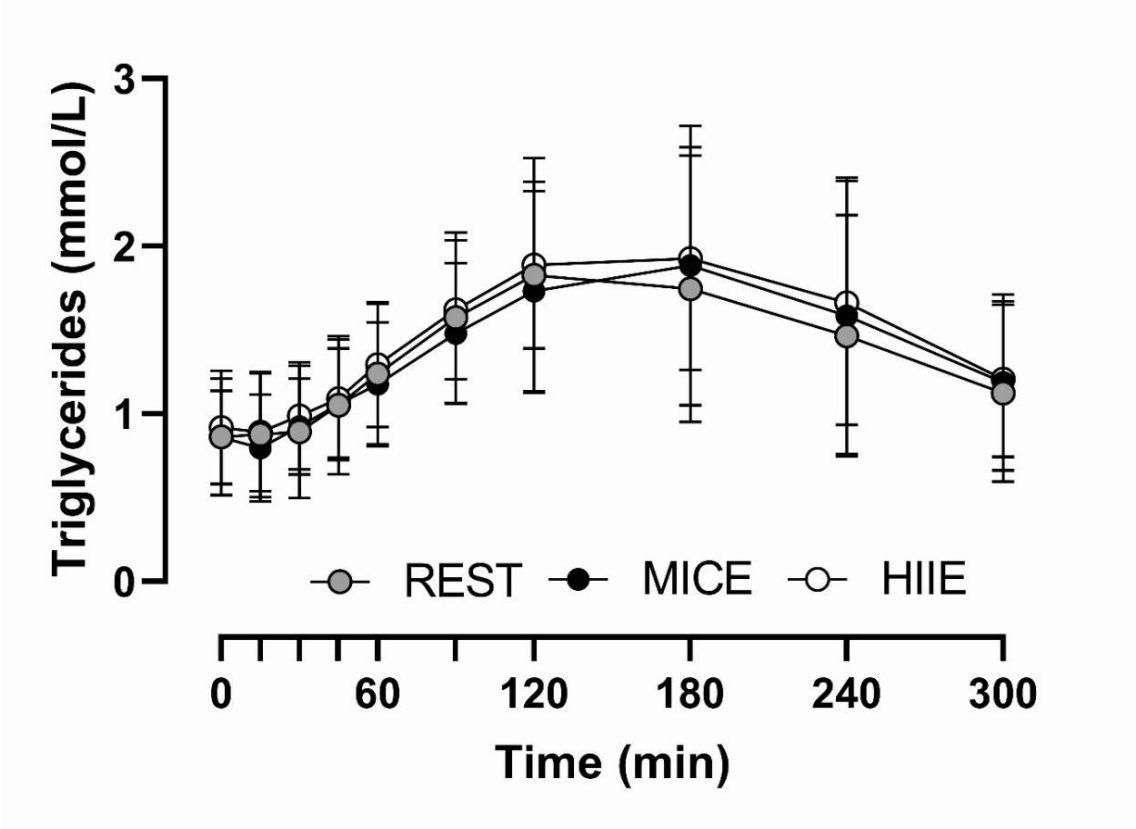
C6 Table 2 Serum blood markers and substrate oxidation rates at baseline for REST, MICE, and HIIE conditions

	REST	MICE	HIIE	*P*
Fasting triglycerides	0.86 ± 0.35	0.86 ± 0.28	0.92 ± 0.34	0.64
Fasting glucose (mmol·L^{-1})	5.09 ± 0.54	5.04 ± 0.37	4.94 ± 0.57	0.52
Fasting insulin (pmol·L^{-1})	26.7 ± 12.5	24.4 ± 11.5	29.5 ± 13.8	0.45
Carbohydrate oxidation	0.10 ± 0.07	0.10 ± 0.06	0.08 ± 0.05	0.45
Fat oxidation (g·min^{-1})	0.09 ± 0.02	0.10 ± 0.03	0.11 ± 0.03	0.15

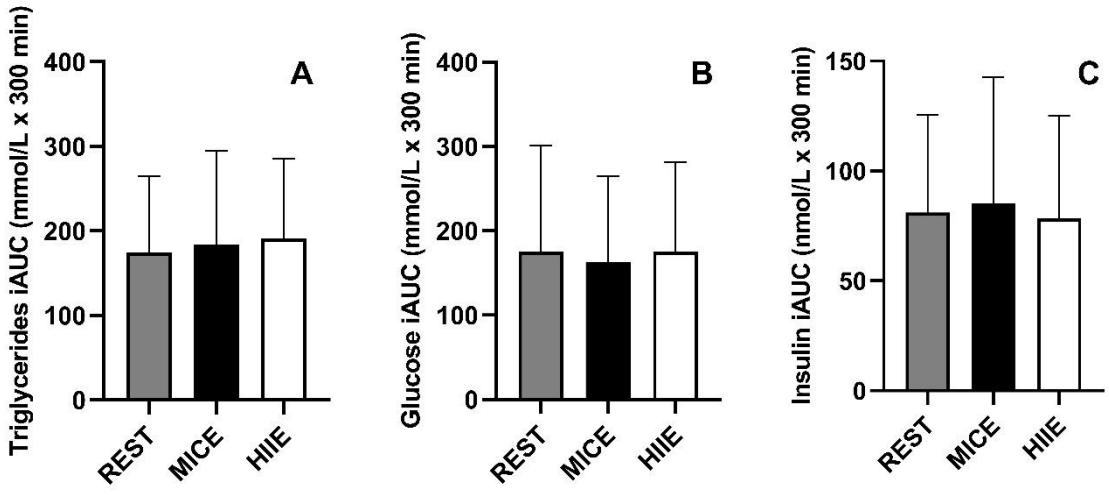
Data presented as Mean ± SD

Postprandial metabolism

There were no differences in fasting triglycerides, glucose, and insulin concentrations or carbohydrate and fat oxidation rates at baseline (Table 2). There were no significant interaction effects between conditions at any time point for serum triglycerides (P=0.99; Figure 4), glucose (P=0.86), or insulin (P=0.98). There were no significant differences in incremental area under the curve (iAUC) between conditions for triglycerides (P=0.46), glucose (P=0.91), or insulin (P=0.59) (all Figure 5). There were no significant differences in total area under the curve (TAUC) between conditions for triglycerides (P=0.39), glucose (P=0.28), or insulin (P=0.71). There were no significant interaction effects between conditions at any time point for carbohydrate oxidation (P=0.85) or fat oxidation (P=0.69). There were no significant differences in iAUC or TAUC for carbohydrate (P=0.71 and P=0.50) and fat oxidation (P=0.54 and P=0.50).



C6 Figure 4 Serum concentrations of triglycerides after consumption of the MMTT for REST, MICE, and HIIE conditions



C6 Figure 5 Incremental area under the curve (iAUC) for serum triglycerides (A), glucose (B), and insulin (C) after consumption of the MMTT.

Discussion

The purpose of this study was to determine if different intensities of arm-crank ergometry exercise were effective at attenuating PPL in healthy adults. Contrary to the hypothesis, HIIE or MICE performed the evening prior to a mixed-macronutrient meal test did not reduce the triglyceride iAUC in comparison to the no-exercise condition. There were also no changes in glycaemic and insulinemic responses, or carbohydrate and fat oxidation rates.

Postprandial lipaemia

The primary observation that upper-body exercise performed the evening prior to a mixed-macronutrient meal test was insufficient to reduce the postprandial triglyceride response contrasts with findings from previous studies utilizing whole and lower-body exercise, which have largely reported an attenuation of PPL (Freese et al., 2014; Peddie et al., 2012). It is likely that this discrepancy can be explained by the comparatively low skeletal muscle mass utilized during upper-body exercise, which we speculate is unlikely to result in sufficient activation of LPL to reduce PPL at a whole-body level.

Previous studies have reported that HIIE is more effective than MICE at improving postprandial lipid metabolism (both iso-energetic or non iso-energetic) (Lee et al., 2018; Trombold et al., 2013). Trombold et al. (2013) found that an iso-energetic bout of HIIE (intervals of 2 min at 90% $V\dot{O}_{2PEAK}$) reduced PPL to a greater extent than MICE (50% $V\dot{O}_{2PEAK}$ for 1 h). Lee et al. (2018) reported lower postprandial triglyceride concentrations following HIIE (10 x 60 s at 85% $\dot{V}O_{2PEAK}$) compared to MICE (65% $V\dot{O}_{2PEAK}$ for 50 min) despite a considerably lower energy expenditure (330 ± 64 vs. 610 ± 85 kcal). This is likely due to a greater oxidation of muscle glycogen during HIIE, stimulating higher rates of post-exercise fat oxidation. We observed no change in PPL or postprandial fat oxidation following upper-body HIIE, which suggests there may be insufficient muscle glycogen degradation in localized skeletal muscle to cause changes in fat oxidation at the whole-body level. An insufficient energy expenditure of the exercise bouts in the present study may explain the lack of attenuation in PPL, with participants expending 141 ± 21 and 141 ± 28 kcal during the HIIE and MICE bouts respectively. It has been reported that the

energy expenditure of a prior exercise has a moderating effect (*r*=-0.62) on the magnitude of PPL (Petitt & Cureton, 2003), however this appears to only be true for continuous aerobic exercise (Freese et al., 2014). For aerobic exercise, there appears to be an exercise energy expenditure threshold (~2-2.5 MJ) needed to elicit a reduction in PPL (Maraki & Sidossis, 2013), and therefore it is perhaps unsurprising that the ~0.6 MJ expended during MICE in the present study was insufficient to reduce PPL.

Given the low energy expenditure of upper-body HIIE and MICE, careful consideration should also be given to post-exercise energy intake when making comparisons to the control condition. Participants in the present study consumed a standardised evening meal (697 kcal: 77 g carbohydrate, 28 g fat and 33 g protein) within 2 h of exercise completion, and at the same time for the control condition. It is important to note that participants would be in an energy deficit (vs. control condition) for the MICE and HIIE conditions, and therefore a reduction in PPL would still be expected with post-exercise feeding (Freese et al., 2011). However, both the carbohydrate composition and glycaemic index (GI) of post-exercise meals can affect subsequent PPL responses (Kaviani et al., 2016; Trombold et al., 2014). Therefore, it possible that any effect of the exercise protocols employed in the present study may have been eliminated or reduced to within measurement error as a result of the post-exercise meals. To maximize the magnitude of any reduction in PPL, future studies assessing the effect of upper-body exercise may consider restricting post-exercise energy intake.

It is also possible we found no attenuation in PPL after exercise due to a phenomenon that has been termed ‘exercise resistance’. Recent studies have demonstrated that if physical activity is restricted in the days prior to PPL assessment, the effect of a single about of exercise on PPL is reduced or abolished (Atkins et al., 2019; Burton & Coyle, 2021). In a randomised cross-over design, recreationally active individuals restricted their daily step count to 2,500, 5,000 and 8,5000 steps in the 2 days prior to a high-fat tolerance test (Burton & Coyle, 2021). On the evening prior to PPL assessment, participants completed a standardised 1-h run. The postprandial iAUC for triglycerides was 22-23% higher for the conditions preceded by the sedentary behavior (i.e., 2,500 and 5,000 steps/day). In the present study, we asked participants to avoid strenuous exercise in the 2 days prior to the

MMTT. There were no other physical activity restrictions imposed; however, we did not measure physical activity *per se* in this period. Therefore, despite the self-reported physical activity levels of participants in the present study being high, it is possible that participants reduced their step-count below the 'exercise resistance' threshold.

Glycaemic control

Upper-body MICE and HIIE performed in the evening had no effect on fasting or postprandial glucose and insulin responses. This contrasts previous work in ambulatory and non-ambulatory adolescents, that demonstrated a single bout of moderate-to-vigorous handcycle exercise performed immediately prior can improve glucose tolerance (Short et al., 2017). Additionally, work in individuals with chronic paraplegia highlighted a trend (p=0.06) towards a reduction for insulin iAUC when upper-body MICE was performed immediately prior to a MMTT (Farrow et al., 2021). Taken together, this evidence suggests that upper-body exercise may only offer a transient improvement in insulin sensitivity and glucose tolerance, that does not persist when exercise is performed the day before. This differs from the well-established evidence from whole/lower-body exercise modalities that a single bout of MICE or HIIE performed in the evening improves peripheral insulin sensitivity assessed the following morning (Ryan et al., 2020).

Implications

The present study matches findings from two studies involving persons with spinal cord injuries, who reported no change in PPL when upper-body MICE or HIIE was performed immediately prior to meal test consumption (Farrow et al., 2021; McMillan et al., 2021). Taking these findings with those from the present study, it appears that an acute bout of arm-crank exercise elicits no effect on PPL, irrespective of exercise intensity (MICE or HIIE) or timing of exercise (14-h prior or immediately prior). We speculate that this is likely due to the limited active skeletal muscle mass and consequent energy expenditure of upper-body exercise, making an energy deficit difficult to achieve and maintain in the post-exercise period.

To help further inform exercise recommendations for non-ambulatory populations, future research should attempt to determine if upper-body exercise of a longer duration is able to attenuate PPL. However, if an energy expenditure threshold of 2-2.5 MJ exists (Maraki & Sidossis, 2013), this would be the equivalent of ~90 min of MICE and this likely represents an unrealistic exercise session for habitually inactive populations. An alternative exercise strategy that warrants further investigation in this area is upper-body sprint interval training (SIT), often described as 'all-out' or 'supramaximal' efforts (MacInnis & Gibala, 2017). SIT produces a greater excess post-exercise oxygen consumption than both MICE and HIIE (Panissa et al., 2021), and may result in a greater sustained energy-deficit, at least in a controlled study setting. There is also evidence that LPL activation is muscle fibre type specific (Hamilton et al., 1998), and it is therefore plausible that SIT may induce a greater LPL activation due to the higher proportion of fast-twitch muscle fibres recruited. Therefore, upper-body SIT could have the potential to attenuate PPL without the need for a large exercise time-commitment.

This study was performed in individuals who were not physically disabled, and therefore participants were metabolically healthy, and physically active. This is in contrast to disabled populations, who are more likely to be obese (Liou et al., 2005), physically inactive (Carroll et al., 2014), have a lower muscle mass, and therefore have exaggerated basal PPL (Mekki et al., 1999; Miyashita et al., 2011). Consequently, the results cannot be generalized to clinical populations with hypertriglyceridemia and/or mobility limitations. However, given the limited evidence based for upper-body exercise, the findings from this study can help inform design of future acute studies in SCI and other physically disabled individuals (i.e., the need for alternative exercise strategies to reduce PPL). It is important to note that these forms of exercise utilizing a small volume of muscle mass are unable to induce changes to metabolism at the whole-body level, and future mechanistic studies should try to determine if this is due to a lower total energy expenditure or the limited active skeletal muscle mass, per se.

Conclusions

A single bout of upper-body MICE or HIIE performed 14-h prior to the consumption of a mixed-macronutrient meal does not reduce PPL in healthy non-disabled adults. Combined with findings from previous studies, it appears alternative upper-body exercise strategies are needed to reduce PPL. One such exercise strategy that should be investigated is upper body SIT, which may induce a greater muscle glycogen depletion and activation of LPL.

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Authorship The study was designed by MF, JM, and JB; data were collected and analyzed by MF, JN, JO, and SK; data interpretation and manuscript preparation were undertaken by MF. All authors reviewed, edited, and approved the final version of the paper.

Conflicts of interest None to report

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Relevance of the Findings from Chapter 6 to Thesis

This study found that a single-bout of isocaloric upper-body HIIE or MICE had no effect on PPL when exercise was performed 14 h prior to a MMTT in non-injured individuals. Combined with findings from Chapter 5, it can be concluded that upper body HIIT (8-10 x 60 s intervals at 70-80% P_{PEAK}) and MICE (of ~25 min duration) are insufficient to reduce PPL irrespective of the timing of exercise (1 to 14 h prior). Whilst these protocols fall considerably short of an exercise EE threshold of 2.0-2.5 megajoule (MJ) that has been reported in the general population (Maraki and Sidossis, 2013), they represent realistic and achievable exercise protocols for individuals with a SCI. Consequently, alternative exercise strategies are likely needed to reduce PPL in individuals with chronic SCI. Recently published studies have supported the feasibility and safety of upper body SIT in individuals with SCI (Graham et al., 2019; McLeod, Diana and Hicks, 2020). Therefore, it would be prudent to establish if a single bout of upper-body SIE can ameliorate PPL in individuals with SCI. Furthermore, whilst a bout of prolonged upper-body MICE is likely not feasible for regular exercise participation in this population, a sensible next step in this field would be to also determine if it is physiologically possible to reduce PPL through upper-body MICE. For example, based on an EE threshold of 2.0 MJ (~478 kcal) (Maraki and Sidossis, 2013), it would require ~90 min of MICE (50% PPO) to reduce PPL.

Chapter 7 - Effect of high-intensity interval training on cardiometabolic component risks in persons with chronic paraplegia: a randomised controlled trial

7.1 Introduction

Globally, it is estimated that there are ~2 million people living with a SCI (Lee et al., 2014). In the UK, one in three deaths in persons who sustained a traumatic SCI and survived the first year (i.e., chronic SCI) can be attributed to CVD. When adjusted for age and sex, standardised mortality rates associated with CVD are three times greater among people with SCI, compared to the non-injured population (Savic et al., 2017). Persons with a chronic SCI have a high prevalence of component risks associated with CVD, including T2D (Cragg et al., 2013a), central adiposity (Edwards, Bugaresti and Buchholz, 2008), chronic inflammation (Wang et al., 2007), and dyslipidaemia (Gilbert et al., 2014). Therefore, therapeutic solutions are required for this population, to reduce their risk of developing CVD.

