Measurement of Physical Activity and its Role in the Maintenance of Health in Wheelchair Users

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MEASUREMENT OF PHYSICAL ACTIVITY AND ITS ROLE IN THE MAINTENANCE OF HEALTH IN WHEELCHAIR USERS

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ABSTRACT

There are clear recommendations regarding the amount of physical activity necessary for achieving health benefits and reducing the risk of chronic disease in able-bodied humans. However, there is a paucity of empirical evidence to inform the development of equivalent guidelines for various disabled populations. In order to better understand the role of physical activity in the health and wellbeing of wheelchair users, the logical foundation was to develop valid and reliable methods to accurately quantify physical activity. Therefore, the initial aim of this thesis was to assess the validity of objective wearable technologies in the prediction of physical activity energy expenditure (PAEE). Chapter 3 identified the wrist as the most appropriate anatomical location to wear a tri-axial accelerometer during outdoor wheelchair propulsion. In Chapter 4, a device comparison study was conducted in a controlled laboratory environment, using bespoke PAEE prediction equations, developed for this population. Mean absolute error for devices worn on the wrist were lower for the GENEActiv (21%) device compared to GT3X+ (33%), across all activities. Using a multi-sensor Actiheart device, the absolute prediction error was further reduced when an individual heart rate calibration was applied (16.8%), compared to a generic system calibration (51.4%) (Chapter 6). Incorporating accelerometry and physiological signals with individual calibration seemingly offered an improvement in the prediction of PAEE in wheelchair users.

This rigorous method development process permitted the habitual monitoring of free-living physical activity behaviour, during a home-based moderate-intensity exercise intervention in persons with chronic paraplegia. In comparison to a lifestyle maintenance control group, the intervention group completed a 6-week arm crank ergometry intervention, exercising 4 times per week for 45 minutes at 60 – 65% $\dot{V}O_2$ peak. The intervention improved fasting markers of insulin resistance, increased fasting fatty acid oxidation, and cardiorespiratory fitness. There were also positive changes in health and wellbeing constructs and an excellent compliance rate. Hence, home-based upper body exercise may have the potential to be used as a long-term behavioural strategy to improve the health and wellbeing of persons with chronic paraplegia.

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LIST OF ABBREVIATIONS

ACE	Arm Crank Exercise
ADL	Activities of Daily Living
AHR	Actiheart
AMP	Adenosine Monophosphate
AMPK	AMP Activated Protein Kinase
ANOVA	Analysis of Variance
ATP	Adenosine Triphosphate
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BP	Blood Pressure
CAD	Coronary Artery Disease
CI	Confidence Interval
CO_2	Carbon Dioxide
CON	Control Group
CRP	C-Reactive Protein
CV	Coefficient of Variation
CVD	Cardiovascular Disease
DEXA	Dual- Energy X-ray Absorptiometry
DIT	Dietary Induced Thermogenesis
DLW	Doubly Labelled Water
DNL	De Novo Lipogenesis
EE	Energy Expenditure
EDTA	Ethylenediaminetetraacetic Acid
EL	Endothelial Lipase
ELISA	Enzyme-Linked Immunosorbent Assay
FES	Functional Electronic Stimulation
FPG	Fasting Plasma Glucose
GLUT-4	Glucose Transporter Protein 4
GPS	Global Positioning Systems
HDL	High Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment- Insulin Resistance
HR	Heart Rate
HRV	Heart Rate Variability
HRR	Heart Rate Reserve
HSL	Hormone-Sensitive Lipase
iAUC	Incremental Area Under Curve
ICC	Intra-class Correlation Coefficients
IFNɣ	Interferon Gamma
IL-6	Interleukin- 6
IMF	Intramuscular Fat
INT	Intervention Group
LDL	Low Density Lipoprotein
LoA	Limits of Agreement
LPL	Lipoprotein Lipase

LTPA	Leisure Time Physical Activity
MAST	Multi Axis Shaker Table
MET	Metabolic Equivalent
MEMS	Microelectromechanical System
MLM	Multiple Linear Modelling
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NEFA	Non-Esterified Fatty Acids
NMES	Neuromuscular Electrical Stimulation
O_2	Oxygen
OGTT	Oral Glucose Tolerance Test
PA	Physical Activity
PAC	Physical Activity Counts
PAL	Physical Activity Level
PADS	Physical Activity and Disability Survey
PAEE	Physical Activity Energy Expenditure
PARA-SCI	Physical Activity Recall Assessment for People with SCI
PASIPD	Physical Activity Scale for Individuals with Physical Disabilities
PQCT	Peripheral Quantitative Computed Tomography
RCT	Randomised Controlled Trial
RER	Respiratory Exchange Ratio
RMR	Resting Metabolic Rate
RPE	Ratings of Perceived Exertion
SCI	Spinal Cord Injury
SD	Standard Deviation
SEE	Standard Error of the Estimate
SNS	Sympathetic Nervous System
SVF	Stromal Vascular Fraction
SVM	Signal Vector Magnitude
SWA	SenseWear Armband
TAG	Triglycerides
TWB	Total Body Water
TEE	Total Energy Expenditure
TEF	Thermic Effect of Food
TNFα	Tumor Necrosis Factor Alpha
TSI	Time since Injury
T2DM	Type-II diabetes mellitus
ULAM	Upper Limb Activity Monitor
UTI	Urinary Tract Infection
VAT	Visceral Adipose Tissue
$\dot{V}CO_2$	Carbon Dioxide Production
$\dot{V}O_2$	Oxygen Consumption
$\dot{V}O_2$ peak	Peak Oxygen Uptake
WC	Waist Circumference
WERG	Wheelchair Ergometer

CHAPTER 1: INTRODUCTION

Our understanding of the mechanisms whereby physical activity (PA) exerts beneficial effects on human health has seen major advances over the past twenty five years (Hawley *et al.*, 2015). Regular PA and/or structured exercise is now widely established as an important strategy in preventing obesity and chronic diseases such as Type-2 Diabetes Mellitus (T2DM) and Cardiovascular disease (CVD) in the general population (Booth *et al.*, 2000; Kesaniemi *et al.*, 2001; Haskell *et al.*, 2007). However, for the last ten years at least, the UK Chief Medical Officer's Report has made the same statements regarding the lack of evidence to inform policy on the recommended levels of PA for people with disabilities:

"A good understanding of the health and functional benefits derived from physical activity by persons with disabilities is still limited due to a lack of research."

This is despite the fact that we now have over 11 million people (750 million worldwide) living in the UK with long-term illness or disability. It has been suggested that individuals with disabilities should strive to meet the American College of Sports Medicine PA guidelines of 150 minutes of moderate-intensity PA per week (World Health Organisation, 2004; Nash *et al.*, 2012). Yet there is a degree of uncertainty as to whether these able-bodied guidelines are realistically achievable for people with disabilities, due to altered physical functioning and numerous personal and environmental barriers that they face when trying to become more physically active (Figure 1.1). There is also conflicting evidence as to whether people with a disability even accrue the same health benefits from meeting these guidelines.