Despite the well-established link between physical activity and CVD, the majority of persons with chronic SCI are habitually inactive, performing little to no moderate-to-vigorous physical activity (Buchholz et al., 2009; Nightingale et al., 2017c). The latest bespoke exercise guidelines for adults with SCI recommend 90 min per week of moderate-to-vigorous exercise to improve cardiometabolic health (Martin Ginis et al., 2018). However, a RCT found that performing 4 x 45 min per week of MICT (60-65% $\dot{V}O_{2PEAK}$) was only sufficient to improve CRF and fasting insulin sensitivity, with no changes observed in the lipid profile, body composition, or postprandial glycaemic control, amongst physically inactive individuals with chronic SCI (Nightingale et al., 2017d). This quantity of exercise (180 min per week) is higher than the physical activity guidelines for SCI and non-injured humans (150 min per week), and suggests that a higher-intensity, or greater volume of exercise may be required to achieve further cardiometabolic health benefits for this population. Given the complex barriers to exercise participation this population face (Kehn and Kroll, 2009), promoting a higher volume of exercise seems unrealistic.

Instead, a viable solution may be to maximise the intensity of exercise performed, by prescribing upper-body HIIT. This form of exercise can be generally characterised as involving short intervals eliciting ≥80% (but often 85-95%) of HR_{PEAK} (MacInnis and Gibala, 2017), and is an established training method to improve insulin sensitivity, BP, and body composition in individuals at risk of CVD (Campbell et al., 2019). Several meta-analyses have also reported superior effects of HIIT in comparison to MICT for CRF (Weston et al., 2014), insulin resistance (Jelleyman et al., 2015), and diastolic BP (Ramos et al., 2015), at least in non-injured humans. Meta-analyses have also reported that HIIT is equally effective as MICT at improving the lipid profile (Wood et al., 2019) and inflammatory markers (Khalafi and Symonds, 2020) in non-injured humans.

There has been growing interest in prescribing HIIT for persons with SCI since Nightingale et al. (2017a) proposed a plausible biological mechanism for improving cardiometabolic health outcomes in this population. Of particular note, a RCT determined that five weeks of upper-body SIT (3 x 20 s 'all-out' sprints) was equally as effective as 25 min of MICT (45% PPO) for improving PPO in individuals with acute SCI (McLeod, Diana and Hicks, 2020). Additionally, a pilot study in persons with chronic SCI (n=7) found that six weeks of upper-body SIT (4 x 30 s at 276% PPO) was equally effective as MICT for improving fasting insulin sensitivity and CRF, despite a reduced weekly training volume (40 min vs. 90 min) (Graham et al., 2019). However, to date, there are no RCT's that have assessed the effect of upper-body HIIT on a range of cardiometabolic component risks in persons with SCI.

Therefore, the purpose of this RCT is to determine the effect of an upper-body HIIT intervention on cardiometabolic component risks in persons with chronic paraplegia. Participants were randomly assigned using a 2:1 allocation to a six week home-based HIIT intervention, or a CON group who were asked to maintain their normal lifestyle over the study period, chosen to reflect the habitually low physical activity levels in this population. The primary outcome measures are fasting insulin, $\dot{V}O_{2PEAK}$, and PPO. We hypothesised that fasting insulin concentrations would decrease and both $\dot{V}O_{2PEAK}$ and PPO would increase following six weeks of HIIT compared to the CON group. Other secondary and exploratory outcome measurement categories included: i) body composition, ii) postprandial glycaemic control, iii) lipid concentrations, iv) physical activity, v) EI, vi) resting BP, and vii) subjective perceptions of health and wellbeing.

7.2 Methods

7.2.1 Study design

This study was approved by the South West (Bristol) National Research Ethics Committee (REC reference number 20/SW/005, Version 2, dated 9th April 2020) and was registered on ClinicalTrials.gov (ID: NCT04397250) on 21st May 2020. The results presented in this thesis are part of a larger RCT (Farrow et al., 2021). Participants were randomly assigned to either a home-based upper-body HIIT intervention or a CON group. Participants in the HIIT group were asked to perform exercise (4 sessions per week) for six weeks. Participants in the CON group were asked to maintain their habitual diet and physical activity routine during the six week period. Baseline and follow-up assessments for both groups were conducted at the DASH laboratory at the University of Bath to determine the effectiveness of the intervention. A waiting-list control group was utilised, with participants initially allocated to the CON group being offered the chance to take part in the intervention, however no further measurements were taken from these participants. The study was conducted in accordance with ethical principles for studies involving human participants set out in the Declaration of Helsinki.

7.2.2 Recruitment

The primary recruitment pathways were social media advertisements through non-NHS charities and clinical partners. A local R&D office (Welsh Centre for Spinal Trauma) also sent out letters and participant information sheets to individuals on their database who were aged 18-65 years, with a SCI between T2 and L2. Participants were invited to contact the research team at the University of Bath directly if they were interested in taking part in the study. Interested potential participants were asked to contact the principal researcher for further information via email/telephone correspondence. The principal researcher emailed a participant information sheet and health screening questionnaire (see Appendix A) and conducted a follow up phone call >48 hours after the participant expressed their initial interest to fully explain what the trial entailed and answer any questions. Providing the potential participant indicated that they wished to take part in the

study, the first visit was scheduled. On the first visit, participants were asked to provide written informed consent.

7.2.3 Randomisation

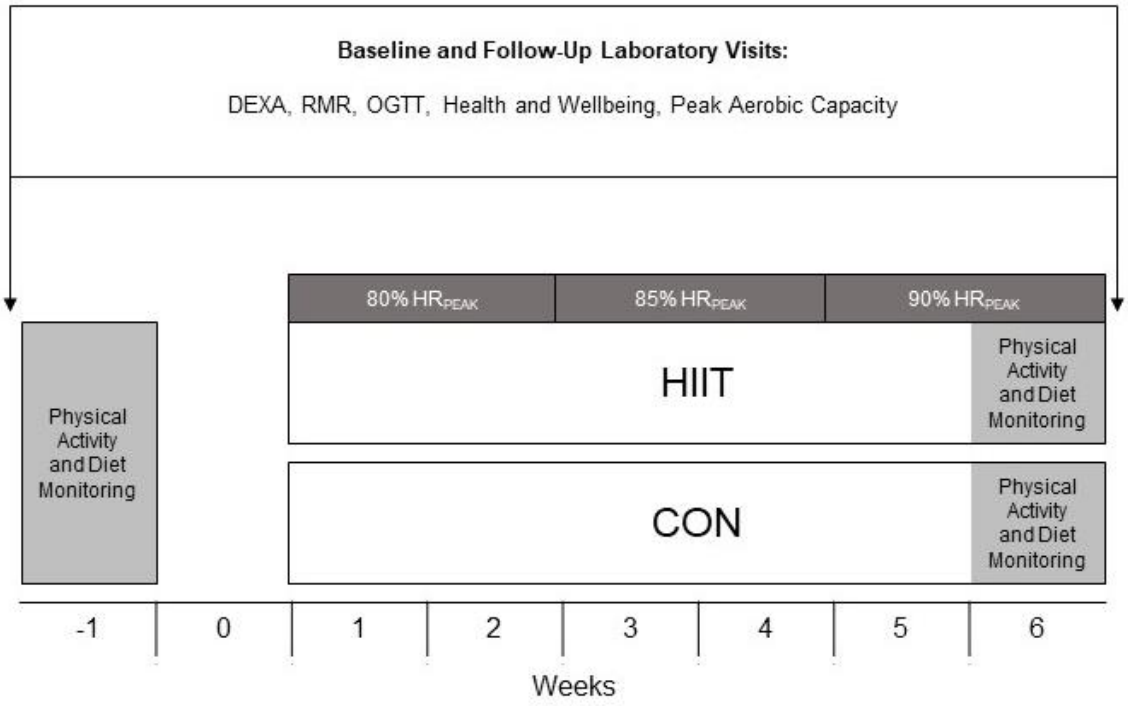
Eligible individuals were randomly assigned to either the HIIT or CON group. Randomisation took place after the baseline visit and was performed by an independent researcher using a list generated with a web-based platform (www.randomization.com) using a 2:1 allocation ratio, with no stratification and a fixed blocked sized of nine (Dumville et al., 2006). An unequal allocation was chosen to allow for a greater number of participants to be assigned to the HIIT group, as it was expected that there will be large inter-individual variation compared to the CON group. The research team and participants were not blinded to group assignments following the randomised allocation. As recommended for trials involving small sample sizes (Altman and Bland, 2005), a minimisation approach was used to balance groups for key characteristics (age, sex, and TSI) at baseline. This was performed using a free programme, with factors weighted equally and no random elements (https://www-users.york.ac.uk/~mb55/guide/minim.htm).

7.2.4 Participants and eligibility criteria

The participants recruited were aged between 18 and 65 years, had a chronic SCI (>1 year post-injury) between T2 and L2, self-reported use of a wheelchair for >75% of their waking day, and were weight stable (body mass not changed by ≥3%) for the previous three months. Individuals who self-reported active medical issues such as pressure sores, urinary tract infections, cardiac disorders, cardiovascular contraindications for exercise testing, or musculoskeletal complaints of the upper extremities were excluded (Goosey-Tolfrey, 2007). Individuals who self-reported the use of T2D medication or drugs that effect glucose metabolism were excluded. This was checked on a case-by-case basis using the British National Formulary. Finally, any participants who planned to change their lifestyle (i.e., diet or physical activity) level during the study period were also excluded.

7.2.5 Laboratory Assessments

The same experimental procedures were completed on both laboratory visits (C7 Figure 1). Before each laboratory visit, participants were asked to refrain from performing any moderate or strenuous exercise in the 48 h prior, and consuming alcohol and caffeine in the 24 h prior. Participants arrived at the laboratory at the same time for both main visits following an overnight fast (>10 h). Participants were asked to mimic their food and drink intake in the two days before these visits using a non-weighed food diary. Assessments were conducted during the follicular phase of the menstrual cycle (3-10 days after the onset of menses) for all eumenorrheic females.



C7 Figure 1 Study diagram

7.2.6 Body Composition

Body mass was measured (to the nearest 0.1 kg) using platform wheelchair scales (Decto ® BRW1000, Missouri, USA), with the wheelchair and participant's shoes weighed separately and subtracted from the total mass. Participants were asked to void prior to this measurement and remove all heavy clothing. For all body composition measurements, participants laid flat on a DEXA scanning table (Discovery, Hologic, Bedford, UK). DEXA is a precise and accurate measure of whole-body FM and FFM, in the general population (Borga et al., 2018), and for

individuals with an SCI (van der Scheer et al., 2021a). A quality control check was performed immediately prior to each scan as per manufacturer recommendations. Participants were in the fasted state for each scan and asked to drink ~1 pint (568 mL) of water on the morning of each scan. Participants were positioned centrally on the scanning table with their feet spaced evenly either side of the mid-point of the body, and arms placed mid-prone with an equal gap to the trunk on both sides. For participants who experienced leg spasms, a pillow support was provided. Participants were asked to wear light clothing, remove all metal (where possible), and to remain as still as possible for the duration of the scan. This position was replicated as close as possible for the follow-up scan. Scans were analysed using software (QDR for Windows, Hologic, UK) according to the manufacturer guidelines provided to determine total and regional (trunk, legs, arm) FM (kg), total FFM (kg), in addition to total body fat percentage and gynoid and android FM.

Supine length was measured with participants lying flat on the bed, with their feet close together, and arms at the side. Length was measured (to the nearest 0.5 cm) alongside the left-hand side of the body, using a non-elastic tape measure (Lufkin, Sparks, MD, US). A wooden board was pressed against the feet, in an attempt to achieve dorsal flexion. Waist and hip circumferences (to the nearest 0.1 cm) were taken in duplicate, using a non-metallic tape measure. Waist circumference was measured at the end of normal expiration, at the mid-way point between the lowest palpable rib and the iliac crest. Hip circumference was measured at the widest portion of the buttocks.

7.2.7 Resting Metabolic Rate

RMR was estimated via indirect calorimetry from 5-minute expired gas samples, collected into pre-evacuated Douglas Bags (Hans Rudolph, MO, USA) through a mouthpiece connected to a two-way valve. Fractions of O_2 and CO_2 were measured using a paramagnetic O_2 and infrared CO_2 analyser (miniMP 5200, Servomex, Crowborough, UK), calibrated with known concentrations of gas (100% Nitrogen, and 20% O_2, 8% CO_2) on the morning of testing. During each collection, ambient O_2 and CO_2 fractions was measured at close proximity to the participant to account for changes in an enclosed laboratory environment (Betts and Thompson, 2012). Expired fractions of O_2 and CO_2, total volume of expired gas (Harvard Apparatus,

Kent, UK), and expired gas temperature (model C, Edale Instruments, Cambridge, UK) were measured for each sample. All values were corrected to reflect atmospheric pressure and temperature during each collection. RMR was calculated using stoichiometric equations (Frayn, 1983), and taken as the average of three samples differing by ≤100 kcal·day^{-1}. During the final 5-minutes of RMR, resting HR (Polar H10, Polar Electro, Vansbro, Sweden) was recorded every 30-seconds, and an average taken. After the assessment of RMR, resting BP was measured in triplicate using an automated BP monitor.

7.2.8 Oral Glucose Tolerance Test

A cannula was inserted into an antecubital vein, and a 15 mL blood sample drawn. Whole blood (and all blood samples during the OGTT) were dispensed into serum and plasma separation tubes. For serum, whole blood was placed in serum separation tubes and left to stand at room temperature for 15 min before centrifugation. For plasma, whole blood was placed in tubes coated with EDTA and centrifuged immediately. Samples were centrifuged at 4000 g for 10 min at 4°C, with aliquots then obtained for serum and plasma. Aliquots were immediately cooled on dry ice, before being stored in a -80°C freezer for long term storage.

Participants consumed 113 mL of PolyCal (PolyCal, Nutricia Advanced Medical Nutrition, Trowbridge, UK), equivalent to 75 g of glucose, and 87 mL of water, within five minutes. This test was chosen to allow for comparison with the majority of upper-body exercise interventions in persons with SCI. Blood samples (5 mL) were drawn every 15 minutes for the following two hours. To ensure the cannula was kept patent, 0.9% NaCl was flushed through following each blood draw.

Fasting measures of insulin resistance, insulin sensitivity and pancreatic ß-cell function were calculated using the HOMA-2 calculator (Levy, Matthews and Hermans, 1998).

QUICKI (Katz et al., 2000) was calculated as follows:

$$= \frac{1}{(\text{Log}(\text{Fasting Insulin}) + \text{Log}\ (\text{Fasting Glucose}))}$$

Insulin and glucose TAUC and iAUC were determined using the trapezoidal rule (Narang et al., 2020) to characterise responses to the OGTT. The Matsuda Index (Matsuda and Defronzo, 1999) was calculated as follows:

$$= \frac{10{,}000}{\sqrt{((\text{Fasting Glucose x Insulin}) \text{ x } (\text{Mean OGTT Glucose x Insulin}))}}$$

Serum insulin concentrations were determined using ELISA's (Mercodia AB, Uppsala, Sweden). Plasma glucose and serum TG, NEFA, TC, HDL-C, LDL-C concentrations were determined using an automated analyser (Randox RX Daytona, Randox Laboratories, Co. Antrim, UK).

7.2.9 Measures of Health and Wellbeing

Health-related quality of life was assessed using the wheelchair user adapted version of the SF-36 (Ware and Sherbourne, 1992). The SF-36 assessed eight health phenomena relating to physical functioning, bodily pain, general health, vitality, social functioning, mental health, and limitations on social functioning due to physical or emotional problems. A transformed total score (ranging from 0 to 100) was calculated (Ware et al., 1993), with a higher score indicating greater health-related quality of life. Functional independence (i.e., ability to perform activities of daily living) was assessed using the Spinal Cord Independent Measure III (SCIM-III) (Fekete et al., 2013). The SCIM-III compromises of 19 questions relating to daily tasks (self-care, respiration and sphincter management, and mobility). A total score (ranging from 0-100) was calculated by summing together scores from the individual questions, with a higher score indicating greater functional independence.

Shoulder pain was assessed using the Wheelchair User's Shoulder Pain Index (WUSPI) (Curtis et al., 1995). The WUSPI is a 15-item questionnaire, whereby participants are asked to rate their shoulder pain during activities of daily living in the past week, on a visual analogue scale ranging from 'no pain' to 'worst pain ever experience'. A total score (ranging from 0-100) was calculated by summing together scores from the individual questions, with a higher score indicating a greater degree of perceived shoulder pain. The SCI Exercise Self-efficacy Scale (ESES) (Kroll et al., 2007) was used to assess confidence in performing regular physical activities (i.e. self-efficacy). Th ESES is a 10-item questionnaire, whereby participants are asked to respond on a 4-point Likert scale (1 – not at all true; 4 – always true). The

questionnaire is designed specifically for individuals with a SCI. A total score (ranging from 10-40) was calculated by summing together scores from the individual questions, with a higher score indicating a greater perceived self-efficacy. Severity of fatigue, and its effect on activities of daily living was assessed using the Fatigue Severity Scale (FSS) (Anton, Miller and Townson, 2008). The FSS is a 9-item questionnaire, whereby participants are asked to rate the severity of their fatigue on a 7-point Likert scale (1 -strongly disagree; 7 – strongly agree), with a higher total score (ranging from 9-63) indicating greater perceived fatigue.

7.2.10 Submaximal Exercise and Peak Aerobic Capacity

A sub-maximal incremental exercise test was then performed on an electronically braked arm-crank ergometer (Lode Angio, Groningen, Netherlands) consisting of four 3-minute stages, starting at 5 W and increasing by either 10 or 15 W (depending on self-reported fitness level). Participants were instructed to maintain a cadence of ~75 rpm throughout. They wore wear a rubber facemask connected to a two-way breathing value throughout, with expired gases (Douglas Bag method, as previously described) and HR recorded in the final minute of each stage.

Participants were given a small snack (Waitrose Classic Fruit Salad, 112 kcal), before performing a maximal exercise test to determine $\dot{V}O_{2PEAK}$. The ramp-based protocol on an electronically braked arm-crank ergometer began with a two-minute warm-up at 10 W before increasing by 1 W every 6 seconds. Participants wore a rubber facemask connected to a two-way breathing valve, which was connected to a computerised metabolic system (TrueOne® 2400, ParvoMedics, Salt Lake City, UT) calibrated with known concentration of gases (20% O_2, 8% CO_2) and a 3-L calibration syringe, on the morning of testing. HR and expired gas analysis data were recorded simultaneously on the software throughout the test. A cadence of ~75 rpm was encouraged throughout, and test was terminated at volitional fatigue or when cadence fell below 50 rpm. $\dot{V}O_{2PEAK}$ was defined as the highest 15-breath rolling average for $\dot{V}O_2$. PPO was defined as the highest power output achieved before termination of the test. In each test, at least two of the following criteria were met: peak HR ≥ 95% age-predicted maximum for upper-body exercise (200 bpm - Age), RPE ≥ 19, and a peak RER ≥ 1.10.

7.2.11 Exercise Intervention

Participants in the HIIT group were asked to perform four sessions per week of home-based HIIT, involving 10 x 60 s intervals at 80-90% HR_{PEAK} on a mechanically braked arm-crank ergometer (Monark 881 E, Vansbro, Sweden). To account for changes in fitness and ensure progression, the intensity was increased by 5% every two weeks (i.e., 80% HR_{PEAK} for Weeks 1 and 2, 85% HR_{PEAK} for Weeks 3 and 4, and 90% HR_{PEAK} for Weeks 5 and 6). Specifically, participants were asked to ensure their HR reached the required $\%HR_{PEAK}$ by the end of each high-intensity phase. Each exercise session included a 5-min warm-up and cool-down at a low intensity (~5 W), with 60 s recovery intervals at ~5 W, resulting in a total exercise time of 29 minutes. During each exercise training session (Weeks 1-5), participants were asked to wear a chest-worn HR monitor (Wahoo® Tcker X, Wahoo Fitness, Atlanta, USA) and view their HR response in real-time using a phone application. In the final week of intervention, HR data from the Actiheart™ was used to measure compliance.

Participants were asked to avoid performing two exercise training sessions on the same day and advised they should avoid performing the training sessions within 1 h of food consumption to avoid gastrointestinal issues (see Appendix B). Given that some concerns have been raised regarding the effect of upper-body HIIT on shoulder pain (Gauthier et al., 2018), participants were given examples of upper-body stretches to perform if they desired (see Appendix B). No other time or dietary restrictions were required for the training sessions.

Participants were asked to send their HR and RPE data remotely to the researcher at the end of each training week (Weeks 1-5) to help monitor adherence and compliance. Specifically, $\%HR_{PEAK}$ against time was plotted for each exercise session. Participants were contacted by the researcher on a weekly basis and adjustments to the exercise intensity were made if necessary. Participants were monitored for the following both during and after the peak $\dot{V}O_{2PEAK}$ and first home-based HIIT session: chest pain, headaches, changes in vision, dizziness, and light-headedness. BP was measured immediately following the $\dot{V}O_{2PEAK}$ test to identify any individuals exceeding the limits for systolic BP (<85 mmHg and >200 mmHg). The researcher visited the participant's home to supervise the first home-based HIIT session. Participants were also required to sign a consent form stating that they must be accompanied by an adult for all exercise training sessions at home.

Additionally, any individuals who self-reported regular or uncontrolled episodes of autonomic dysreflexia were asked to obtain written consent from their GP to take part in the study.

A home-based exercise programme was chosen due to i) the anticipated difficulties in recruiting participants in the local area, and ii) to help overcome some of the reported barriers to exercise participation for individuals with an SCI, including transportation difficulties and a lack of accessible exercise equipment (Kehn and Kroll, 2009). The length of the intervention (six weeks) and number of sessions per week (four) were chosen to allow for findings to be directly compared to a previous study assessing the effect of MICT in individuals with chronic paraplegia (Nightingale et al., 2017d).

To assess the acceptability of the exercise intervention, an exit questionnaire (see Appendix C) was administered on the follow-up visit for individuals in the HIIT group. Participants were asked a range of open-ended questions (benefits, difficulties, and proposed changes) regarding the exercise programme. Participants were also asked to rate their enjoyment (5-point scale ranging from 1: not at all enjoyable; 5: very enjoyable) and perceptions of the exercise programme on a 5-point scale (1: strongly disagree; 5: strongly agree).

7.2.12 Physical Activity and Energy Intake

Participants were asked to wear a physical activity monitor (Actiheart^{TM}, Cambridge Neurotechnology Ltd, Papworth, UK) for 7-days after the baseline visit, and in the final week of the HIIT/CON period. The physical activity monitor was individually calibrated using the HR and corresponding EE measured during the RMR assessment and sub-maximal exercise test, as previously described in manual wheelchair users (Nightingale et al., 2017e). PAL and time spent in different intensities of activities according to METs were calculated. Due to a lower than anticipated wear time at follow-up, a valid day was defined as >50% wear time for a given 24 h period. Participants were asked to record their habitual food and fluid intake for the same 7-day period using a set of weighing scales. Total EI and macronutrient composition were subsequently calculated using diet analysis software (Nutritics Ltd., Dublin, Ireland).

EI at follow-up was also calculated by re-arranging the energy balance equation, using measures of FM and FFM, as previously validated (Racette et al., 2012). The equations used were:

$$EI\ (kcal \cdot day^{-1}) = EE + \frac{\Delta\ Energy\ stores\ (kcal \cdot day^{-1})}{\Delta\ time\ (d)}$$

$$\Delta\ Energy\ stores\ (kcal) = \Delta\ FM\ (g) \times 9300\ (kcal \cdot g^{-1}) + \Delta\ FFM\ (g) \times 1100\ (kcal \cdot g^{-1})$$

7.2.13 Sample size

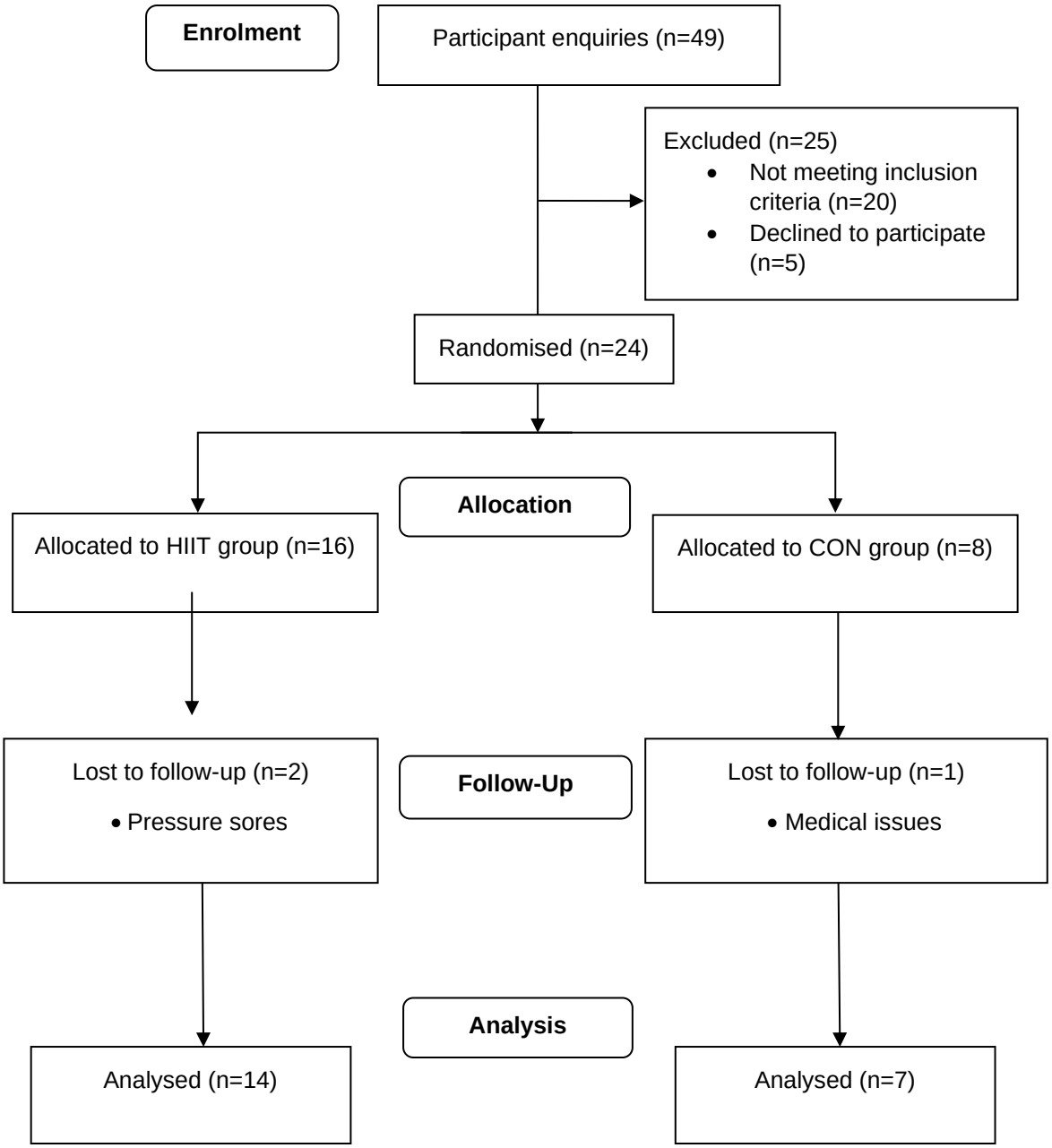
A pilot study in individuals with SCI reported that upper-body SIT reduced fasting insulin by 9.7 ± 7.0 ml·dL^{-1} in 6 weeks (*d*=1.10, n=3) (Graham et al., 2019). To adjust for the 2:1 allocation adopted, an unequal size sample size calculation was performed (https://www.statstodo.com/UnequalSSize_Exp.php). This returned a target sample size of 35 participants (23 HIIT: 12 CON). Based on an expected drop-out of approximately 15%, and α=0.05 and β=0.80, we aimed to recruit a total of 40 participants (26 HIIT: 14 CON).

7.2.14 Statistical analyses

The final analysis was based on a modified intention-to-treat principle, whereby each participant had to complete >75% (18/24 sessions) of planned exercise sessions to be in the included. Any changes in outcome measures between groups were determined using a series of analysis of co-variance (ANCOVA)'s, with the follow-up value as a dependent variable, the baseline value as a co-variate, and group allocation as a fixed effect. Bonferroni comparisons were performed to confirm the location of any differences, where significance interaction or main effects were observed. Effect sizes (Cohen's *d*) were calculated for all variables, and interpreted as: small effect = 0.20-0.50, medium effect = 0.50-0.79, and large effect ≥0.80. Statistical significance was accepted at P≤0.05. Data in text is presented as mean ± SD. Figures and tables also include 95% CI's.

7.3 Results

Twenty-one participants completed the baseline and follow-up assessments and were therefore included in the final analysis (C7 Figure 2). Three of the 24 participants who attended the initial baseline assessments did not complete follow-up assessment, equating to a drop-out rate of 12.5%.



C7 Figure 2 Study Flowchart (using CONSORT template)

7.3.1 Participant characteristics

We were unable to obtain a fasting blood sample (n=2, both HIIT) or perform the OGTT (n=4; 2 HIIT, 2 CON) for some participants. Therefore, data for 19 participants is presented (12 HIIT, 7 CON) for all fasting blood measurements, and data for 17 participants (12 HIIT, 5 CON) for OGTT data is presented.

No significant differences were present at baseline for age (p=0.51), time since injury (p=0.56), or sex (p=0.61) (C7 Table 1). Alcohol consumption at baseline was significantly higher for CON vs. HIIT at baseline (p=0.05). Systolic BP was higher for HIIT vs. CON at baseline, although this was not statistically significant (p=0.06). There were no other significant differences in any CMS outcome measure at baseline between groups (all p>0.08).

At baseline, twenty participants presented with obesity (body fat percentage >22%), 16 participants reported with reduced HDL-C (males: <1.03 mmol·L^{-1}, females: <1.29 mmol·L^{-1}), three participants presented with hypertension (≥130/85 mmHg), four participants presented with hypertriglyceridemia (fasting TGs ≥1.7 mmol·L^{-1}), and two participants presented with hyperglycemia (fasting glucose ≥5.6 mmol·L^{-1}). Six participants (4 HIIT, 2 CON) presented with CMS at baseline and follow-up as defined in Section 2.4.5. Twenty participants the participants lifestyles could be described as ‘sedentary or light activity’ (Nocito, Ballard and Shaw, 2005).

C7 Table 1 Participant descriptive characteristics**.**

	HIIT	**CON**
n	14	7
Age (yrs)	44 ± 8	45 ± 8
Sex, M/F	7/7	3/4
AIS Classification		
A	11	5
B	3	2
LOI		
Range	T3-L2	T4-12
T6 or ↑	5	2
↓T6	9	5
TSI (yrs)	16 ± 10	11 ± 12

Data presented as Mean ± SD. AIS *American Spinal Injury Association Impairment Scale*, LOI *level of injury*, *TSI time since injury*

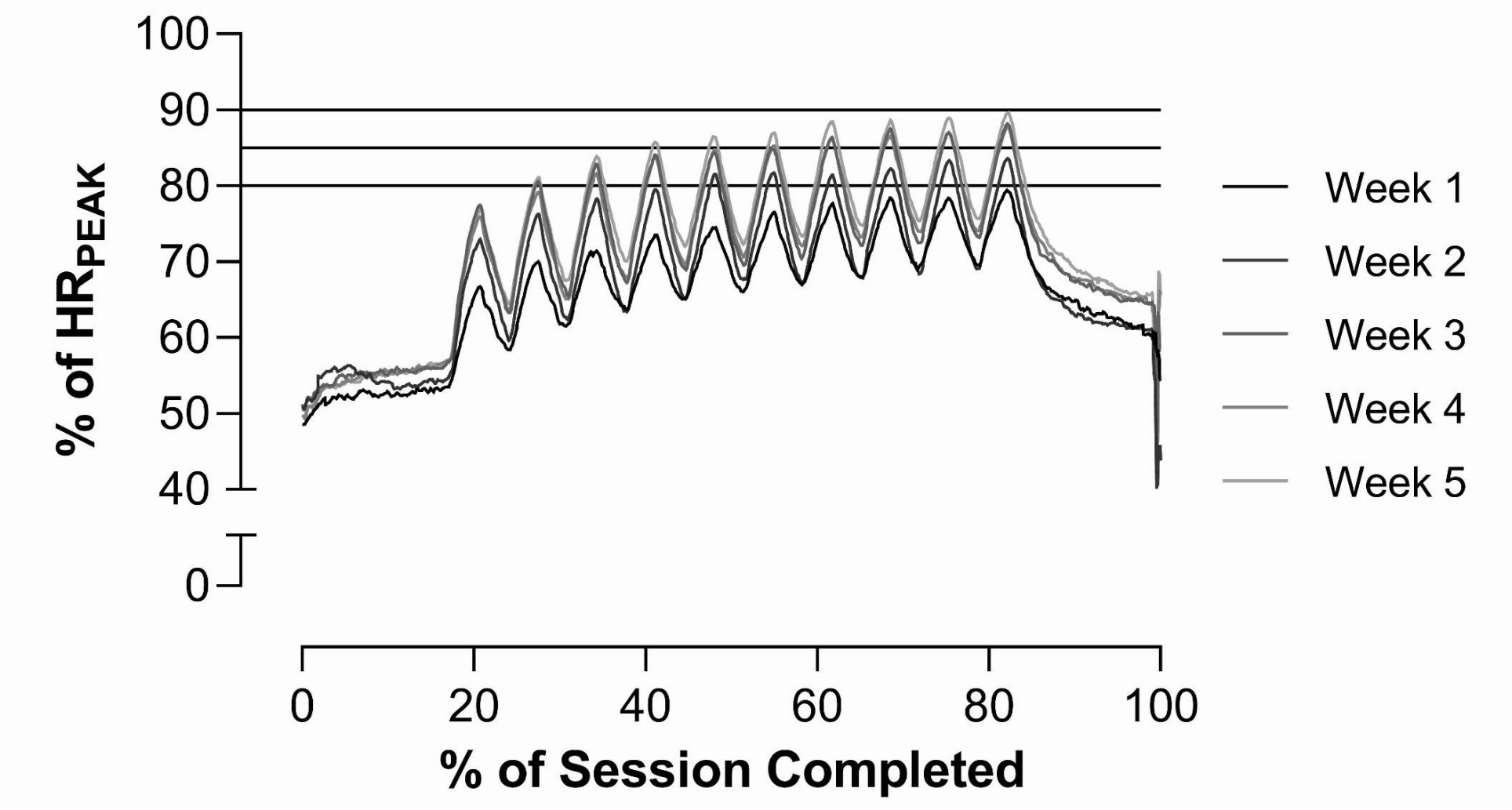
7.3.2 Exercise intervention

All participants in the HIIT group completed the required number of exercise sessions (18/24) to be included in the final analysis. 11 participants in the HIIT group completed all prescribed exercise sessions (24/24); three participants completed 23/24 (96%) of the prescribed exercise sessions. The mean session RPE was 15 ± 2, 15 ± 2, 16 ± 2, 16 ± 2, 17 ± 2, 17 ± 2 for Weeks 1-6 respectively. Participants spent 2.7 ± 3.3%, 10.9 ± 8.9%, 23.2 ± 8.8%, 23.4 ± 12.7%, and 31.7 ± 15.8% of exercise sessions at an intensity greater than 80% HR_{PEAK} during Weeks 1-5 respectively (C7 Figure 3).