Human metabolic control is determined by complex interactions between our behaviours, our environment and our genes. From an evolutionary standpoint, the human genome was selected in an environment where high PA was the norm (Late-Palaeolithic era), to ensure the procurement of food through hunting and foraging (Booth *et al.*, 2002). At the same time, we must consider that there were likely periods of restricted energy intake for our

prehistoric ancestors, whereby cyclical periods of feast were interspersed with famine (Chakravarthy & Booth, 2004). Consequently, metabolic pathways which prioritise storing energy for future famine were favoured. It has been suggested that the human genome is therefore programmed to expect regular PA (Booth *et al.*, 2002; Chakravarthy & Booth, 2004). Disability can negatively impact PA behaviour, as described by the Conceptual model of Disability-Associated Low Energy Expenditure Deconditioning Syndrome (DALEEDS) (Rimmer *et al.*, 2012; Figure 1.1). Forty seven percent of adults with disabilities who are able to do aerobic PA do not get any at all, and an additional twenty two percent are considered not active enough (Centers for Disease Control, 2014). This creates a dramatic change to the environment where these genes were naturally selected. For the vast majority of individuals with a disability the feast/famine cycle is no longer applicable; due to inactivity combined with the broad availability of relatively inexpensive, highly palatable food (Schrauwen, 2007). As it is unlikely that humans genetic make-up has changed over the last 40,000 years (Eaton & Konner, 1985), metabolic genes selected to expect a high level of PA are now maladapted (Booth *et al.*, 2002; Chakravarthy & Booth, 2004).

As a result of the reduction in fuel utilization/turnover excess energy is stored as triglycerides (TAG) in adipose tissue. Obesity is rapidly becoming a serious problem in disabled populations, with a 1.2 to 3.9-fold increase in prevalence (Liou *et al.*, 2005). The accumulation of excess adiposity (along with increased ectopic fat in various tissues) leads to the induction of local and systemic inflammation, and eventually insulin resistance and T2DM (Lebovitz & Banerji, 2005). As such, obesity has been implicated as one of the key drivers in the development of T2DM and CVD (Bastard *et al.*, 2006; Waki & Tontonoz, 2007). Whilst the impact of obesity on metabolic health is currently receiving a lot of attention, there is a growing appreciation that a greater emphasis should be placed upon physical inactivity (Blair, 2009; Weiler, 2010; Kohl *et al.*, 2012). Particularly with reference to recent findings from the multi-centre European Prospective Investigation into Cancer and Nutrition (EPIC) study, which suggest that inactivity is a larger contributor to all-cause mortality than obesity (Ekelund *et al.*, 2015). Laboratory experiments have implicated reduced PA with impaired metabolic function (Thyfault & Krogh-Madsen, 2011). Even as little as three days of reduced PA can negatively affect the body's ability to regulate plasma glucose concentrations (Mikus *et al.*, 2012). Whilst

there is evidence for the independent effects of PA on metabolic health (Walhin *et al.*, 2013), it also plays an important (and possibly primary) role in the prevention of obesity, helping contribute to the maintenance of energy balance through increasing energy expenditure.

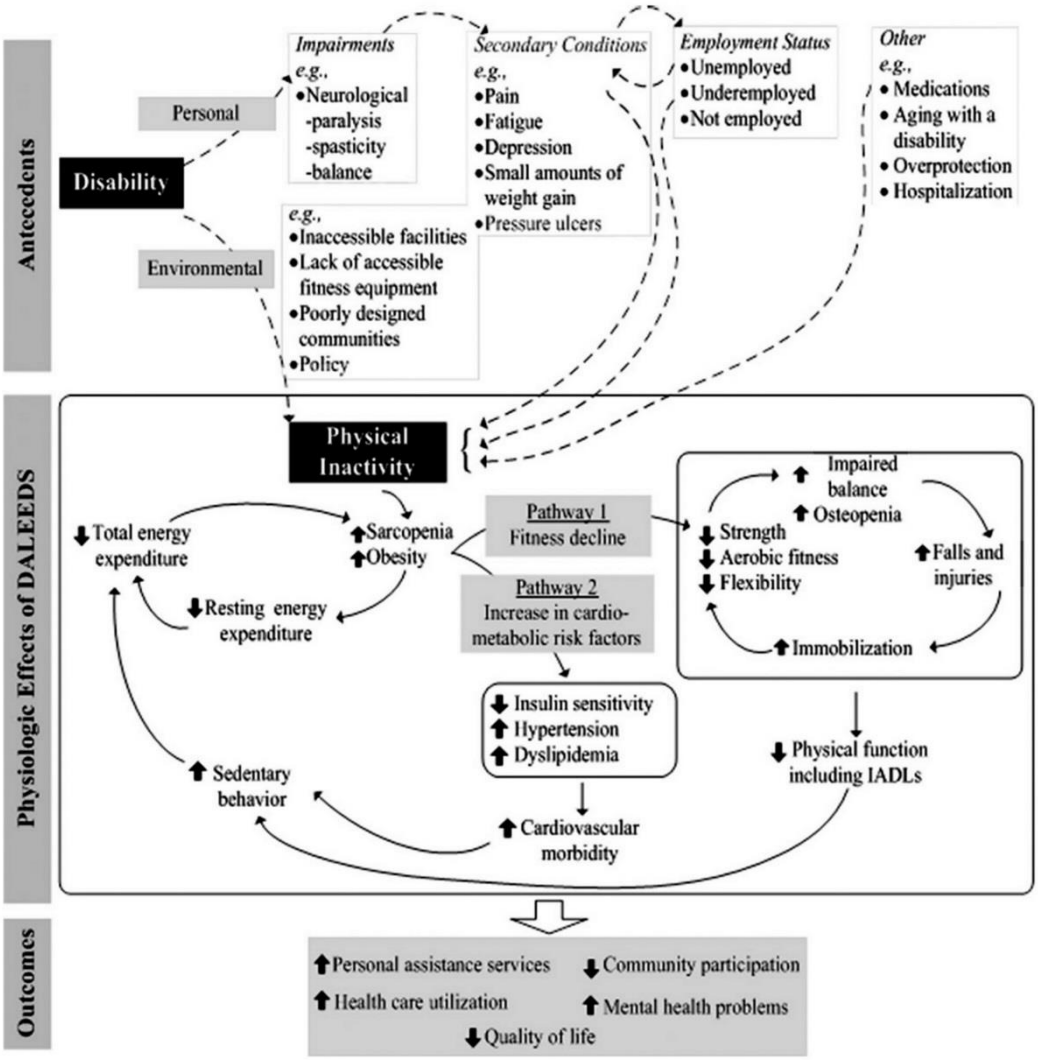

Figure 1.1: Conceptual model of Disability-Associated Low Energy Expenditure Deconditioning Syndrome (DALEEDS). This model provides an overview of the barriers that contribute to physical inactivity in disabled populations, and the subsequent knock on effects on health. Taken from (Rimmer *et al.*, 2012). *IDALs; instrumental activities of daily living.*

The World Health Organisation (WHO) has addressed physical inactivity as a global public health concern. However, a recent survey conducted by the English Federation of Disability Sport concluded that only two in ten disabled people in England are currently active (Slater, 2013). This is particularly concerning as figures from the Centers for Disease Control and Prevention in the USA suggest that adults with a disability who do not perform any PA are 50% more likely than their active peers to report at least one chronic disease (cancer, diabetes, stroke or heart disease). This thesis will focus on PA and health in wheelchair users, specifically individuals with spinal cord injury (SCI). SCI creates a complex pathology whereby level and completeness of injury, plus other lifestyle factors can lead to increased sedentary behaviours and alterations in body composition. The reasons for the adoption of a more sedentary lifestyle are of course multifactorial in many populations, but perceived psychosocial and environmental barriers to engage in PA are numerous for individuals that use wheelchairs. These include reduced self-esteem, a lack of accessible facilities, unaffordable equipment, fear of injury and parental or medical over protection (Kehn & Kroll, 2009; Gorgey, 2014).