All participants reported that they found the exercise programme 'quite enjoyable' (n=7) or 'very enjoyable' (n=7). Participants self-reported benefits of the exercise programme including establishing a regular exercise routine (n=5), feeling stronger and fitter (n=2), improved motivation to exercise (n=2), improved sleep (n=2), feelings of well-being (n=2), perceived weight loss (n=2), reduced swelling (n=2), reduced pain/stiffness in joints (n=1), enjoyment of sensation of working hard (n=1), and improvements in bowel function (n=1).

Participants self-reported difficulties of the exercise programme including finding time to complete exercise sessions (n=4) and difficulties in reaching target HR (n=3). Participants also suggested improvements to the programme including the option to exercise for longer or more often (n=2), and two participants stated that the Wahoo® Tcker X monitor was uncomfortable to wear.

Most participants stated they 'agreed' or 'strongly agreed' that they were able to do the exercise programme with little difficulty or assistance (n=13), and that other individuals with SCI would find the exercise programme enjoyable (n=12). All participants stated they 'agreed' or 'strongly agreed' that they felt it was worth their time to do the exercise programme, that the programme helped them stay fit and strong, and that it would help maintain their fitness and health in the long-term. Nine participants stated they 'disagreed' or 'strongly disagreed' that the exercise programme interfered with their other priorities.



C7 Figure 3 Heart rate (expressed as a percentage of peak) during Weeks 1-5 of HIIT intervention

7.3.3 Functional Capacity

There was a significant improvement in PPO for HIIT vs. CON (p<0.01, *d*=1.47). PPO increased by 12.9% from baseline to follow-up in the HIIT group and decreased by 1% in the CON group (C7 Figure 4). However, there were no significant differences in absolute (p=0.27, *d*=0.55) or relative (p=0.37, *d*=0.43) $\dot{V}O_{2PEAK}$ between groups (C7 Figure 5). There was an 8.6% and 1.6% increase in absolute $\dot{V}O_{2PEAK}$ for the HIIT and CON groups respectively. Specifically, 13 out of the 14 participants in the HIIT group had a higher absolute $\dot{V}O_{2PEAK}$ at follow-up compared to baseline. Four of the 7 participants in the CON group had a higher absolute $\dot{V}O_{2PEAK}$ at follow-up compared to baseline.

7.3.4 Physical Activity and Energy Intake

There were no significant differences in maximum HR (p=0.28, *d*=0.54), PAL (p=0.20, *d*=0.66), time spent in sedentary (p=0.17, *d*=0.69), light (p=0.10, *d*=0.85), moderate (p=0.65, *d*=0.22), or vigorous (p=0.16, *d*=0.71) activities between groups (C7 Table 2). There was a trend towards a significant decrease in TDEE for HIIT vs. CON (p=0.074; *d*=0.92). There were no significant differences in EI (p=0.80) or carbohydrate (p=0.33, *d*=0.47), fat (p=0.61, *d*=0.25), protein (p=0.84) or alcohol (p=0.94) consumption between groups (C7 Table 3). There was no significant difference in calculated EI at follow-up between the HIIT (2174 ± 561 kcal) and CON (1975 ± 418 kcal) groups (p=0.38, *d*=0.40).

7.3.5 Resting Metabolic Rate and Blood Pressure

There were no significant differences in RMR (p=0.33, *d*=0.47), RER (p=0.84), resting HR (p=0.27, d=0.53), or systolic (p=0.67, *d*=0.21) and diastolic (p=0.39, *d*=0.42) BP between groups (C7 Table 4).

7.3.6 Body Composition

There were no significant differences in body mass (p=0.17, d=0.73), BMI (p=0.09, d=0.86), waist circumference (p=0.45, *d*=0.36), or waist to hip ratio (p=0.10, *d*= 0.82) between groups (C7 Table 5). There were no significant differences in android (p=0.45, *d*=0.36) or gynoid (p=0.08, *d*=0.83) FM between groups (C7 Table 5). There were no significant differences in total FM (p=0.20, *d*=0.63), total soft-tissue

FFM (p=0.78), or body fat percentage (p=0.42, *d*=0.39) between groups (C7 Table 5). There were no significant differences in arm (p=0.47, d=0.35), leg (p=0.29, d=0.51), or trunk (p=0.34; *d*=0.49) soft-tissue lean mass between groups (C7 Table 5). There were no significant differences in arm (p=0.35, *d*=0.45), leg (p=0.27, *d*=0.55) or trunk (p=0.89) FM between groups (C7 Table 5).

7.3.7 Insulin and Glucose Responses to OGTT

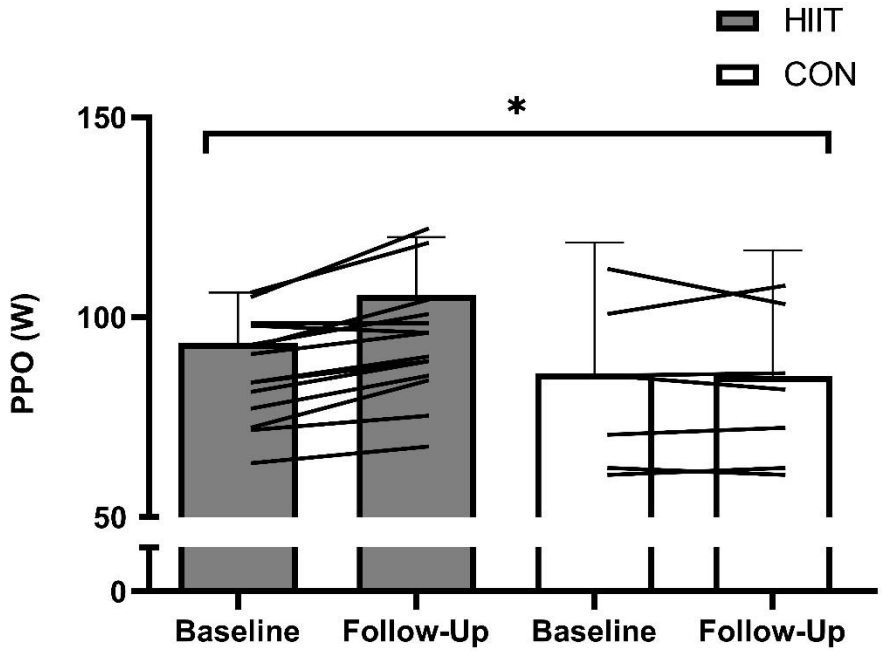
There was a significant reduction in HOMA2-IR for HIIT vs. CON (p=0.05, *d*=1.05; C7 Figure 6). HOMA2-IR decreased by 13.0% in the HIIT group and increased by 26.8% in the CON group. There was no significant difference in HOMA-β (%) between the groups (p=0.47, *d*=0.38). There were trends towards significant improvements in QUICKI (p=0.062, *d*=1.00) and $ISI_{Matsuda}$ (p=0.057, *d*=1.10; C7 Figure 8) for HIIT vs. CON. $ISI_{Matsuda}$ increased by 6.8% in the HIIT group and decreased by 22.4% in the CON group. There were no significant differences in fasting glucose (p=0.66, *d*=0.23) or insulin (p=0.23; *d*=0.62, C7 Figure 8) between groups. There was no significant interaction effect between groups for glucose (p=0.92, C7 Figure 9) or insulin (p=0.43; C7 Figure 10) concentrations during the OGTT. There were no significant differences in glucose iAUC (p=0.97) or TAUC (p=0.60, *d*=0.28) between the groups (C7 Figure 11). There were no significant differences in insulin iAUC (p=0.43, *d*=0.41) or TAUC (p=0.27, *d*=0.59) between the groups (C7 Figure 11).

7.3.8 Lipid Profile

There were no significant differences in TG (p=0.15, *d*=0.76), NEFA (p=0.54, *d*=0.31), or TC: HDL-C (p=0.72) between the groups (C7 Table 6). However, there was a significant increase in TC (p=0.02, *d*=1.32) and LDL-C (p=0.03, *d*=1.23), and a trend towards a significant increase in HDL-C (p=0.065, *d*=0.99) for HIIT vs. CON (C7 Table 6).

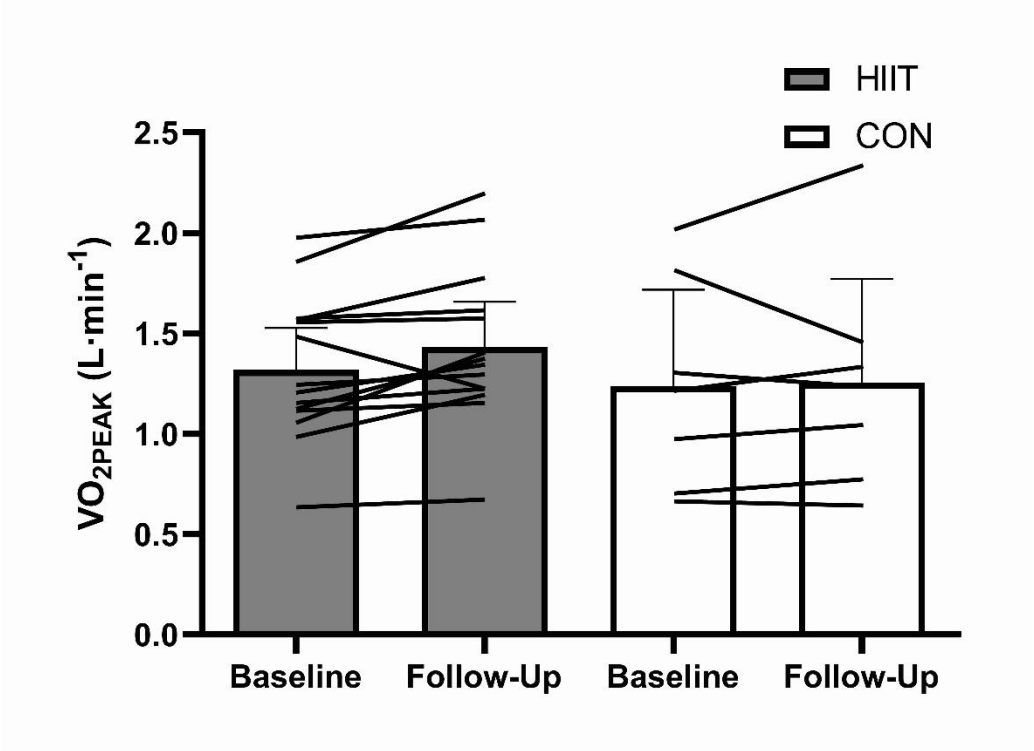
7.3.9 Health and Wellbeing

There were no significant differences in shoulder pain (p=0.44, *d*=0.38), exercise self-efficacy (p=0.51, *d*=0.33), fatigue severity (p=0.12, *d*=0.76), functional independence (p=0.19, *d*=0.65), or health-related quality of life (p=0.88) between groups (C7 Table 7).



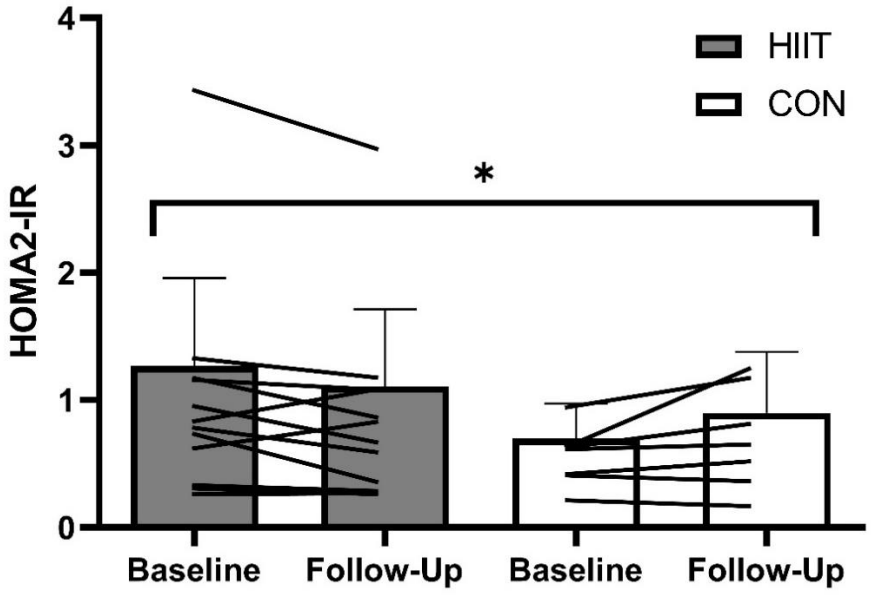
C7 Figure 4 Peak power output (PPO) at baseline and follow-up for the HIIT and CON group

Values are Mean ± 95% CI's. Individual responses are also denoted. *denotes p≤0.05 HIIT vs. CON at follow-up (after adjustment for baseline)



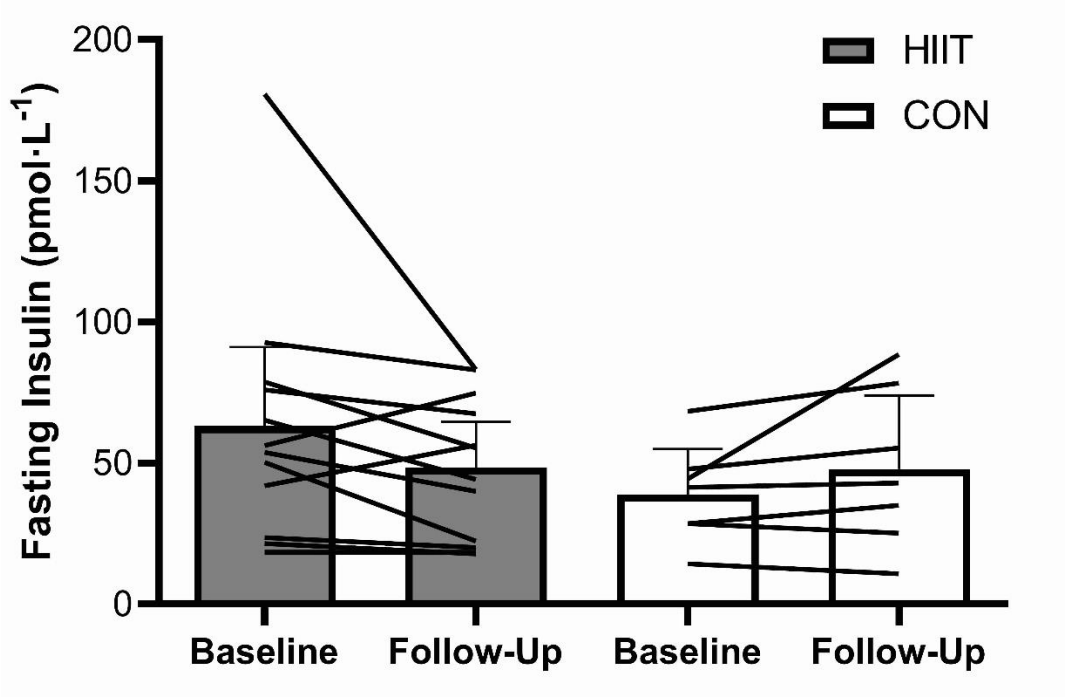
C7 Figure 5 Absolute peak oxygen uptake at baseline and follow-up for the HIIT and CON group

Values are Mean ± 95% CI's. Individual responses are also denoted.



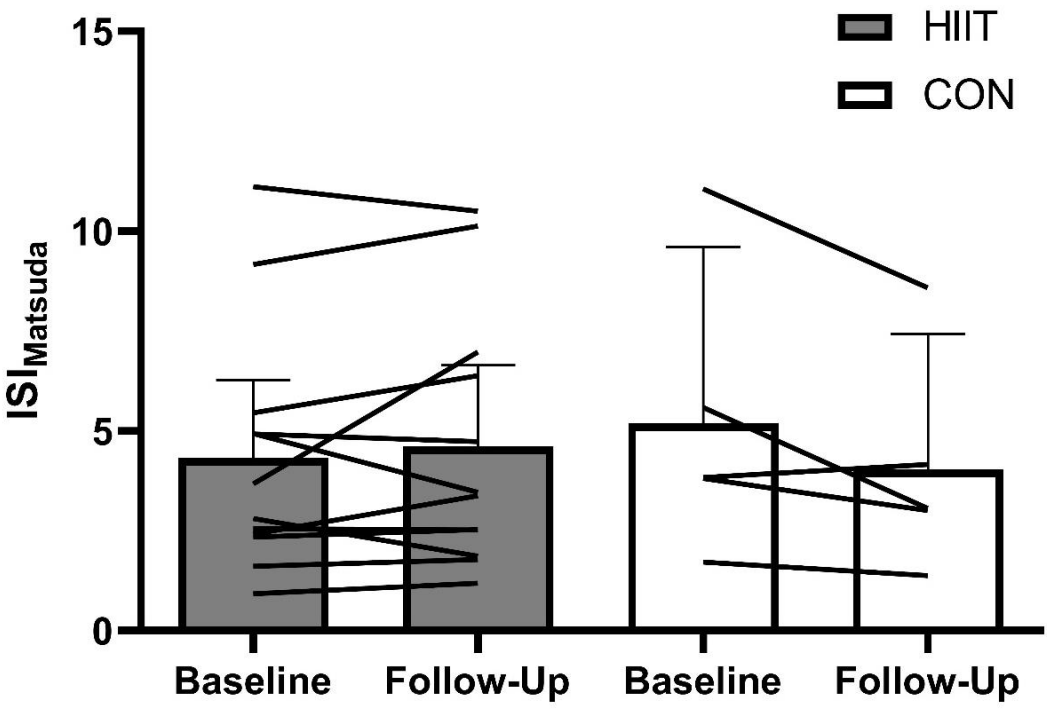
C7 Figure 6 Homeostasis Model Assessment Insulin Resistance (HOMA2-IR) at baseline and follow-up for the HIIT and CON group

Values are Mean ± 95% CI's. Individual responses are also denoted. *denotes p≤0.05 HIIT vs. CON at follow-up (after adjustment for baseline)



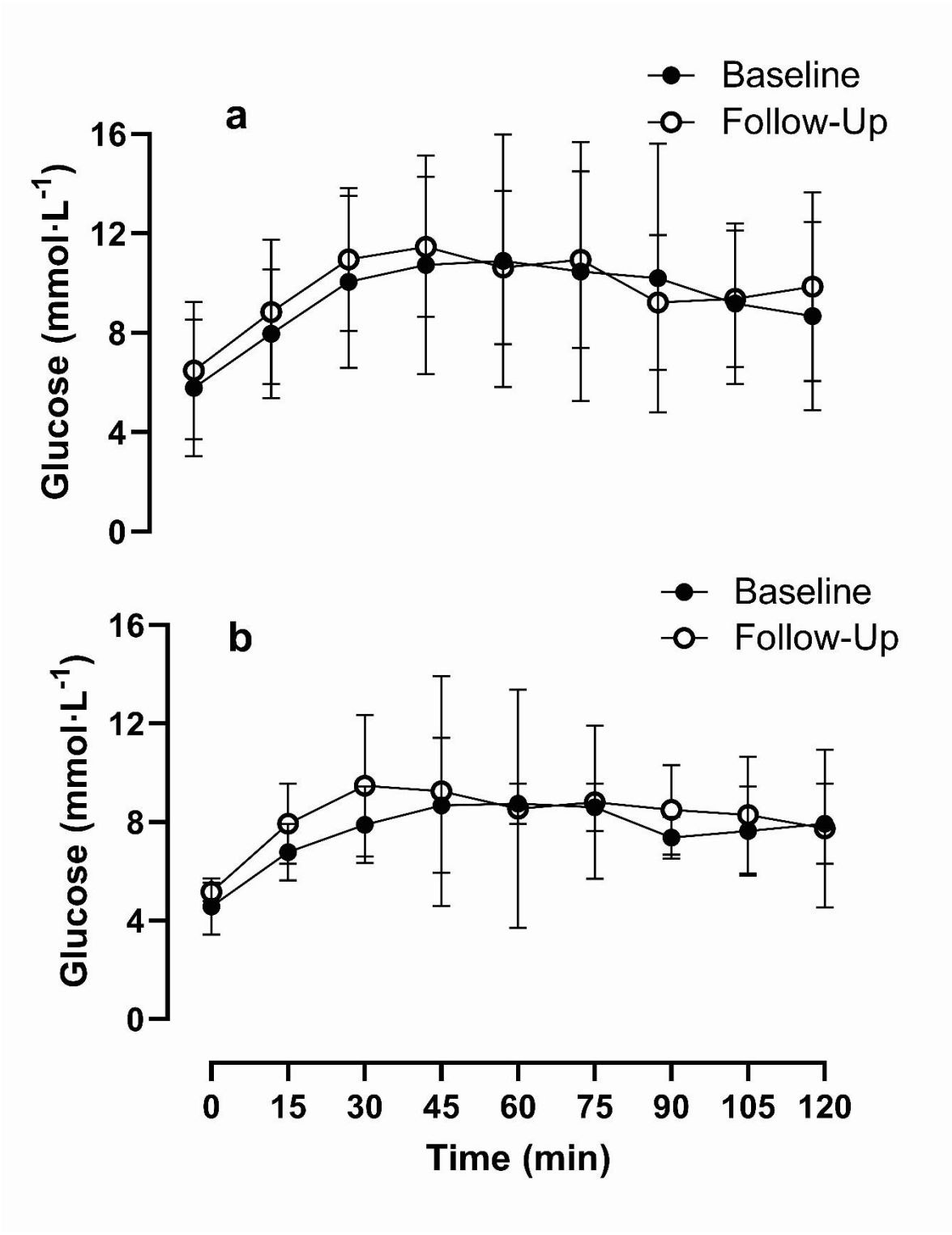
C7 Figure 7 Fasting insulin at baseline and follow-up for the HIIT and CON group

Values are Mean ± 95% CI's. Individual responses are also denoted.



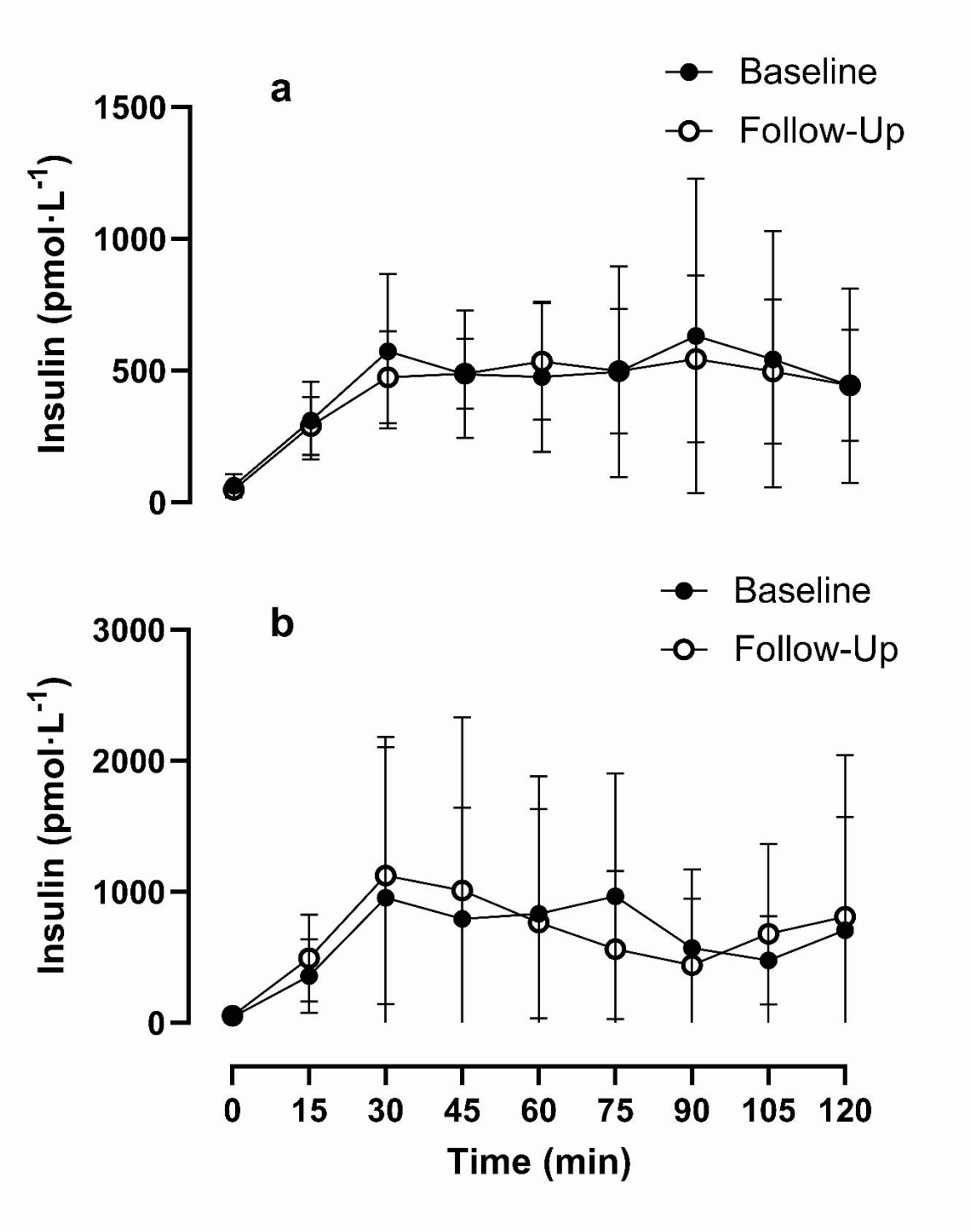
C7 Figure 8 Matsuda Index at baseline and follow-up for the HIIT and CON group

Values are Mean ± 95% CI's. Individual responses are also denoted.



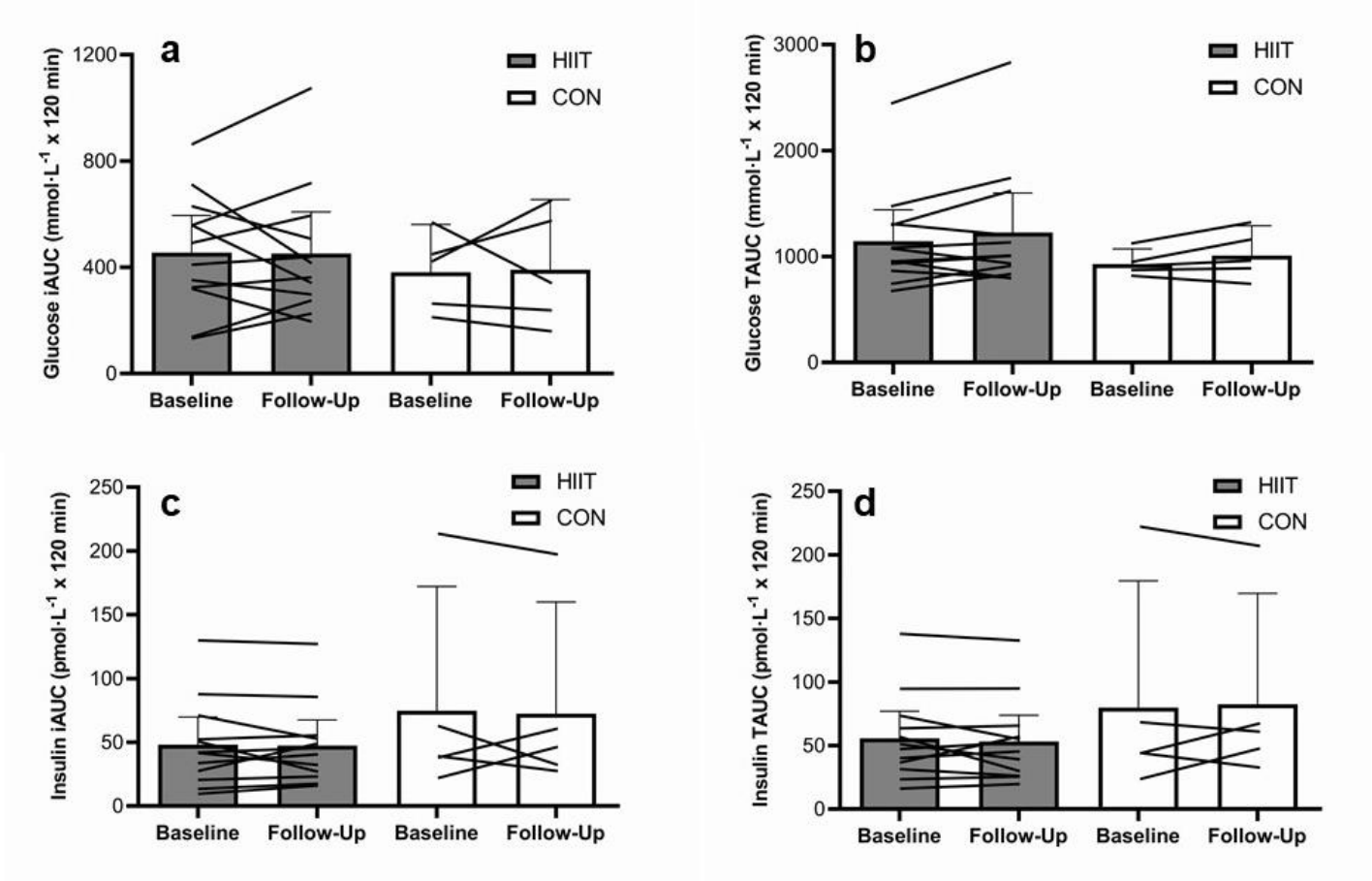
C7 Figure 9 Plasma glucose concentrations during the OGTT at baseline and follow-up for the a) HIIT and b) CON group

Values are Mean ± 95% CI's.



C7 Figure 10 Serum insulin concentrations during the OGTT at baseline and follow-up for the a) HIIT and b) CON group

Values are Mean ± 95% CI's.



C7 Figure 11 Plasma glucose iAUC (a) and TAUC (b), and serum insulin iAUC (c) and TAUC (d) at baseline and follow up for HIIT and CON group

Values are Mean ± 95% CI's.

C7 Table 2 Physical activity data at baseline and follow-up for HIIT and CON group.

	HIIT			CON		
	Baseline	**Follow-up[a]**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
PAL	1.46 ± 0.09	1.43 ± 0.13	-0.03 (-0.08, 0.02)	1.41 ± 0.10	1.50 ± 0.16	0.09 (0.02, 0.16)
TDEE	2048 ± 316	2025 ± 355	-22 (-188, 143)	1854 ± 355	2074 ± 355	263 (-43, 483)
Sedentary (min·day^{-1})	645 ± 96	700 ± 127	55 (4, 105)	703 ± 132	622 ± 190	-81 (-179, 17)
Light (min·day^{-1})	298 ± 93	229 ± 115	-69 (-118, -21)	247 ± 131	322 ± 188	75 (-21, 172)
Moderate (min·day^{-1})	18 ± 14	21 ± 25	3 (-4, 11)	10 ± 9	15 ± 15	5 (-1, 12)
Vigorous (min·day^{-1})	0 ± 1	0 ± 1	0 (0, 0)	0 ± 0	0 ± 0	0 (0, 0)
Max HR (beats·min^{-1})	148 ± 16	153 ± 15	5 (-3, 13)	148 ± 14	146 ± 17	-2 (-13, 8)
Day >50% Wear Time[b]	7 ± 1	7 ± 1	0 (0, 0)	7 ± 0	6 ± 1	-1 (-1, 0)
Days >80% Wear Time	6 ± 2	5 ± 2	-1 (-2, 0)	6 ± 1	4 ± 2	-2 (-3, -1)
Total Wear Time (%)	92 ± 7	87 ± 9	-5 (-9, -2)	90 ± 6	85 ± 9	-4 (-9, 0)

PAL *physical activity level*; TDEE *total daily energy expenditure*

Sedentary, <1.5 METs; Light, ≥ 1.5 to <3 METs; Moderate ≥ 3 to < 6 METs; Vigorous, ≥ 6 METs.

[a]Device monitoring failed for one participant in the HIIT group at follow-up, therefore n=13 for all physical activity data.

[b]All data calculated based on wear time >50% for given 24 h period.

C7 Table 3 Total daily energy intake and macronutrient composition at baseline and follow-up for HIIT and CON group.

	HIIT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
EI (kcal·day^{-1})	1571 ± 257	1588 ± 252	17 (-103, 138)	1514 ± 392	1524 ± 377	10 (-133, 153)
Carbohydrate (g·day^{-1})	161 ± 51	176 ± 38	15 (-10, 40)	155 ± 43	157 ± 43	2 (-21, 25)
Fat (g·day^{-1})	63 ± 12	64 ± 13	1 (-7, 8)	59 ± 18	59 ± 13	0 (-4, 5)
Protein (g·day^{-1})	71 ± 20	69 ± 18	-1 (-7, 5)	68 ± 12	67 ± 12	-1 (-8, 5)
Alcohol (g·day^{-1})	6 ± 8	8 ± 18	2 (-7, 11)	13 ± 14	14 ± 18	1 (-2, 4)

EI *energy intake*

C7 Table 4 Resting physiological measurements at baseline and follow-up for HIIT and CON group.

	HIIT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
RMR (kcal·day^{-1})	1426 ± 208	1432 ± 194	6 (-39, 50)	1315 ± 243	1378 ± 194	64 (-4, 131)
RER	0.81 ± 0.06	0.79 ± 0.04	-0.02 (-0.04, 0.01)	0.79 ± 0.04	0.79 ± 0.03	0.00 (-0.04, 0.03)
Resting HR (beats·min^{-1})	63 ± 7	64 ± 10	1 (-1, 4)	68 ± 9	67 ± 8	-1 (-3, 1)
Systolic BP (mmHg)	125 ± 7	121 ± 11	-4 (-8, 0)	111 ± 13	109 ± 76	-2 (-5, 2)
Diastolic BP (mmHg)	81 ± 6	78 ± 8	-3 (-6, 0)	76 ± 7	76 ± 6	0 (-1, 1)

RMR *resting metabolic rate*, RER *respiratory exchange ratio*, HR *heart rate*, BP *blood pressure*

C7 Table 5 Body composition at baseline and follow-up for HIIT and CON group.