Compared to matched able-bodied counterparts, adults with SCI are 4 times more likely to develop T2DM (Bauman & Spungen, 1994) and twice as likely to develop CVD (Garshick *et al.*, 2005). Furthermore, Spungen *et al.*, (2003) demonstrated persons with SCI had significantly more adipose tissue accumulation for any given body mass index compared to controls. Nevertheless, it is unclear whether the increased risk of chronic disease and/or obesity is a result of pathophysiological consequences of the disability *per se,* such as changes in body composition and energy metabolism, atrophy of lean mass (LM) or the impact of inactivity itself.

Hence the overarching research question of this thesis is to address the role of PA on the health and wellbeing of persons with SCI. The necessary starting point was to develop methods capable of accurately measuring free-living physical activity energy expenditure in wheelchair users. These methods, incorporating validated wearable technology, were then utilised in a randomised controlled trial to ascertain the impact of increased PA on functional health, wellbeing and metabolic health in individuals with SCI (Figure 1.2).

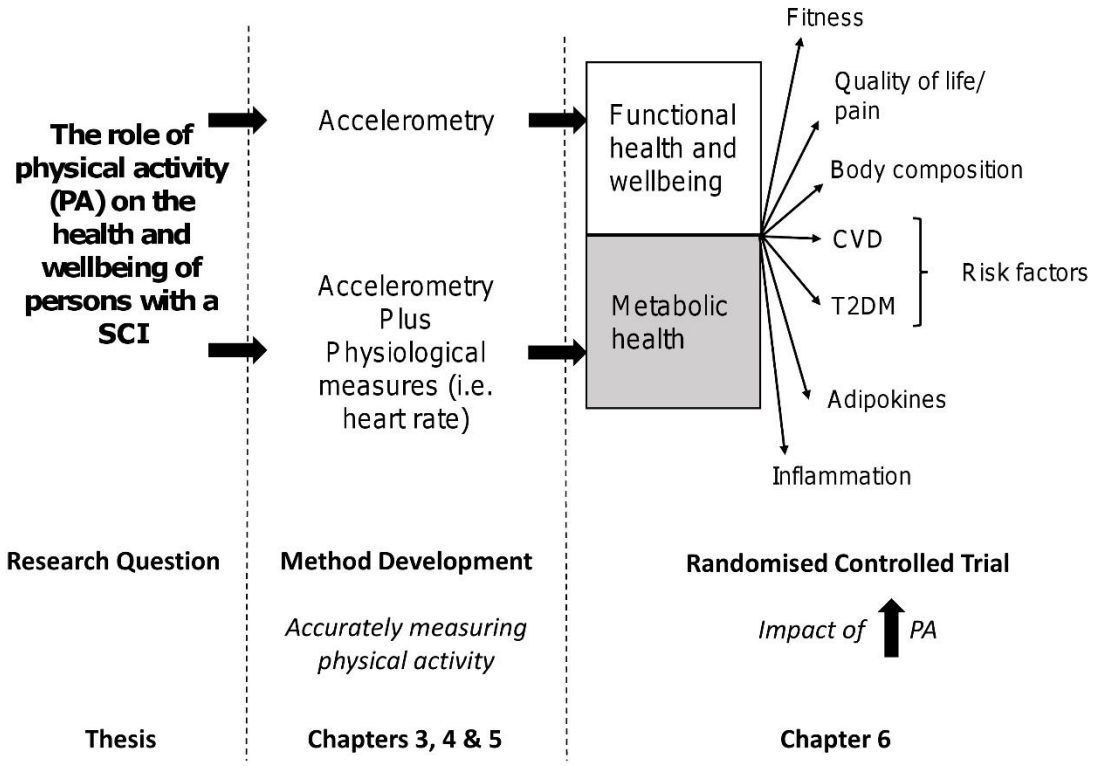

Figure 1.2: Schematic of the research questions and layout of this thesis.

“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it”

Plato (427-327 B.C.).

CHAPTER 2: REVIEW OF THE LITERATURE

The purpose of this literature review is to: i) describe the physiological changes which occur following spinal cord injury (SCI) and their role in the development of chronic disease, with a particular focus on T2DM and CVD, ii) critique the methods available to researchers to measure PA in wheelchair users, and, iii) review the evidence pertaining to the role of PA in alleviating risk factors for T2DM and CVD in individuals with a SCI.

2.1. SPINAL CORD INJURY

The spinal cord is a cylindrical bundle of nerve fibres, connecting the brain and the peripheral nervous system. It is encased within 31 vertebrae; eight cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal (Figure 2.1). A spinal cord injury is a significant life changing event which has wide ranging implications for multiple body systems. SCI invariably leads to a loss of sensory and motor control beneath the lesion level, irrespective of its pathophysiology, be it direct trauma (e.g. a car crash) or from disease or degeneration (e.g. cancer). Injuries can be classified as i) complete - an absence of sensory and motor functions in the lowest sacral segments or; ii) incomplete - preservation of some sensory or motor function below the level of the injury. The axons in different regions of the spinal cord correspond to different information being relayed between the brain and the peripheral tissues. For example, information regarding proprioception is transported via the dorsal column at the back of the cord, whereas pain and temperature information is carried in the spinothalamic tract located more laterally (Webborn, 2008). As such, when different areas of the cord are damaged this can have different physiological consequences. The exact level of the injury sustained also dictates the degree of impairment, i) tetraplegia - injury to the cervical region of the spinal cord with associated loss of muscle strength in all four extremities, ii) paraplegia - injury sustained to the spinal cord in either the thoracic, lumber or sacral segments with strength loss in the legs.