	HIIT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
Body Mass (kg)	75.4 ± 14.3	75.9 ± 14.5	0.5 (-0.2, 1.2)	69.5 ± 12.7	68.9 ± 13.3	-0.6 (-1.8, 0.06)
BMI (kg · m^{-2})	26.0 ± 5.1	26.4 ± 5.4	0.3 (0.1, 0.6)	24.3 ± 3.9	24.0 ± 4.4	-0.2 (-0.7, 0.3)
Waist Circumference (cm)	88.0 ± 14.6	86.4 ± 13.4	-1.5 (-3.1, 0.3)	83.5 ± 9.4	83.2 ± 11.3	-0.3 (-2.3, 1.8)
Waist: Hip	0.85 ± 0.08	0.85 ± 0.08	0.0 (-0.02, 0.02)	0.86 ± 0.06	0.83 ± 0.08	-0.03 (-0.06, 0)
Fat Mass (kg)						
Total	29.9 ± 11.6	30.9 ± 11.6	0.9 (0.0, 1.9)	24.9 ± 8.1	24.8 ± 8.1	-0.2 (-1.5, 1.2)
Arms	3.1 ± 1.5	3.2 ± 1.4	0.1 (-0.2, 0.3)	2.5 ± 0.8	2.5 ± 0.9	0.0 (-0.2, 0.2)
Legs	10.3 ± 4.6	10.1 ± 4.8	-0.2 (-1.1, 0.8)	8.4 ± 2.8	7.3 ± 2.7	-1.1 (-2.5, 0.4)
Trunk	16.4 ± 7.1	16.1 ± 6.2	-0.3 (-2.3, 1.6)	13.0 ± 4.8	13.3 ± 4.7	0.3 (-0.6, 1.1)
Soft Tissue Fat-Free Mass (kg)						
Total	41.2 ± 8.6	40.9 ± 7.8	-0.3 (-1.2, 0.6)	40.5 ± 8.2	40.0 ± 9.0	-0.5 (-1.9, 0.9)
Arms	5.9 ± 1.8	5.8 ± 1.6	-0.1 (-0.3, 0.1)	5.7 ± 2.0	5.5 ± 2.1	-0.2 (-0.5, 0)
Legs	9.6 ± 3.1	10.9 ± 5.0	1.4 (-0.8, 3.5)	9.9 ± 2.1	9.2 ± 2.2	-0.4 (-0.9, 0.1)
Trunk	22.2 ± 4.6	21.0 ± 4.9	-1.2 (-3.3, 0.9)	21.9 ± 4.4	20.9 ± 6.8	-1.0 (-3.1, 1.1)
Body Fat (%)	39.9 ± 10.5	40.7 ± 9.9	0.8 (-0.3, 2.0)	36.5 ± 8.9	36.6 ± 9.3	0.1 (-1.8, 2.1)
Android Fat Mass (kg)	2.7 ± 1.1	2.8 ± 1.1	0.1 (-0.1, 0.2)	2.1 ± 1.0	2.1 ± 0.9	0.0 (-0.2, 0.1)
Gynoid Fat Mass (kg)	4.8 ± 2.2	4.9 ± 2.1	0.1 (0.0, 0.2)	4.1 ± 1.4	4.0 ± 1.5	-0.1 (-0.3, 0.1)

C7 Table 6 Fasting lipid profile at baseline and follow-up for HIIT and CON group.

	HIIT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
Triglycerides (mmol·L^{-1})	1.26 ± 0.66	1.09 ± 0.05	-0.17 (-0.41, 0.07)	1.17 ± 0.77	1.30 ± 0.81	0.13 (-0.17, 0.43)
NEFA (mmol·L^{-1})	0.64 ± 0.30	0.60 ± 0.23	-0.04 (-0.19, 0.10)	0.52 ± 0.32	0.48 ± 0.26	-0.03 (-0.14, 0.07)
TC (mmol·L^{-1}) *	4.93 ± 0.77	5.41 ± 0.80	0.48 (0.17, 0.80)	5.39 ± 2.15	5.15 ± 2.07	-0.23 (-0.51, 0.04)
HDL-C (mmol·L^{-1})	0.98 ± 0.19	1.14 ± 0.27	0.16 (0.05, 0.28)	1.17 ± 0.50	1.17 ± 0.52	-0.01 (-0.04, 0.03)
LDL-C (mmol·L^{-1}) *	3.39 ± 0.80	3.75 ± 0.96	0.37 (0.10, 0.64)	3.54 ± 1.62	3.30 ± 1.59	-0.24 (-0.61, 0.13)
TC: HDL-C	5.2 ± 1.2	4.9 ± 1.1	-0.3 (-0.5, 0.0)	4.9 ± 2.2	4.7 ± 2.1	-0.1 (-0.5, 0.2)

NEFA *non-esterified fatty acids*, HDL-C *high-density lipoprotein-cholesterol*, LDL-C *low-density lipoprotein-cholesterol*, TC *total cholesterol*

* p≤0.05 HIIT vs. CON at follow-up (after adjustment for baseline)

C7 Table 7 Self-reported measures of health and wellbeing at baseline and follow-up for HIIT and CON group.

	HIIT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
Exercise Self-Efficacy (ESES)	33.5 ± 4.5	34.8 ± 3.6	1.2 (-0.6, 3.0)	33.0 ± 3.5	33.7 ± 2.8	0.7 (-0.4, 1.8)
Shoulder Pain (WUSPI)	14.4 ± 13.2	13.8 ± 13.1	-0.7 (-4.2, 2.9)	13.3 ± 8.7	18.5 ± 26.5	5.3 (-13.5, 24.0)
Fatigue Severity (FSS)	3.8 ± 1.2	3.5 ± 1.2	-0.3 (-0.9, 0.2)	4.1 ± 1.5	4.4 ± 1.6	0.3 (-0.4, 1.0)
Health-related Quality of Life (SF-36)	73.8 ± 13.8	78.0 ± 12.4	3.9 (1.7, 6.0)	61.8 ± 16.0	66.9 ± 16.5	5.1 (-0.2, 10.4)
Functional Independence (SCIM-III)	69.1 ± 4.2	68.1 ± 6.2	-1.0 (-2.3, 0.3)	66.1 ± 4.8	67.6 ± 2.1	1.4 (-1.9, 4.8)

7.4 Discussion

The aim of this RCT was to determine the effect of a six-week home-based upper-body HIIT intervention on cardiometabolic component risks in individuals with chronic paraplegia. In contrast to our primary hypothesis, there was no change in fasting insulin concentrations between groups. However, a reduction in fasting insulin resistance (HOMA2-IR) was observed following HIIT in comparison to the CON group. There was also a tendency for an improvement in whole-body insulin sensitivity ($ISI_{Matsuda}$) following HIIT in comparison to the CON group. With respect to functional capacity, there was a significant improvement in PPO following HIIT in comparison to the CON group. Despite there being no significant improvement in $\dot{V}O_{2PEAK}$, 93% of the participants in the HIIT group increased their relative $\dot{V}O_{2PEAK}$. There was a significant increase in TC and LDL-C following HIIT in comparison to the CON group. Whilst there were several medium to large effect sizes, there were no significant changes in measures of body composition, physical activity, EI, postprandial glycaemic control, perceptions of health and wellbeing, or resting BP between groups.

7.4.1 Insulin Resistance/Sensitivity

There was a significant reduction in fasting insulin resistance (HOMA2-IR) following HIIT compared to the CON group. Several studies have reported that upper-body exercise is effective at improving fasting insulin resistance in individuals with chronic SCI (Kim et al., 2015; Nightingale et al., 2017d; Bresnahan et al., 2018). There is also evidence from a meta-analysis that HIIT is effective at reducing insulin resistance and fasting insulin concentrations in the general population (Jelleyman et al., 2015). These measures represent a reduction in hepatic insulin resistance following exercise training (Matthews et al., 1985), with a reduction in insulin secretion by the pancreas likely a key driver of this (Richter, Sylow and Hargreaves, 2021). Despite not reaching statistical significance (p=0.23), a medium effect size (d=0.62) was observed towards a reduction in fasting insulin concentrations following HIIT compared to the CON group.

There was also a tendency for a reduction in $ISI_{Matsuda}$-derived insulin sensitivity (p=0.057, d=1.10). The Matsuda Index considers both fasting and postprandial

glucose/insulin concentrations, and therefore provides an estimate of both peripheral and hepatic insulin (i.e., whole body) sensitivity. It is possible that this tendency towards a reduction in $ISI_{Matsuda}$ following HIIT is being primarily driven by hepatic insulin sensitivity (i.e., balance between fasting glucose and insulin). However, two previous studies reported no difference in $ISI_{Matsuda}$ following six weeks (180 per week, 60-65% $\dot{V}O_{2PEAK}$) and 10 weeks (90 min per week, 70% $\dot{V}O_{2PEAK}$) of upper-body MICT despite significant reductions in fasting insulin and HOMA-IR (Nightingale et al., 2017d; Bresnahan et al., 2018). Instead, it appears that upper-body HIIT may also improve peripheral insulin sensitivity. Given that this study has not yet met it's sample size calculation (21 out of 35 participants), it is likely that this trend towards significance for $ISI_{Matsuda}$ may reach statistical significance once the study is complete. Based on the observed effect size (*d*=1.10), 35 participants would be sufficient identify a significant effect for $ISI_{Matsuda}$.

A recent meta-analysis concluded that HIIT is effective at reducing postprandial glycaemia and insulinaemia, but only in participants with impaired glucose control (fasting glucose ≥5.6 mmol·L^{-1} or 2 h plasma glucose ≥7.8 mmol·L^{-1}) and the effect was only present in interventions lasting ≥8 weeks (Khalafi et al., 2022). Insulin sensitivity ($ISI_{Matsuda}$) increased following HIIT in three of the four participants meeting this definition of impaired glucose control. If upper-body HIIT can improve peripheral insulin sensitivity, it is likely due to localised skeletal muscle adaptations. For example, increased GLUT4, 5-adenonise monophosphate kinase (AMPK) and peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) abundance in the triceps muscle have been reported following 16 weeks of arm crank exercise (200 min per week, 75% HR_{PEAK}) in five individuals with chronic paraplegia (Gorgey et al., 2017). However, this did not result in any change in insulin sensitivity (assessed via IVGTT).

The prevalence of impaired glucose tolerance and insulin resistance in individuals with SCI is high (Cragg et al., 2013a), and our sample appears to be representative of this. The most valid diagnostic index of insulin sensitivity in individuals with chronic SCI is the QUICKI (Farkas et al., 2021a). Using this index, insulin resistance (QUICKI ≤0.339) was detected at baseline in 37% of our participants. At follow-up, one participant in the HIIT group was no longer classified as insulin resistant using this criterion. Fasting hyperglycaemia (fasting glucose ≥5.6 mmol·L^{-1}) was identified

in 21% of our participants at baseline and follow-up. This included one participant with fasting plasma glucose concentrations meeting the criteria for T2D (≥7.0 mmol·L^{-1}) (American Diabetes Association, 2020). Furthermore, 18% of our participants presented with undiagnosed T2D following the OGTT (2 h plasma glucose ≥11.1 mmol·L^{-1}) at baseline and follow-up (American Diabetes Association, 2020).

7.4.2 Functional Capacity

PPO increased by ~13% (range: -3% to +29%) following HIIT and remained unchanged in the CON group. This increase in physical capacity is consistent with previous upper-body HIIT interventions in individuals with SCI (Tordi et al., 2001; Hasnan et al., 2013; McLeod, Diana and Hicks, 2020). Improvements in physical capacity are likely to make activities of daily living easier to perform and have been associated with increased life satisfaction in persons with SCI (Manns and Chad, 1999; van Koppenhagen et al., 2014). The magnitude of the increase in PPO is lower than the 20% increase reported following six weeks of MICT (180 min per week, 60-65% $\dot{V}O_{2PEAK}$) (Nightingale et al., 2017d). However, our HIIT intervention involved just 40 min per week of 'active' exercise, and therefore a ~13% increase in PPO represents a substantial improvement in this context.

Alternatively, the modest improvements in PPO may be due to the above average baseline fitness levels of our participants. The relative $\dot{V}O_{2PEAK}$ of the male participants could be classified as excellent (n=4, >22.4 mL·kg^{-1}·min^{-1}), good (n=3, 17.7-22.4 mL·kg^{-1}·min^{-1}), average (n=2, 15.31-17.69 mL·kg^{-1}·min^{-1}), and fair (n=1, 12-15.3 mL·kg^{-1}·min^{-1}) (Simmons, Kressler and Nash, 2014). Ten of the eleven female participants had a baseline relative $\dot{V}O_{2PEAK}$ above the median (>13.2 mL·kg^{-1}·min^{-1}) for this population (Simmons, Kressler and Nash, 2014).

Despite the improvement in PPO, there was no significant difference in $\dot{V}O_{2PEAK}$ between groups. This is in contrast to consistent findings from HIIT interventions in non-injured populations (Weston et al., 2014). However, there was an increase in relative $\dot{V}O_{2PEAK}$ (+10%) for 13 of the 14 participants in the HIIT group. This is likely due to inter-individual variation in a relatively small sample. One participant in the HIIT group had a lower absolute (-22%) and relative (-13%) $\dot{V}O_{2PEAK}$ at follow-up

compared to baseline, despite achieving a higher PPO. Additionally, one participant in the CON group had a higher relative (+16%) and absolute (+19%) $\dot{V}O_{2PEAK}$ at follow-up compared to baseline.

7.4.3 Lipid Profile and Energy Balance

There was a significant increase in TC and LDL-C, and a trend towards an increase in HDL-C (p=0.065, *d*=0.99) following HIIT compared to the CON group. This is in contrast to evidence from the general population that exercise (both MICT and HIIT) can reduce TC and LDL-C (Wood et al., 2019). Other studies utilising upper-body MICT have reported no changes in the lipid profile in individuals with chronic SCI (Kim et al., 2015; Horiuchi and Okita, 2017; Nightingale et al., 2017d; Bresnahan et al., 2018). Additionally, whilst there were no significant differences between groups, we observed medium to large effect sizes for body mass (*d*=0.73), total FM (*d*=0.63), and gynoid FM (*d*=0.88), suggesting that body composition deteriorated in the HIIT group in comparison to the CON group. Despite there being no significant differences between groups, we observed medium to large effect sizes for a reduction in PAL (*d*=0.66) and light-intensity physical activity (*d*=0.85), and an increase in sedentary time (*d*=0.69), suggesting that individuals in the HIIT group may have 'substituted' the prescribed exercise in place of their habitual non-prescribed physical activity (Thompson, Peacock and Betts, 2014). Therefore, we speculate that individuals in the HIIT group may have been in a small but sustained positive energy balance, which led to an increase in adiposity and dyslipidaemia (Howard, Ruotolo and Robbins, 2003).

Alternatively, it is also possible that individuals in the HIIT group overcompensated their EI in relation to the EE of exercise performed, thus leading to a small but sustained positive energy balance. Firstly, it is important to highlight that we observed no significant changes in total energy or macronutrient intake, although there was a small effect size (*d*=0.47) for increased carbohydrate intake for HIIT vs. CON. However, the inaccuracies of self-reported food diaries to assess EI are well-known and are evident in the mismatch between energy intake and TDEE at baseline (EI ~29% lower than TDEE) (Livingstone and Black, 2003; Ravelli and Schoeller, 2020). Secondly, there is convincing evidence that exercise has no effect on subsequent EI (Schubert et al., 2013). However, a recent study suggests that EI

is increased in anticipation of performing a bout of aerobic exercise (EE of ~636 kcal), although a 24-h negative energy balance remained (~436 kcal) (Barutcu et al., 2020). For the participants in the present study, exercise EE of the HIIT sessions would have been substantially lower (~100-150 kcal). Even if there was a small anticipatory increase in EI prior to performing HIIT in the present study, this is likely to have at least eroded the exercise-induced energy deficit and may explain why (or in combination with substitution of physical activity) we observed an increase in TC and LDL-C concentrations.

7.4.4 Resting Blood Pressure

There were also no significant differences in resting systolic or diastolic BP between the groups. The available evidence suggests that upper-body exercise doesn't reduce resting BP in individuals with a chronic SCI, at least in those not presenting with hypertension at baseline (C3 Figure 2). Studies in the general population have demonstrated that HIIT is effective at reducing BP (Batacan et al., 2016), particularly for those presenting with elevated levels at baseline (Clark et al., 2020). To this regard, two participants in the HIIT group presented with hypertension (≥130/85 mmHg) at baseline, with BP reducing from 134/89 mmHg to 125/76 mmHg for one participant. Systolic and diastolic BP remained almost unchanged in the other participant. Further studies including those presenting with hypertension at baseline are required to determine if upper-body HIIT is effective at reducing BP.

7.4.5 Health and Wellbeing

We observed no significant differences in any self-reported measures of health and wellbeing following upper-body HIIT in comparison to the CON group. This is in contrast to Nightingale et al. (2018) who reported positive changes in exercise self-efficacy, fatigue severity, and health-related quality of life following six-weeks of home-based arm-crank MICT in individuals with chronic paraplegia. The reasons for this discrepancy are somewhat unclear. We observed a medium effect size towards a reduction in fatigue severity (d=0.76, p=0.12). Additionally, exercise self-efficacy and health-related quality of life increased from baseline to follow-up in both HIIT and CON groups. We speculate that the increase in the CON group, may be due to the easing of COVID-19 restrictions that coincided with the study dates (April-Dec

2021). This population were deemed clinically vulnerable, and therefore spent considerable time shielding during the pandemic. Physical activity levels can effect health-related quality of life (Ravenek et al., 2012), and these both decreased during the pandemic in individuals with a neurologically-related mobility disability (Nightingale et al., 2021). As restrictions eased over the study period, it is likely that physical activity levels began to return to normal, and social interactions increased. This theory seems to be apparent in the physical activity data collected, with time spent performing light (+75 min·day^{-1}) and moderate-intensity (+5 min·day^{-1}) physical activity increasing from baseline to follow-up in the CON group. Irrespective of this, all participants in the HIIT group perceived that the exercise programme would help maintain their health in the long-term, and self-reported a number of health-related benefits, including feeling stronger and fitter, improved sleep, feelings of wellbeing, and increased motivation to exercise. Importantly, there was no increase in shoulder pain following HIIT, which helps to alleviate concerns that upper-body HIIT may cause pain and injury (Gauthier et al., 2018).

7.4.6 Compliance, Feasibility, and Safety

Adherence to the HIIT intervention was high, just two participants withdrew from the HIIT group, due to reasons unrelated to the intervention. Compliance was also very high, with 96% of all prescribed HIIT sessions completed, and this is similar to home-based MICT (Nightingale et al., 2017d) in the same population. Our high compliance rate was likely due to the home-based nature of the exercise intervention, which address some of the barriers to exercise participation in this population (i.e., transportation, lack of facilities) (Kehn and Kroll, 2009). Additionally, the weekly check-ins with the research team, use of live visual feedback (i.e., Wahoo® Tcker X), and remote monitoring of compliance, are all likely to have improved exercise compliance (Argent, Daly and Caulfield, 2018).

Participants were able to perform HIIT unsupervised on a table-top arm crank ergometer, supporting the feasibility of this form of exercise in individuals with chronic SCI. Typically, participants used Week 1 of the intervention to become accustomed to the workload and cadence required to elicit meet their target HR response. HR data from Weeks 2 to 5 of the intervention highlight that it took three to four high-intensity intervals to reach the target HR. This is likely due to relatively

short duration of the high-intensity interval efforts and has been observed in cycling-based studies (Currie et al., 2013). Therefore, it could be prudent to either extend the duration (8 x 2 min intervals) or number (e.g., 12-15 x 1 min intervals) of high-intensity intervals to increase the time spent exercising ≥80% HR_{PEAK}.

There was considerable inter-individual variability in HR responses across the HIIT intervention, and three participants self-reported that they struggled to reach the target HR. For example, one participant with a T6 injury spent just 4 ± 3% of each session (averaged across Weeks 1-5) at an intensity meeting the definition of HIIT (≥80% HR_{PEAK}). However, they reported an RPE of 18 ± 0 across the intervention suggesting they were working very hard. $\dot{V}O_{2PEAK}$ and PPO increased by 18% and 10% respectively for this participant. Conversely, one participant with a L2 injury spent 21 ± 17% of each session at an intensity ≥80% HR_{PEAK} but reported an RPE of 13 ± 1 across the intervention. This also highlights the methodological issues of using $\%HR_{PEAK}$ to prescribe exercise intensity in individuals with an SCI, as recently raised by Hutchinson and Goosey-Tolfrey (2021). They demonstrate that for individuals exercising at the same $\%HR_{PEAK}$ (or $\%\dot{V}O_{2PEAK}$), the intensity domain (as defined using lactate thresholds) can vary substantially between individuals. The use of RPE to guide HIIT programmes may be provide more homogenous training responses across participants with an SCI.

Considering the inter-individual variability to exercise at the same $\%HR_{PEAK}$ in persons with SCI, and the difficulties with maximising time spent exercising ≥80% HR_{PEAK} during HIIT protocols involving 60-s intervals, future studies may consider the 4 x 4 min protocol (Rognmo et al., 2004) in individuals with SCI. This protocol also involves a total exercise duration of 30 min, with 3-minute active recovery periods interspersing the 4-min high-intensity efforts and is designed to elicit an intensity of 85-95% HR_{PEAK} in the general population. Taylor et al. (2019) provide recommendations for the adaptation of this protocol for delivery to clinical populations. In brief, this protocol can be adapted to be guided by RPE, with a target of 15 (i.e., hard) for the first interval, progressing to 17-18 (i.e., very hard) by the fourth and final interval.

Importantly, all participants self-reported that they found the HIIT intervention enjoyable. This supports findings from other upper-body HIIT interventions in individuals with SCI (Koontz et al., 2021). Enjoyment of exercise has been reported

to be a barrier to physical activity participation in persons with SCI (Kehn and Kroll, 2009), and predicts adherence to future physical activity behaviour (Lewis et al., 2016). Finally, there were no adverse cardiovascular events reported to the research team across 333 home-based HIIT sessions, supporting other findings from pilot studies that upper-body HIIT is safe for individuals with chronic paraplegia (Gauthier et al., 2018; Koontz et al., 2021).

7.4.7 Strengths and Limitations

This study used a minimisation approach to randomly assign participants to HIIT and CON groups as recommended by Altman and Bland (2005). Consequently, there were no significant differences in age, sex, and TSI between groups. Both groups also had similar proportions of individuals with high thoracic (HIIT: 36% at or above T6, CON: 29% at or above T6) and complete (HIIT: 79% complete, CON: 71% complete) injuries. There were also no significant differences in any outcome measures relating to cardiometabolic health (other than alcohol consumption) at baseline between groups. This is a substantial strength of the study given the huge variation of injury characteristics and potential confounders that SCI encompasses. Furthermore, this is the first study in the context of upper-body exercise interventions to compare means between groups after the adjustment of the baseline value using ANCOVA's, as recommended by Bland and Altman (2015). The benefits of this approach are clear when considering the inter-individual variability in cardiometabolic responses (despite not being statistically significant) that we observed at baseline.

The findings can be applied to both males and females due to the almost equal sex distribution of our sample (48% males, 52% females). This is a significant strength of our study as only ~15% of participants in exercise interventions assessing cardiometabolic outcomes in this population are conducted in females (see Chapter 4). Furthermore, we carefully controlled for the menstrual cycle in eumenorrheic females due to its effect on insulin sensitivity (Escalante Pulido and Alpizar Salazar, 1999). Additionally, our participants also appear to be highly representative of the general SCI population, with respect to the prevalence of cardiometabolic risk factors (i.e., obesity, lipid profile, and physical activity levels).

We used a validated and individually calibrated device to measure physical activity levels at baseline and follow-up (Nightingale et al., 2017e). This should be considered a significant strength of the study as we were able to determine 'physical activity substitution' behaviors in the HIIT group, in addition to any change in the habitual physical activity levels of the CON group. Nightingale et al. (2017f) recommend that at least 4 valid days (>80% of data for that 24 h period) are required to reliability assess PAL. Unfortunately, these criteria were not met for five participants (4 HIIT, 1 CON) in the follow-up period, and this has limited our interpretation of the data, particularly in the HIIT group. We decided to include all days where >50% of data for that 24 h period (C7 Table 2) was recovered to maximize the number of participants included in the final statistical analysis. To improve total wear time, participants should be reminded of the importance of monitoring habitual physical activity during the follow-up period.

This study has yet to meet its a-priori sample size calculation, and this likely explains the moderate effect sizes without statistical significance, that we observed. However, this study is still one of the largest to assess the effect of upper-body exercise on cardiometabolic health outcomes in persons with chronic SCI. Furthermore, the duration of our exercise intervention (six weeks) was relatively short in comparison to the most frequent exercise intervention length (12 weeks, see Chapter 4) in this population. As highlighted by Batacan et al. (2016), the short term (<12 weeks) and long term (≥12 weeks) benefits of HIIT on biomarkers of cardiometabolic health differ, and it is likely that a longer exercise intervention may have revealed additional significant effects.

7.4.8 Conclusion

Home-based arm crank ergometry HIIT is safe, feasible, and enjoyable for individuals with chronic paraplegia. A six-week intervention improved physical capacity and fasting insulin resistance and appeared to also improve peripheral insulin sensitivity. However, deleterious effects on the lipid profile were observed and warrant further investigation.

Chapter 8 - General Discussion

8.1 Overview

The overarching aim of this thesis was to determine the acute and chronic training effects of upper-body high-intensity exercise on markers of CVD risk in persons with SCI. In Chapter 4 we performed a systematic review of the available published literature to determine the effect of exercise (including upper-body exercise) on individual CMS risk factors in adults in chronic SCI. Eligible studies were assessed for study quality and synthesised using a coding system to determine the number of studies reporting an improvement in measures relating to obesity, inflammation, dyslipidaemia, glycaemic control, and thrombotic state. In Chapters 5 and 6, the effect of a single or acute bout of upper-body exercise (HIIE and MICE) on postprandial metabolism were characterised. Specifically, we determined the effect of performing these exercise protocols immediately prior to the ingestion of a mixed-macronutrient meal in individuals with chronic paraplegia (Chapter 5). Comparisons were made to a resting CON condition, and concentrations of glucose, insulin, and TGs were determined. Following this, we determined the effect of performing upper-body HIIE and MICE the evening prior to the ingestion of a mixed-macronutrient meal in non-injured individuals, with a primary focus on PPL (Chapter 6). Finally, the effect of performing chronic upper-body HIIT on biomarkers of cardiometabolic health in individuals with chronic paraplegia was determined (Chapter 7). A RCT design was adopted, whereby individuals performed either six-weeks of home-based HIIT on an arm crank ergometer or were instructed to continue their habitual lifestyles. The primary outcome measures were insulin resistance and functional capacity. Secondary outcome measures included body composition, postprandial glycaemic control the lipid profile, and perceptions of health and well-being. This Chapter will summarise and interpret the findings of the experimental studies presented in this thesis.

8.2 Effect of Exercise on CMS Risk Factors in SCI

Our systematic review found consistent evidence that upper-body aerobic exercise is effective at reducing waist circumference (i.e., central obesity), and improving fasting insulin concentration and HOMA-IR (i.e., hepatic insulin sensitivity) in persons with chronic SCI. There were also consistent findings that upper body aerobic exercise alone is not effective at improving fasting glycaemia, the lipid profile, or resting BP. These findings support the notion that upper-body MICT offers only modest benefits to cardiometabolic health outcomes (Nightingale et al., 2017a). We also concluded that the addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile, which supports the current SCI-specific exercise guidelines (Martin Ginis et al., 2018). Finally, this systematic review also highlighted that the evidence base pertaining to exercise and CMS outcomes lacks high-quality RCT's with a-priori sample size calculations, and gold-standard outcome measures (e.g., DEXA, IVGTT).

8.3 Effect of Upper-Body Exercise on Postprandial Metabolism in SCI

A single bout of lower-body HIIE or MICE can reduce postprandial glucose and TG excursions for up to 24 h (Freese, Gist and Cureton, 2014; Cassidy et al., 2017), however it is unclear if upper-body exercise can have a similar effect in individuals with a SCI. We demonstrated that following an overnight fast, an acute bout of upper-body HIIE (8 x 60 s at 70% PPO) or MICE (25 min at 45% PPO) were both ineffective at reducing postprandial glucose and TG responses to a MMTT in persons with chronic paraplegia. This is line with recent findings that upper-body MICE (40 min at 30% PPO) and HIIE (~8 x 2 min intervals at 70% PPO) were also both ineffective at reducing these postprandial responses in individuals with chronic paraplegia (McMillan et al., 2021c). However, there was a trend ($p=0.06$, $d=0.30$) towards a significant reduction in insulin iAUC following MICE compared to the resting control condition. Although no statistically significant time-course differences were observed between these conditions, this trend appeared to occur due to reductions in insulin concentrations at 60, 90, and 120-min post meal consumption, and suggests that an acute bout of upper-body MICE may improve postprandial insulin sensitivity. Finally, participants reported a preference for HIIE compared to MICE, in addition to a greater fondness and exercise self-efficacy, supporting

existing evidence that upper-body HIIE is enjoyable and a viable training modality for persons with SCI (Astorino and Thum, 2018a).

8.4 Effect of Upper-Body Exercise on PPL in Non-Injured Individuals

Lower-body HIIE performed 12-18 h prior to meal tolerance assessment appears to be more effective than MICE at reducing PPL in non-injured individuals (Trombold et al., 2013; Lee, Kuo and Cheng, 2018), however it is unclear if upper-body exercise can offer the same benefit. Our study demonstrated that an acute bout of upper-body HIIE (10 x 60 s at 80% P_{PEAK}) and iso-energetic (~140 kcal) MICE (50% P_{PEAK}) performed the evening prior to a MMTT were both ineffective at reducing PPL in heathy non-injured adults. There were also no differences in glycaemic or insulinemic responses between conditions, suggesting the well-established acute improvement in insulin sensitivity (lasting up to 24-h) following lower and whole-body exercise is not true for upper-body exercise. We speculate that these discrepancies are due to the substantially lower EE achieved during upper-body exercise.

8.5 Effect of Upper-Body HIIT on Cardiometabolic Health in SCI

Upper-body HIIT and SIT studies have demonstrated that this form of exercise is feasible, enjoyable, and effective at improving functional capacity in individuals with SCI (Tordi et al., 2001; Graham et al., 2019; McLeod, Diana and Hicks, 2020), however any metabolic adaptations are unclear. We found that fasting insulin resistance (HOMA2-IR) significantly improved following six weeks of arm-crank ergometry based HIIT, with a trend towards an improvement in postprandial insulin sensitivity ($ISI_{Matsuda}$). This data suggests upper-body HIIT may be effective at improving both hepatic and peripheral (i.e., at the skeletal muscle) insulin sensitivity. In addition, upper-body HIIT significantly improved physical capacity (i.e., PPO). However, there were negative changes to the lipid profile (increased TC and LDL-C) following HIIT compared to the CON group. We speculate that this could be due to physical activity substitution and/or increased EI, although no significant differences in these variables were found between groups. Finally, we demonstrated

that home-based upper-body HIIT (10 x 60 s at 80-90% HR_{PEAK}) is feasible, safe, and enjoyable for individuals with chronic paraplegia.

8.6 Research Limitations and Considerations

The HR profiles across the HIIE sessions presented experimental chapters in this thesis reveal that participants typically only reached an intensity meeting the definition of HIIT (≥80% HR_{PEAK}) (MacInnis and Gibala, 2017) in the final four to six high-intensity work intervals. It is possible that this could explain the lack of significant differences in postprandial metabolites following acute exercise (Chapters 5 and 6) and somewhat limited changes in metabolic health markers (Chapter 7) that we observed. Future studies should consider using alternative upper-body HIIE protocols. For example, 2:2 min HIIE protocol (e.g., 70%: 10% PPO) has been shown to be feasible in individuals with SCI, and resulted in a substantial proportion (~30%) of the session spent above 80% HR_{PEAK} (McMillan et al., 2021d).

Stringent standardisation procedures were adopted for the experimental chapters presented in this thesis, including instructing participants to abstain from exercise, caffeine and alcohol in the 24 to 48 h before each laboratory visit. In Chapters 5 and 7, participants were also instructed to record and replicate a non-weighed food diary in the two days prior to main laboratory visits. Despite this, there was still substantial intra-individual variation in fasting metabolite concentrations between visits in Chapter 5. To carefully control for prior diet and physical activity, and reduce intra-individual variation, future studies should consider the feasibility of providing standardised meals and overnight accommodation in the 24 h prior to testing.

Postprandial metabolism in Chapters 5 and 6 was assessed using a MMTT. Whilst the macronutrient composition of the MMTT reflected a typical meal, we fed a large bolus of liquid calories (~1000-1200 kcal) that isn't typically consumed from the fasted state. A more ecologically valid approach would be to consider feeding typical breakfast and lunch meals, each followed by a 2-3 h postprandial period, as recently employed by Bailey et al. (2020). In Chapter 7, the OGTT was used to determine the effect of upper-body HIIT on postprandial glycaemic control. This decision was taken primarily to compare this form of exercise with other MICT interventions in this

population (Kim et al., 2015; Nightingale et al., 2017d; Bresnahan et al., 2018). However, the reproductivity of the OGTT across multiple tests has been reported to be low (Ko et al., 1998; Jimenez-Navarro et al., 2010). Furthermore, the indices generated from the OGTT (e.g., $ISI_{Matsuda}$) only provide a surrogate estimate of peripheral insulin sensitivity as the glucose absorbed from the gut most first pass through the liver. Therefore, we were not able fully decipher the effect of upper-body HIIT on peripheral (i.e., at the skeletal muscle) and hepatic insulin sensitivity. Future studies should consider using the IVGTT to assess skeletal muscle insulin sensitivity (Bergman, 1989). The IVTT involves the direct infusion of glucose into the bloodstream, and therefore bypasses the liver. To our knowledge, only one study has employed this method to determine the effect of upper-body aerobic exercise training on insulin sensitivity in persons with SCI (Gorgey et al., 2017).

Physical activity and RMR were assessed at baseline and follow-up to calculate TDEE in Chapter 7. However, due to the inaccuracies of self-reported EI, it was not possible to accurately determine if individuals in the HIIT group were in a greater positive energy balance in comparison to the CON group, which limited our understanding as to why TC and LDL-C increased following exercise training. Self-reported food diaries typically underreport total EI by 20-30% (Freedman et al., 2014), which was consistent with our findings under the assumption that participants were at least in energy balance at baseline. This is largely due to participant burden, and technologies are being developed to overcome this (e.g., digital photography), although they are not yet deemed to have acceptable precision for research use (Höchsmann and Martin, 2020). Nightingale et al. (2017f) reported an order effect when asking individuals with SCI to complete a seven-day food diary, whereby participants reported consuming fewer calories on day seven compared to day one. Therefore, to help reduce participant burden and potentially improve accuracy, future studies in this area should consider asking participants to record a food diary on selected days throughout the exercise intervention (e.g., three days per week), in addition to a seven-day diary at baseline and follow-up. Furthermore, it would have been prudent to attempt to capture additional physical activity (e.g., wrist-worn monitor and/or physical activity diary) in both the HIIT and CON groups throughout the study period to enhance our understanding of ‘physical activity substitution’ in the HIIT group or changes in the CON group.