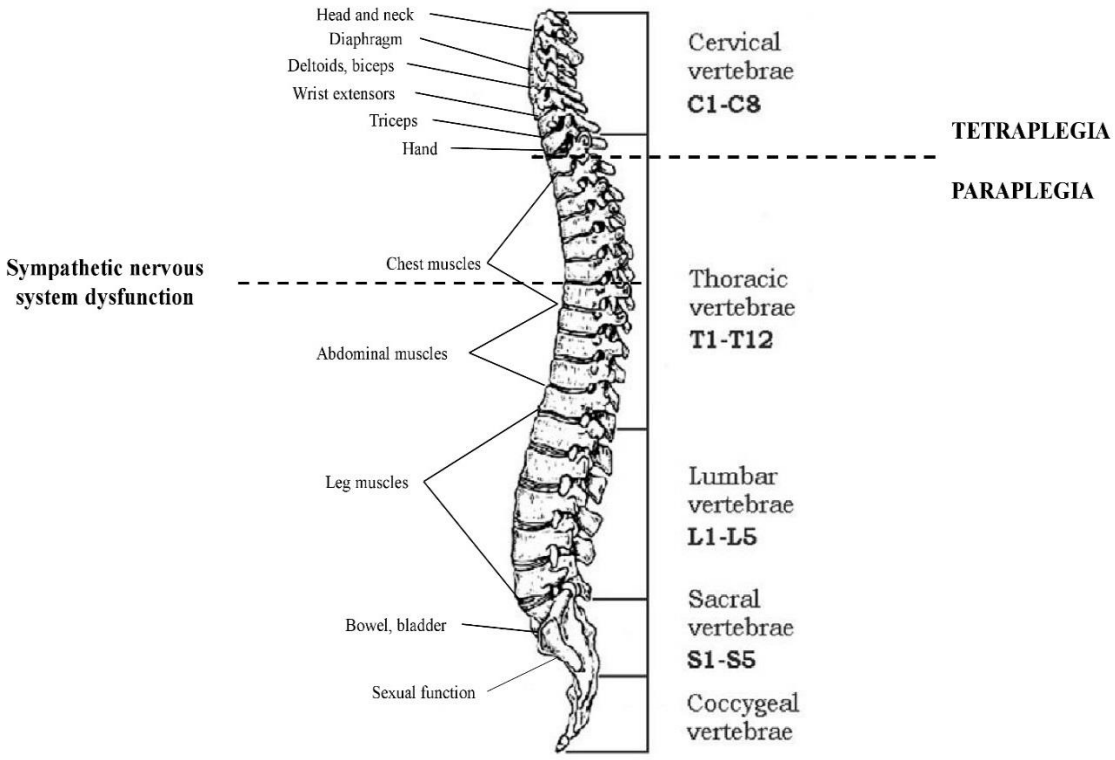

Figure 2.1: Spinal cord showing the various segments and the degree of motor function associated with lesions occurring at specific levels. Sympathetic nervous function is disrupted with injuries occurring above T6. *Adapted from Spinal Cord Injury Treatment Center Society online (SCITCS.org) (http://scitcs.org/about-us/spinal-cord-injury/)*

2.2. EPIDEMIOLOGY OF SPINAL CORD INJURY

2.2.1. Incidence and Prevalence

There are no reliable estimates of the global prevalence of SCI, perhaps reflecting the need for improvements in international standards and guidelines for reporting SCI. A systematic review of the literature published between 1950 and 2012 suggested that global prevalence varied from 236 to 1,298 per million inhabitants (Furlan *et al.*, 2013), implying a broad variation of prevalence rates between geographical locations. The estimated annual global incidence of SCI is between 40 to 80 cases per million (World Health Organization, 2013). Recent figures would suggest that in the UK around 1,200 people become paralysed every year, with a new person sustaining an injury roughly every 8 hours (Apparelyzed, 2014).

A report from the National Spinal Cord Injury Statistics Centre (2011) conveys various demographic trends with regards to an increased likelihood of sustaining a SCI. SCI primarily affects young adults, approximately 50% of cases occur between the ages of 16 – 30 years. Males are also approximately 4 times more likely than females to have a SCI (80.7% reported on the USA national database). Since 2005, the most frequent neurologic category at discharge of persons reported to the USA national database was incomplete tetraplegia (39.5%), followed by complete paraplegia (22.1%), incomplete paraplegia (21.7%) and complete tetraplegia (16.3%). Unfortunately these statistics are not easily available for the UK and hence the USA has been used as a reference. The most common causes for traumatic SCI in the USA since 2000 were road traffic accidents (48.3 %), falls (21.8 %), acts of violence (12.0 %) and sport (10.0 %) according to a systematic review of outcomes (DeVivo, 2012).

Over the past 60 years there has been a worldwide improvement in the acute survival of patients with a traumatic SCI through rapid transportation to a specialised unit, medical treatment advancements and improved rehabilitation. As a consequence there has been a shift in focus from acute life support medicine to addressing other secondary health complications associated with aging in a wheelchair. Consequently the long-term demands on medical and support resources are high. Approximately 21% of people discharged from SCI Centres go into nursing homes, hospitals or other institutionalised settings rather than back to their own homes. In the UK, it is conservatively estimated that the current annual cost of caring for people paralysed by SCI is more than £500 million (Apparelyzed, 2014). Besides the decreased functional ability and independence, secondary medical complications and common co-morbidities also add to treatment costs for individuals with SCI.

2.2.2. Incidence of Chronic Disease and Mortality

The medical history of SCI dates back to ancient Egyptian documents written around 2500 years BC, which describes “crushed vertebra in his neck” with accompanying neurological symptoms (Anderberg *et al.*, 2007). The message portrayed was that this was an ailment which was not to be treated. Widely this belief was maintained until the

end of the Second World War when the Stoke-Mandeville National Spinal Centre was opened by Sir Ludwig Guttmann, kick-starting the modern era of rehabilitation. At present, due to improved healthcare and medical innovations, people with SCI can expect to live almost as long as those without (Yeo *et al.*, 1998). That said, a recent systematic review looking at survival worldwide after SCI concluded that overall mortality in SCI is up to three times higher than in the general population (van den Berg *et al.*, 2010). Historically, renal and respiratory conditions were the most prevalent comorbidities (Frankel *et al.*, 1998). Whilst they remain common causes of mortality, evidence now suggests that CVD is the leading cause of mortality in individuals with chronic SCI (Garshick *et al.*, 2005). An invited review on CVD in SCI (Myers *et al.*, 2007) suggested the rate of symptomatic CVD is between 30 – 50% compared to 5 – 10% in the general able-bodied population. Morbidity from CVD causes, primarily coronary artery disease (CAD), also tends to occur earlier in the lifespan in individuals with SCI compared to the general population (Devivo *et al.*, 1992; Garshick *et al.*, 2005). This was summarised as a nearly 4-fold higher rate of cardiac death prior to turning the age of 45 years, in comparison to the general population (Yekutiel *et al.*, 1989).

Perhaps equally as worrying as their risk of developing CVD, persons with SCI have decreased awareness of the presence of CAD due to a lack of moderate-vigorous PA which may precipitate angina. Consequently there is an increased incidence of asymptomatic disease (Bauman *et al.*, 1994; Groah *et al.*, 2001). SCI, dependent on the exact level of injury, is characterised by a disruption of normal autonomic cardiovascular control mechanisms (Krassioukov & Claydon, 2006; Wecht & Bauman, 2013). These physiological changes lead to; i) a loss of normal regulation of the peripheral vasculature, ii) autonomic dysreflexia, iii) abnormal heart rate variability (HRV) and, iiii) a higher prevalence of cardiac rhythm disturbances (Myers *et al.*, 2007). There is now growing recognition that these factors could be contributing to the increased risk of CVD (Bauman *et al.*, 1999; Villareal *et al.*, 2002; Jacob *et al.*, 2005).

Besides CVD, population based studies have also revealed the incidence of T2DM to be high in individuals with SCI (LaVela *et al.*, 2006; Cragg *et al.*, 2013; Lai *et al.*, 2014). Indeed, it has been suggested that adults with SCI are 4 times more likely to develop

T2DM than able-bodied controls (Bauman & Spungen, 1994). Metabolic abnormalities caused by T2DM are associated with endothelial dysfunction that predisposes individuals to the development of atherosclerosis and subsequent cardiovascular events (Beckman *et al.*, 2002). As such, individuals with T2DM are 2-5 times more likely to develop CVD than individuals without T2DM (Garcia *et al.*, 1974). Other secondary health complications associated with SCI, such as pressure ulcers and urinary tract infections, contribute to sedentary behaviours and are a substantial expense to health services. Annual prevalence rate for pressure ulcers has been reported around one third (Kruger *et al.*, 2013) and they have been implicated as the second leading cause of rehospitalisation after SCI (Cardenas *et al.*, 2004).

Although pioneering research and significant advances are being made in finding a cure for SCI in order to reverse paralysis, it is important that we develop treatments to reduce secondary complications associated with aging with the disability. Thankfully the aforementioned excess mortality through chronic diseases is related to potentially treatable factors such as obesity and PA. This will be discussed in more detail later on in this review. It is important to understand why individuals with SCI are at an increased risk of developing chronic diseases. To facilitate this, it is necessary to appreciate the physiological and behavioural changes that occur after sustaining a SCI.

2.3. PATHOPHYSIOLOGY OF SPINAL CORD INJURY

2.3.1. Inactivity and Functional Capacity

Sedentary lifestyles and reduced physical function contribute to the increased morbidity and mortality observed in this population. Both PA and physical work capacity are influenced by the type and level of SCI. The higher the level of lesion, the greater the impairment of muscle function and therefore the greater the decline in functional capacity (Jacobs & Nash, 2004). Individuals with higher level injuries (≥ T6) also exhibit a blunted cardiovascular response to exercise, as a result of autonomic dysregulation, and they can also lack the adequate sympathetic drive to increase heart rate above 120 – 125 $b \cdot min^{-1}$ (Myers *et al.*, 2007). This is a consequence of the loss of supraspinal control of the

sympathetic nervous system (Furlan & Fehlings, 2008) and a reduced catecholamine response to exercise (Steinberg *et al.*, 2000). However even in lower level injuries, the action of the skeletal muscle pump (intermittent contraction and relaxation) to assist in the redistribution of blood flow during exercise can be compromised, leading to inadequate venous return and blunting of cardiac output (Myers *et al.*, 2007). Consequently these factors reduce the capability of the human body to adapt appropriately to a bout of exercise, which can lead to early fatigue. Combined with numerous psychosocial and environmental barriers to engage in PA for persons with SCI, this can lead to avoidance of physical exertion. Fatigue, reduced self-esteem, lack of accessible facilities, unaffordable equipment, fear of injury and parental or medical over protection have all been cited as barriers preventing engagement in PA (Rimmer *et al.*, 2004; Kehn & Kroll, 2009; Craig *et al.*, 2012; Gorgey, 2014).

Due to lower limb paralysis, exercise options are also often limited to the upper extremities. Subsequently, overuse injuries and shoulder pain are common (Dyson-Hudson & Kirshblum, 2004; Samuelsson *et al.*, 2004), further contributing to physical inactivity. With the development of a compendium, describing energy expenditure for physical activities specific to the everyday lives of wheelchair users, it is clear that the energy cost of most exercise and recreation activities are considerably lower (- 27%) than those reported in the general population (Collins *et al.*, 2010; Conger & Bassett, 2011). The most likely explanation for this is that these activities involve a smaller skeletal muscle mass, predominantly restricted to the upper body, instead of recruiting larger muscle groups in the legs. Therefore, it is not possible to achieve the same whole-body oxygen uptake.

Van den Berg-Emons *et al.*, (2008) assessed the change in PA over time after a SCI, using an accelerometer capable of detecting the duration of dynamic activities and the intensity of everyday activities. Whilst physical activity levels increased during inpatient rehabilitation, this increase did not persist after discharge. At 1 year after discharge (n = 16) physical activity levels were significantly lower, measured as the mean duration of dynamic activities, compared to matched, able-bodied subjects (49 vs. 143 $min \cdot day^{-1}$). However, physical activity level was only monitored during 2 consecutive weekdays.

Persons with chronic (time since injury: 13 ± 10 years) paraplegia also exhibit low physical activity level (PAL; daily total energy expenditure/ resting metabolic rate) (mean 1.56 ± 0.34), measured using the flex heart rate (HR) method (Buchholz *et al.*, 2003b). Self-report questionnaire data also supports the notion that individuals with SCI engage in little to no PA (Washburn *et al.*, 2002; Ginis *et al.*, 2010b). The current available evidence on PA levels in persons with SCI, albeit some of which is limited by the measurement tools adopted (discussed in detail in section 2.7), suggests that the majority of this population are inactive.

Cardiorespiratory fitness

Common measures of cardiorespiratory fitness are the peak attainable rate of oxygen uptake ($\dot{V}O_2$ peak) or peak workload achieved during an incremental test to volitional exhaustion. In wheelchair users these variables can be assessed using continuous or discontinuous protocols using wheelchair propulsion (treadmill or wheelchair ergometer) or arm crank ergometry. Poor cardiorespiratory fitness has been widely reported in individuals with SCI (Janssen *et al.*, 2002; Haisma *et al.*, 2006). This is concerning as there is a wealth of evidence identifying cardiorespiratory fitness as an important determinant of all-cause morbidity and mortality in the able-bodied population (Blair *et al.*, 1996; Lee *et al.*, 1999; Myers *et al.*, 2002; Kaminsky *et al.*, 2013). The variance between individuals in cardiorespiratory fitness can be attributed to both hereditary (~ 50%) and environmental (~ 50%) factors (Bouchard *et al.*, 1999). Additional variance in the SCI population can be attributed the exact level and type of neurological injury sustained, and the degree of functional impairment. It is important to distinguish that the only environmental factor known, with any relevance, to influence $\dot{V}O_2$ peak is PA (Church, 2009). Perhaps unsurprisingly, physical activity level has been correlated to cardiorespiratory fitness in persons with SCI (Muraki *et al.*, 2000; de Groot *et al.*, 2010; Nooijen *et al.*, 2012). Thus as it is widely believed cardiorespiratory fitness is an outcome of habitual PA, epidemiological data linking cardiorespiratory fitness with long term health, at least indirectly, implies that PA has a key role to play in the prevention of chronic disease.

In a large-scale epidemiological study assessing the relationship between cardiorespiratory fitness and functional limitations in able-bodied men (n = 3495) and women (n = 1175) over the age of 40, Huang *et al.,* (1998) showed a strong relationship between low levels of cardiorespiratory fitness and functional limitations. These findings also translate to individuals with SCI; Noreau and Shephard (1995) concluded that only 1 in 4 young people with paraplegia were able to achieve peak functional capacity necessary to maintain independent living. More recently, Hetz *et al.,* (2009b) demonstrated participants with higher levels of cardiorespiratory fitness spent more time participating in activities of daily living and leisure time physical activity. The intricate link between PA and cardiorespiratory fitness means a debilitating cycle exists whereby even less activity leads to further deconditioning and therefore more problems engaging in PA and activities of daily living (ADL) (Nash, 2005; Fernhall *et al.,* 2008). This process is also exacerbated by the aging process.

2.3.2. Impact on Body Composition

Obesity

The first law of thermodynamics states; *'energy cannot be destroyed but can only be transformed from one form to another'*. Simplistically, human energy balance can be expressed as:

Energy Balance = Energy Intake – Energy Expenditure

The components of energy expenditure will be explained later on (Section 2.5). In the context of SCI, besides a reduction in physical activity energy expenditure, energy balance is influenced by changes in dietary habits and a loss of metabolically active tissue. Feasel & Groah, (2009) suggested physical barriers (e.g. transport to shops and supermarket store shelving), environment (e.g. hospital food), functional challenges (e.g. problems encountered when preparing food) and social factors (comfort food provided by family/friends) contribute to an 'obesogenic environment'. Yet data reported since 2008 revealed individuals with SCI consume fewer kilocalories (males; ~500 – 600

kcal·day^{-1}, females; ~100 kcal·day^{-1}) than the general population (Groah *et al.*, 2009: Walters *et al.*, 2009). At present there is a lack of information on energy balance in this population, due to the lack of accurate methods to measure habitual energy expenditure (discussed in Section 2.7). Furthermore, there are several limitations with self-report diet data (Livingstone & Black, 2003: Dhurandhar *et al.*, 2014), and it is perhaps advisable at this moment in time not to equate these two methods to derive energy balance. Nevertheless, data comparing resting metabolic rate and energy intake in individuals with SCI indicate a surplus of ~ 300 – 500 kcal·day^{-1} (Lee *et al.*, 1985:Aquilani *et al.*, 2001: Perret & Stoffel-Kurt, 2011). Whilst this difference might appear trivial, even a small yet sustained energy surplus will eventually lead to an increase in body mass.

Regardless of the macronutrient composition of ingested food, when there is a sustained energy surplus, excess energy is ultimately stored as TAG within adipose tissue. This is not simply restricted to the processing of dietary fats. As the capacity of the human body to store glucose as glycogen is limited, biological pathways such as de novo lipogenesis (DNL) exist. Surplus dietary carbohydrate is converted to fatty acids in the liver and, to a lesser extent in adipocytes (Hellerstein *et al.*, 1996). This takes full advantage of the impressive capacity for adipose tissue to store excess energy. Adipose tissue is capable of expanding to more than 80% of body weight in obese individuals (Thompson *et al.*, 2012). Yet this capacity for storing energy becomes problematic when in a chronic state of energy surplus, i.e. as a result of reduced PA following SCI. De Groot *et al.*, (2014) recently monitored changes in BMI following a SCI; 29% of participants were obese (BMI $\geq$ 25 kg/m^2) at baseline (n = 195), 34% at discharge (n = 185) and 54% at the 5 year follow-up (n = 126). However, BMI has limited applicability to estimate obesity as it does not differentiate between fat mass (FM) or LM, this is a considerable limitation for its use in individuals with SCI. For example, (Clasey & Gater, 2005) reported that 10 out of 13 persons (77%) who had paraplegia, had body fat percentages in the obese range, despite a mean BMI $\leq$ 25 kg/m^2. This study is the only one, to our knowledge, to report body composition by four-compartment modelling (utilising estimates of body density, total body water (TBW) and total body bone mineral). Incorporating these estimates has been recommended as the most appropriate method to determine body composition in this population (Clasey & Gater, 2007). Furthermore, Spungen *et al.*, (2003), demonstrated using dual-energy X-ray absorptiometry (DEXA) that 133 men with chronic SCI were on

average 13% fatter per unit of BMI compared to age, height-, and ethnicity- matched able-bodied controls.

Consequently, the true prevalence of obesity in this population might be higher than the 53% (BMIs $\geq$ 25 kg/m^2) reported in a large scale epidemiological study (n = 7959) managed in Veterans Affairs hospitals in the USA (Weaver *et al.*, 2007). In a detailed review on obesity after SCI, Gater (2007) suggested when considering the best data available that two in every three persons with SCI are likely to be obese. Besides an increased prevalence of obesity, the location of adipose tissue is also different. Edwards *et al.*, (2008) found that persons with SCI had 58% more visceral adipose tissue (VAT; quantified by computed tomography) than waist circumference matched able-bodied controls once differences in weight were accounted for. Worryingly this was in a relatively young cohort (age: 39 ± 8 years), who also considered themselves active and healthy. The increase in central obesity, particularly the accumulation of VAT, has been identified as an independent risk factor for T2DM and CVD in the able-bodied population (Nakamura *et al.*, 1994; Boyko *et al.*, 2000; Shah *et al.*, 2014), and for impaired carbohydrate and lipid metabolism in SCI (Gorgey *et al.*, 2011). This might be due to elevated levels of inflammation from VAT and fatty acid output directly to the liver via the hepatic portal vein (Jensen, 2008). The role of obesity on insulin resistance and chronic inflammation will be discussed in more detail later on (Section 2.4.3 and 2.4.5, respectively).

Muscular atrophy

The lack of stimulation and disuse as a result of paralysis can have a profound impact on skeletal muscle below the level of injury. The atrophy of LM has been widely documented (Nuhlicek *et al.*, 1988; Kocina, 1997; Dionyssiotis *et al.*, 2008; Biering-Sorensen *et al.*, 2009), which facilitates a reduction in substrate storage capacity. After as little as 24 weeks, Castro *et al.*, (1999) noticed that the cross-sectional area of paralysed muscle is between 45 - 80% of that in age and weight matched controls. Besides the loss of LM, the quality of skeletal muscle that remains also deteriorates. Adipose tissue accumulates within and between muscle groups in the legs of individuals with SCI (Gorgey & Dudley,

2007; Shah *et al.*, 2008). Gorgey & Dudley (2007) demonstrated using magnetic resonance imaging (MRI), that relative intramuscular fat (IMF) in both thighs was three times higher in persons with incomplete SCI 6 weeks after injury compared to age and weight matched able-bodied controls. The accumulation of IMF has been linked with impaired glucose tolerance in persons with SCI (Elder *et al.*, 2004; Ryan *et al.*, 2012) and skeletal muscle insulin resistance in inactive able-bodied individuals (Eckardt *et al.*, 2011).

There is less available research commenting on the effects of chronic (> 1 year) SCI on lower-extremity muscle size and quality, with most small-scale studies reporting changes after acute SCI. Spungen *et al.*, (2000) assessed body composition via DEXA in eight pairs of monozygotic twins, one twin in each pair had paraplegia (time since injury; 3 – 26 years). The authors found trunk and leg LM was significantly lower in the paralysed twin. The continuous lean tissue loss represents accelerated and progressive sarcopenia (age-induced skeletal muscle atrophy) in the SCI population. Using peripheral quantitative computed tomography (PQCT) scans of the calf, Moore *et al.*, (2015) has recently shown that participants with motor complete SCI (mean duration of injury 16 ± 10 years) had ≈ 32% lower muscle area, and ≈ 43% lower muscle density values compared to controls. These changes are perhaps best visualised in Figure 2.2.

Figure 2.2: Whole body Dual-energy X-ray absorptiometry (DEXA) scan of a female participant in Chapter 6. This participant sustained a neurological complete T7 injury 6 years ago. Whilst total percentage body fat was high (58%), percentage body fat specifically in the legs was 69%. This figure visually highlights the drastic atrophy of LM in the lower extremities of individuals with SCI. *Colour scheme- amber; adipose tissue, red; LM, blue; skeleton*

Besides the loss in LM, immobilisation of the lower-extremity muscles can also facilitate dramatic morphological and contractile changes. Following SCI there is a muscle fibre type transformation; with a shift from type I fibres (occurring around 4 – 7 months post SCI) to predominantly fast glycolytic IIb fibres years after the injury (Biering-Sorensen *et al.*, 2009; Pelletier *et al.*, 2014). The oxidative enzyme activity begins to decline after the first few moths post SCI, and > 1 year post injury has been shown to be well below the level seen in able-bodied individuals (Rochester *et al.*, 1995; Gerrits *et al.*, 2003). This may reflect the concurrent transformation of muscle fibres from slow to fast twitch. Furthermore, below the neurological level of SCI, remodelling of the peripheral vasculature occurs (Olive *et al.*, 2003). These changes, along with reduced PA, have profound implications in the progression of chronic diseases in this population and will be discussed in more detail in future sections.

2.4. BIOMARKERS OF CHRONIC DISEASE

Various biological mechanisms, integral in the maintenance of metabolic control, are influenced by physical inactivity and have been implicated in the progression of certain chronic diseases. These mechanisms ensure cellular energy balance is achieved, through regulating the distribution and storage of nutrients and their release from stores and delivery to individual tissues as required. The aforementioned processes are intricately controlled via complex cross-talk between tissues (adipose tissue & skeletal muscle) and organs (liver, endocrine pancreas & brain). Energy homeostasis is achieved through feedback signalling of peripheral tissues to the central nervous system (Jordan *et al.*, 2010), which is the focus of this next section.

2.4.1. Overview of Metabolic Control in Humans

The human body is well adapted to cope with rapid changes in metabolic flux, brought about through ingesting a meal or a bout of PA. In response to major disturbances in the supply and demand for energy, human cells are readily able to switch between glucose and fatty acid oxidation to meet their ATP requirements (Kelley & Mandarino, 2000). This ability is a characteristic of healthy humans and can be termed '*metabolic flexibility'*. Growing evidence (Kelley *et al.*, 2002; Storlien *et al.*, 2004) has implicated metabolic inflexibility as a key dysfunction in metabolic syndrome (Section 2.4.3).

Metabolic flux between tissues is largely regulated by insulin and reflects the body's current nutritional state. Carbohydrates are absorbed via the small intestine, after being hydrolysed into monosaccharides, such as glucose and/or fructose, prior to absorption. Dietary fats are also absorbed in the small intestine and enter the circulation as TAG-rich chylomicrons via the lymphatic system. Consequently there is a rise in plasma glucose and lipid availability following a mixed meal or oral glucose challenge. As such, there is the drive for nutrient uptake and storage, whereby the human body switches from a predominantly catabolic state to an anabolic state. TAG is hydrolysed from plasma chylomicrons by the action of endothelial lipoprotein lipase (LPL). Most of the released fatty acids then enter adipocytes (and other cells including myocytes and hepatocytes),

where they become esterified with α-glycerol-phosphate (synthesised in the adipocytes from glucose metabolites) and stored as TAG. Glucose is stored as glycogen within skeletal muscle (~500g) and the liver (~100g), and becomes the primary substrate for oxidation during the postprandial state. These storage processes are achieved through the release of insulin into the circulation in combination with reduced glucagon secretion (Wasserman, 2009). Insulin acts to supress adipose tissue lipolysis and hepatic glucose production (discussed below) and is the main driver of glucose removal from the blood stream via peripheral tissues.

In contrast, in the fasted state, non-esterified free-fatty acids (NEFA) are preferentially oxidised in tissues such as skeletal muscle (Frayn & Karpe, 2014). NEFA are liberated by the hydrolysis of stored TAG within adipocytes, by the enzyme hormone-sensitive lipase (HSL). Consequently in the fasted state adipose tissue receives a greater blood flow than resting skeletal muscle, and this adipose tissue blood flow is capable of increasing ~ 8-fold in the postprandial state (Bickerton *et al.*, 2007). Plasma glucose concentrations are primarily maintained through the coordination of hepatic glycogenolysis and gluconeogenesis for subsequent hepatic glucose output (Wasserman, 2009). These processes protect the brain from a dramatic fall in plasma glucose. Under normal circumstances the brain uses solely glucose; plasma glucose concentrations are therefore tightly regulated (> 2 mmol·l^{-1}) to maintain cognitive processes. The endogenous glucose production from the liver and adipose tissue lipolysis is stimulated by glucagon and low levels of plasma insulin (Abdul-Ghani & DeFronzo, 2010). Catecholamines, namely adrenaline, act in conjunction with the low insulin/glucagon ratio in the circulation to activate hepatic glucose output and adipose tissue lipolysis in the fasted state and during exercise.

2.4.2. The Role of Insulin

Insulin is a peptide hormone, synthesised and released from pancreatic β-cells. As touched upon above, its rate of secretion is in response to the metabolic or nutritional state; the most important regulator being an increase in plasma glucose concentration. Insulin exerts a myriad of cellular effects on various tissues to in order to exert metabolic

control. In the liver insulin acts as a potent inhibitor of endogenous glucose production (through glycogenolysis and gluconeogenesis), which attenuates the postprandial rise in blood glucose concentrations following a meal. It is worth pointing out that the suppression of hepatic glucose output is achieved via relatively low insulin concentrations, although actions in peripheral tissues require a higher insulin concentration (Prager *et al.*, 1986). In adipocytes, insulin stimulates the uptake of glucose and lipids (triglyceride synthesis) and the suppression of NEFA release. In skeletal muscle, insulin also stimulates glucose uptake, oxidation and glycogen synthesis. The transport of glucose into muscle is achieved via the glucose transporter protein 4 (GLUT-4). Insulin stimulates the translocation of GLUT-4, sequestered in membrane vesicles within the cell, to the plasma membrane thereby increasing glucose transport into the cell and an effective clearance of glucose from the blood. Insulin also acts as a vasoactive hormone. It induces vasodilation by stimulating the release of nitric oxide from the endothelium (Steinberg *et al.*, 1994), whereas vasoconstriction is primarily dependent on endothelin-1 (Eringa *et al.*, 2002). These actions alter blood flow dynamics in skeletal muscle and adipose tissue (Baron *et al.*, 1995), influencing the uptake of glucose by peripheral tissues.

2.4.3. Insulin Resistance

Insulin resistance is a pre-requisite to T2DM. It is characterised by the failure of insulin to exert the normal cellular effects on various tissues, leading to the impairment of insulin mediated glucose disposal described above. Fasting hyperglycaemia can persist due to the insensitivity of the liver to the suppressive effects of insulin on gluconeogenesis and reduced glycogenolysis (Lee *et al.*, 2009). Consequently this can lead to impaired glucose tolerance, which is clinically diagnosed as a fasting plasma glucose concentration between 5.6 – 6.9 $mmol \cdot l^{-1}$ (Amer Diabet, 2014). Persistently elevated blood glucose concentrations can have significant macro-vascular complications - coronary artery disease, peripheral artery disease and stroke (King *et al.*, 2005).

In the presence of peripheral insulin resistance, the normal homeostatic response to elevated plasma glucose is for an increased pancreatic β-cell secretion of insulin, leading

to hyperinsulinemia (Bauman *et al.*, 1999). Since fasting plasma glucose concentrations have been shown to correlate with basal rates of hepatic glucose output (Campbell *et al.*, 1988), and fasting plasma glucose concentrations are only mildly elevated in subjects with SCI (Bauman *et al.*, 1999); it is most likely that peripheral insulin resistance is the major driver responsible for impaired glucose tolerance in this population. Skeletal muscle plays a huge role in insulin mediated glucose disposal. For example following a high carbohydrate mixed meal (75 g carbohydrates, 37 g protein, and 17 g fat), skeletal muscle glucose uptake accounted for ~ 50% of the absorbed glucose (Capaldo *et al.*, 1999). However, lower extremity paralysis results in a decrease in the quantity and quality of muscle mass as well as morphological, physiological and biomechanical changes (Section 2.3.2). Type IIb muscle fibres are less sensitive to the action of insulin (Lillioja *et al.*, 1987), and these fibres also have a reduced capillary density. Furthermore, Long *et al.*, (2011) demonstrated that mRNA and protein expression of skeletal muscle genes essential for glucose storage are reduced in persons with SCI, along with mitochondrial proteins that are essential for oxidative phosphorylation.

The vasodilatory actions of insulin are also blunted in individuals with insulin resistance (Tousoulis *et al.*, 2008). These haemodynamic actions are substantially blunted in the microvasculature below the level of SCI lesion (La Fountaine *et al.*, 2013). Karlsson, (1999) implicated sublesion sympathetic nervous system (SNS) dysfunction in the decreased systemic insulin sensitivity observed in individuals with high SCI (C6 – T4). Therefore, impaired microcirculation below the lesion level might also be contributing to the increased risk of CVD related mortality, as well as further accentuating the insulin resistant state in persons with SCI. Plus there is the potential for impaired insulin-mediated vasodilation to be a primary factor in the aetiology and persistence of pressure sores (La Fountaine *et al.*, 2013).

Able-bodied PA restriction studies have implicated physical inactivity as the primary pathological driver of insulin sensitivity. For example, Krogh-Madsen *et al.*, (2010) showed, using a two-week step reduction model (transition from ~10,000 to 1,500 steps·day^{-1}), a 17% reduction in insulin sensitivity in healthy men. During this period there was also an accumulation of visceral fat. It is generally recognised that obesity is

associated with insulin resistance. One of the key factors linking the expansion of adipose tissue with the development of insulin resistance is chronic low grade inflammation (Hotamisligil *et al.*, 1993; Weisberg *et al.*, 2003). This is because adipose tissue, or more likely immune cells (macrophages and T lymphocytes) contained within the stromal vascular fraction (SVF), are a source of inflammatory cytokines such as TNFα and IL-6 (Fain, 2010; Thompson *et al.*, 2012) which can interfere with skeletal muscle insulin signalling (Plomgaard *et al.*, 2005). Insulin resistance can also result in a decreased suppression of lipolysis in adipose tissue. Elevated levels of NEFA in the circulation further exacerbates insulin resistance in the liver and skeletal muscle (Abel *et al.*, 2001), thus creating a vicious cycle. Specifically, in individuals with SCI researchers have started to establish clear associations with obesity (total and regional) and insulin resistance (Bauman & Spungen, 1994; Bauman & Spungen, 2001).

But this brings into question whether the reduction in insulin sensitivity is a result of inactivity *per se* or a consequence of positive energy balance. This question was partly addressed using a short term (7-day) reduced PA and over-feeding model (Walhin *et al.*, 2013). Healthy young men were randomly assigned, either to i) increase their energy intake by 50% and reduced their PA (<4,000 steps·day^{-1}) to induce an energy surplus (SUR) or ii) to the same regime but with 45 minutes of running per day (SUR + EX). Importantly, energy surplus was maintained in the SUR + EX group by providing them with additional calories to account for the energy expended during exercise. Despite an increase in body weight, and in the face of a standardised energy surplus, negative changes observed in insulin action in the SUR group were prevented by the addition of daily vigorous-intensity exercise. Furthermore, Stephens *et al.*, (2011) recently reported the deleterious effects of 1-day of sitting upon insulin sensitivity persisted both with and without an energy surplus. These studies suggest that inactivity, at least in the short-term in able-bodied humans, causes a reduction in peripheral insulin sensitivity. In a subgroup of untrained paraplegic participants, the strongest determinant of insulin sensitivity was cardiovascular fitness (Bauman & Spungen, 1994). It is noteworthy that the only environmental factor known, with any relevance, to alter cardiovascular fitness is PA (Church, 2009). Therefore, it seems reasonable to assume that physical inactivity plays a considerable role in the development of insulin resistance, and in the long term the progression to T2DM in individuals with SCI. This is in conjunction with the

pathophysiology of lower extremity skeletal muscle atrophy and increased relative adiposity observed in this population (Section 2.3.2).

Measurement Techniques

There are a number of different methods available to assess insulin sensitivity/resistance. The hyperinsulinemic euglycemic clamp, originally developed by Defronzo *et al.*, (1979), is widely considered the gold standard measure (Muniyappa *et al.,* 2008). Exogenous insulin is infused at a constant rate to produce a steady state plasma insulin concentration above fasting levels (hence, hyperinsulinemic). Plasma glucose concentrations are frequently monitored every 5 – 10 minutes, and kept constant by the manipulation of the exogenous glucose infusion rate. The theory behind this technique is that the rate of glucose infusion required to maintain constant plasma glucose concentrations can be equated to the rate of glucose disposal into all tissues in the body. This is based on the assumption that endogenous hepatic glucose output is completely supressed by the maintenance of hyperinsulinemic conditions. When combined with isotopic glucose tracers this technique can provide information on tissue specific insulin sensitivity. This technique was deemed unsuitable for Chapter 6 of this thesis, based on numerous practical limitations; i) it is time consuming, ii) requires experienced clinical staff to manage any technical difficulties, and iii) is expensive to perform. Furthermore, the clamp utilises supraphysiological steady state insulin concentrations and ignores absorption from the gastrointestinal tract so does not adequately reflect the normal physiological conditions that a dynamic test such as mixed meal or an oral glucose tolerance test (OGTT) might provide.

The OGTT is a cost-effective and a simple to perform test widely used in clinical practice to detect patients with impaired glucose tolerance and T2DM (Amer Diabet, 2014). Following a 10 – 12 hour overnight fast, blood samples are drawn before and then at various time points for 120 minutes following the ingestion of a standard oral glucose load (75 g). Blood samples are analysed for glucose and insulin concentrations. Whilst the OGTT provides useful information regarding glucose tolerance, the test itself does not provide information on insulin sensitivity/resistance *per se* (Muniyappa *et al.*, 2008).

However, a number of surrogate indices of insulin sensitivity/resistance can be incorporated into results of an OGTT. For example whole body insulin sensitivity can be measured using the Matsuda Index ($ISI_{Matsuda}$), which can be calculated from the ratio of plasma glucose to insulin concentration over the course of the 120 min. This method is highly correlated ($r = 0.73$, $P < 0.0001$) to the rate of whole-body glucose disposal during the gold standard euglycemic insulin clamp (Matsuda & DeFronzo, 1999). Simple surrogate indices can also be derived from fasting samples, such as the Homeostasis Model Assessment (HOMA) model that can be used for the prediction of insulin resistance (HOMA-IR; Turner *et al.*, 1979) and β-cell function (HOMA-β; Matthews *et al.*, 1985).

2.4.4. Metabolic Syndrome