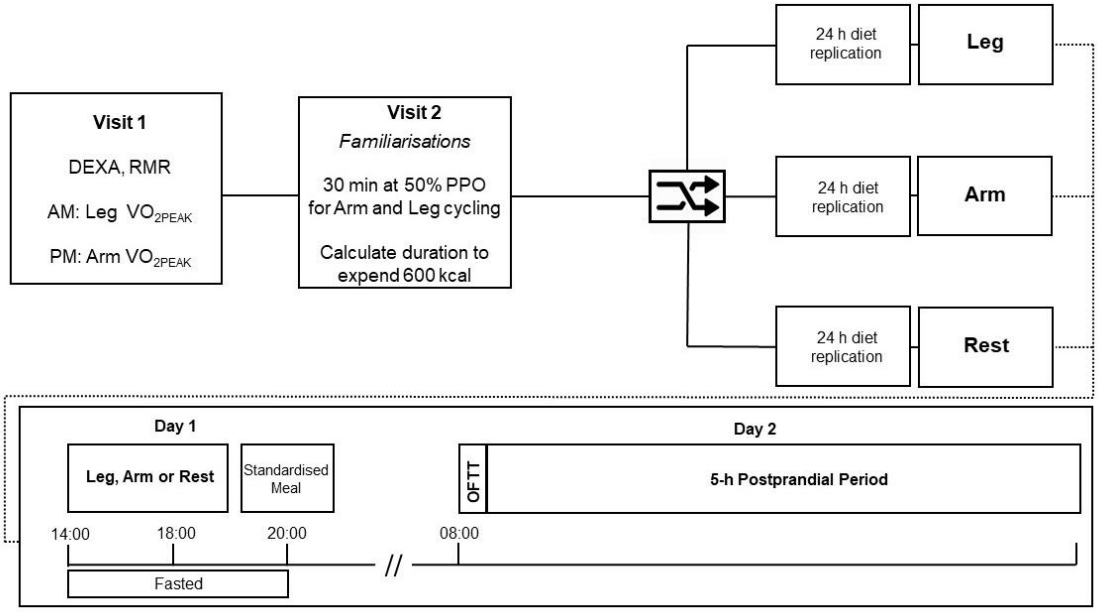
To maximise compliance, no dietary restrictions were imposed on participants performing the HIIT intervention in Chapter 7. Participants were only advised to avoid eating in the hour prior to exercise (to avoid any potential gastrointestinal issues). Whilst performing cycling based HIIT in the fasted or fed state appears to offer similar metabolic adaptations (Gillen et al., 2013), there is evidence to suggest that carbohydrate replacement in the post-exercise period can attenuate improvements in whole-body insulin sensitivity following an acute bout of prolonged moderate-to-vigorous treadmill exercise (Johnson-Bonson et al., 2021). Additionally, post-exercise carbohydrate-energy replacement following HIIE has been shown to attenuate glycaemic control the following day in untrained women (Estafanos et al., 2022). Whether post-exercise carbohydrate replacement in the post-exercise period following upper-body exercise has any effect on these outcomes is not currently unknown, however future interventions in individuals with SCI should consider controlling for this potential confounding variable to reduce inter-individual variation.

8.7 Future Research

8.7.1 PPL: Muscle Mass vs. Energy Expenditure

As highlighted in this thesis, it remains unclear if an acute bout of upper-body exercise can reduce PPL. The lack of change in PPL following upper-body exercise in studies to date, could be either due to an insufficient EE or reduced active skeletal muscle mass (in comparison to cycling or running/walking). Cycling and walking protocols (of moderate intensity) eliciting an EE of ~600 kcal, performed 12-18 h prior to an OFTT have consistently been shown to be sufficient to reduce PPL in healthy individuals (Kolifa, Petridou and Mougios, 2004; MacEneaney et al., 2009; Brandauer et al., 2013). By comparing the effects of a single bout of isoenergetic leg and arm ergometry on subsequent PPL, it may be possible to determine if the lack of attenuation in PPL following arm crank exercise (observed in Chapters 5 and 6, and other published studies) is due to an insufficient EE or smaller volume of active muscle mass. A potential outline of a study protocol to determine this is presented in C8 Figure 1; '*The effect of isoenergetic cycling or arm crank exercise on PPL'*. Whilst the duration of the upper-body exercise bout would extreme (~90 min) and unrealistic for exercise promotion in individuals with an SCI, this study

design would help determine if it physiologically possible to reduce PPL through upper-body exercise alone.



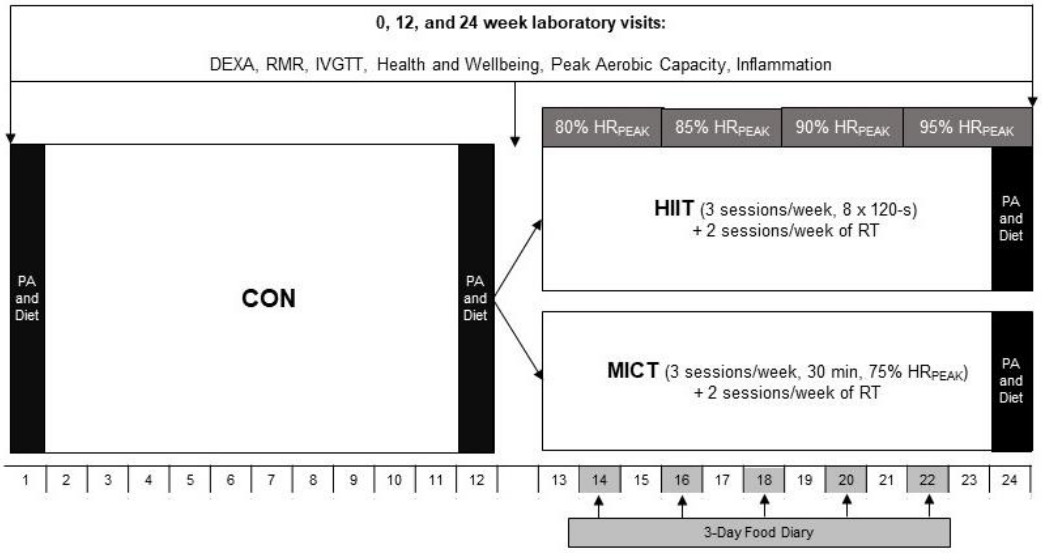
C8 Figure 1 Schematic of a possible study design to compare the effect of isoenergetic lower-body vs. upper-body exercise on PPL in healthy adults

This study would involve healthy non-injured adults initially performing a cycling and arm crank based $\dot{V}O_{2PEAK}$ test. The duration of exercise required to produce an EE of 600 kcal at a set-intensity (e.g., 50% PPO) would be calculated for each exercise modality. In a randomised cross-over design, participants would perform either an iso-energetic bout of cycling or arm crank exercise, or a resting CON condition, the evening prior to an OFTT.

8.7.2 SCI-Exercise Guidelines: MICT vs. HIIT

The findings from the upper-body HIIT intervention presented in this thesis suggest that this form of exercise may be able to elicit improvements in peripheral insulin sensitivity (in addition to fitness and hepatic insulin resistance). However, similar to upper-body MICT (four x 45 min at 60-65% $\dot{V}O_{2PEAK}$, six weeks), this form of exercise appears to be unable to positively change lipid profile or DEXA-derived measures of body composition (Nightingale et al., 2017d). However, as highlighted in the limitations, the intervention length is short which likely limits cardiometabolic adaptations and the HIIT protocol used was potentially not optimal. Both of the

aforementioned studies did not include a RT component, which is in contrast to SCI-specific and global exercise guidelines (Tweedy et al., 2017; Ginis et al., 2018; Bull et al., 2020). The findings from the systematic review presented in Chapter 4, also appear to suggest that benefits to the lipid profile are only seen when upper-body resistance and aerobic exercise are combined. Similarly, in the general population, there is also evidence that combined aerobic and resistance exercise interventions are more effective than aerobic exercise training alone at improving CVD risk factors, including insulin sensitivity, body composition and the lipid profile (Ho et al., 2012; Bird and Hawley, 2017; Schroeder et al., 2019). Therefore, we outline a potential study design to determine to effects of MICT or HIIT (both combined with RT) in C8 Figure 2; '*The effect of upper-body MICT and HIIT on cardiometabolic component risks in persons with chronic paraplegia".*



C8 Figure 2 Schematic of a possible study design to assess effect of upper-body HIIT and MICT (both combined with resistance training) in individuals with chronic paraplegia.

Participants would undergo three laboratory assessments (0, 12, and 24 weeks) in a RCT, with a control lead-in phase. All participants would initially undertake a 12-week habitual physical activity and diet maintenance phase before being randomised to either a 12-week home-based HIIT or MICT exercise programme. This study design removes the need for a third arm of a RCT and allows participants to act as the CON group, therefore a lower total sample size would be required and interindividual variation would be removed. The MICT protocol (three sessions per

week, 30 min, 75% HR_{PEAK}) is designed to meet the SCI-exercise guidelines for improving cardiometabolic health (Ginis et al., 2018), whilst the HIIT (three sessions per week, 30 min, 8 x 2 min at 80-95% HR_{PEAK}) protocol is designed to match the total exercise volume of the MICT group, whilst optimising time spent above 80% HR_{PEAK} (McMillan et al., 2021d). Additionally, participants would be asked to perform twice-weekly home-based upper-body RT (three sets x 10 repetitions, 3-6 RPE) using resistance bands and dumbbells, as per the SCI-exercise and WHO physical activity guidelines (Martin Ginis et al., 2018; Bull et al., 2020).

Ultimately, at least for upper-body exercise, a combination of HIIT, MICT, and RT is likely needed to provide the greatest benefits across various measures of cardiometabolic health for individuals with an SCI. Prolonged bouts of upper-body MICT (45-60 mins) appear to be needed to elicit reductions in markers of central obesity (Chapter 4) and whole body reductions in FM (Farkas et al., 2021b), whilst upper-body RT and HIIT are likely needed to elicit improvements in the lipid profile (Chapter 4) and peripheral insulin sensitivity (Chapter 7) respectively. Future research should look to combine these exercise modalities into a realistic multi-model home-based intervention for persons with SCI.

8.8 Conclusions

To summarise, this thesis systematically reviewed the available literature to determine that upper-body aerobic exercise training is effective at reducing waist circumference, and increasing hepatic insulin sensitivity in individuals with SCI. We also determined that that an acute bout of upper-body exercise, regardless of intensity (HIIE or MICE) or timing (1 h or 14 h prior) had no effect on postprandial metabolism. The limited muscle mass and/or EE of upper-body exercise likely limits any improvement in acute postprandial responses. Finally, a RCT demonstrated that six weeks of home-based upper-body HIIT increased physical capacity and fasting insulin sensitivity in individuals with chronic paraplegia, and therefore may be a therapeutic exercise solution for this population.

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Appendices

Appendix A – Screening Questionnaires

(i) Participant Background Questionnaire
(ii) Health History Questionaire

Appendix B – Home-based HIIT Material

(i) Exercise Training Instructions
(ii) Shoulder Exercises

Appendix C – Exit Questionnaire

Appendix A - (i)

Participant Questionnaire

1. Age _____ years

2. Please state the exact level of spinal cord injury sustained (e.g., T6)

_____

3. What is your completeness of injury based on the American Spinal Injury Association (ASIA) Impairment Scale?

A = Complete

B = Incomplete

C = Incomplete

D = Incomplete

E = Normal

4. How long ago did you sustain the spinal cord injury? _____ years

5. Are you currently engaged in a regular exercise programme?

YES/NO

If 'yes' please provide details:

_____

_____

6. Are you currently taking any medication, vitamins, or supplementations?

YES/NO

If 'yes' please provide details:

_____

_____

7. Do you have any allergies, intolerances or religious needs related to food consumption?

YES/NO

If 'yes' please provide details:

_____

_____

8. Do you smoke? YES/NO

If circled 'yes', please state information on roughly how often, for how long, and any other relevant information below:

9. Are you currently weight stable? (weight not changed by more than 3% in the last 3 months)

YES/NO

10. Do you have any plans to change your current lifestyle (e.g., diet or physical activity) during the study period?

YES/NO

11. Females only, which of the below statement most appropriately describes your menstrual cycle?

A) Eumenorrheic (regular menstrual cycle; 28 ± 7 days)
B) Oligomenorrheic (irregular menstrual cycle; >35 days)
C) Amenorrheic (absence of menstrual cycle; >90 days but <365 days)
D) Postmenopausal (absence of menstrual cycle for ≥365 days)
E) Using Contraception (of any kind)

Based on your choice above,

A) If Eumenorrheic, please state number of days since onset of last menstruation: ……. Day(s). And average menstrual cycle length (i.e., first day of menses to day preceding next menses): …... Days.

B) If Oligomenorrheic, please state number of days since onset of last menstruation: ……. Day(s). And average menstrual cycle length (i.e., first day of menses to day preceding next menses): …... Days.

C) If Amenorrheic, please state approximately number of days since onset of last menstruation: ….. Day(s)

D) If Postmenopausal, approximately how long since your last menstruation:
..... Year(s) ….. Month(s) ….. Day(s)

E) If using contraception, please describe method / type below (e.g., combined pill, IUD, dose):

Appendix A – (ii)

Health History Questionnaire

It is important that volunteers participating in research studies are currently in good health to exercise. This is to ensure (i) their own continued wellbeing and (ii) to avoid the possibility of introducing bias into the study outcomes.

Please complete this brief questionnaire to confirm your eligibility to participate:

Further Health Screen continued overleaf…

1. **At present,** do you have any health problem for which you are:
   (a) on medication, prescribed or otherwise..... Yes ☐No ☐
   (b) attending your general practitioner..... Yes ☐No ☐
   (c) on a hospital waiting list……..Yes ☐No ☐

2. As far as you are aware, **do you suffer** or **have you ever** suffered from:
   (a) Convulsions/epilepsy..... Yes ☐No ☐
   (b) Asthma..... Yes ☐No ☐
   (c) Pressure sores..... Yes ☐No ☐
   (d) Diabetes..... Yes ☐No ☐
   (e) A blood disorder..... Yes ☐No ☐
   (f) Head injury..... Yes ☐No ☐
   (g) Digestive problems..... Yes ☐No ☐
   (h) Heart problems..... Yes ☐No ☐
   (i) Breathing problems……..Yes ☐ No☐
   (j) Disturbance of balance/coordination..... Yes ☐No ☐
   (k) Disturbance of vision..... Yes ☐No ☐
   (l) Ear / hearing problems..... Yes ☐No ☐
   (m) Thyroid problems..... Yes ☐No ☐
   (n) Kidney or liver problems..... Yes ☐No ☐
   (o) Urinary tract infection..... Yes ☐No ☐
   (p) Cognitive impairment..... Yes ☐No ☐
   (q) Problems with immune system……...Yes ☐No ☐
   (r) *Autonomic dysreflexia..... Yes ☐No ☐
   (s) Porphyria……Yes ☐No ☐
   (t) Myasthenia gravis……Yes ☐No ☐
   (u) Adam's-Stokes Syndrome……..Yes ☐No ☐
   (v) Wolff-Parkinson-White Syndrome…… Yes ☐No ☐

3. *__Has any,__ otherwise healthy, member of your family under the age of 35 died suddenly during or soon after exercise?.....Yes ☐ No ☐

a) If YES to any question, please describe briefly if you wish (e.g., to confirm problem was/is short-lived, insignificant or well controlled.)

.....
……
……
.....
.....
.....
.....
.....

b) If YES to questions indicated by (*) requires your Doctor to fill out the 'Doctors Consent Form' prior to participating in the trial.

Signature:

Date:

Thank you for your cooperation!

Appendix B - (i)

Intervention Group

You have been randomly assigned to the exercise group. We would like you to perform **4 exercise sessions per week** (each lasting 30 minutes) on the arm crank ergometer provided. Please see the video below for a guide of how to complete the exercise:

https://www.youtube.com/watch?v=RntfI4-eesk

DO:

- ✓ Ensure that an adult is around to supervise your exercise session
- ✓ Make sure that you empty your bladder prior to exercise
- ✓ Wear the Wahoo Heart Rate Monitor
- ✓ Record your session in your exercise training logbook
- ✓ Stop if you feel ill.
- ✓ Perform any other exercise/stretching you wish to.
- ✓ Contact Matt if you have any questions/issues.

DON'T:

- x Perform 2 HIIT sessions on the same day
- x Eat <1 hour before performing HIIT
- x If you have a mark, sore, or cut on a pressure bearing area, do not do any exercise which will aggravate it.

The researcher will contact you on a weekly basis to discuss how your training is going and make any adjustments if needed.

Appendix B – (ii)

Upper Body Stretches

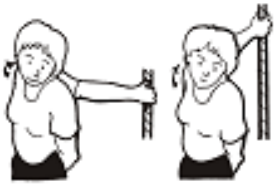
1. Neck Flexion/Extension Stretch
(forward, then back)

2. Neck Lateral Flexion Stretch
(one side, then the other)

3. Latissimus Dorsi and Posterior Deltoid Stretch
(link hands, push elbows together)

4. Triceps Stretch
(pull elbow across and down)

5. Shoulder Rotator Stretch
(using towel, pull up with the top arm then down with the other)



6. Pectoral Stretch at 90° and 120°
(use a doorway or post)

7. Bicep Stretch
(hands apart)

8. Supraspinatus Stretch
(keep elbow parallel to ground)

9. Wrist Extensor Stretch
(tilt head to opposite side, keep elbow straight)

Appendix C

Exit Questionnaire

1. How enjoyable do you find the exercise programme?

1	2	3	4	5
Not at all enjoyable	A little enjoyable	Neither enjoy or dislike	Quite enjoyable	Very enjoyable

2. Please list any benefits to you from taking part in the exercise.

3. Please list any difficulties you have found in doing the exercise programme.

4. Is there anything about the exercise programme that you would like to see changed?

Please let us know how much you agree/disagree with the following statements.

5. I am able to do the exercise programme with little difficulty or assistance.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

6. I feel it is worth my time to do the exercise programme.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

7. I think other individuals with spinal cord injuries will find the exercise programme enjoyable.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

8. I think the exercise programme is helping me to stay fit and strong.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

9. The exercise programme has interfered with my other priorities.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree

10. It is clear to me that this exercise programme would help maintain my fitness and health in the long-term.

1	2	3	4	5
Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree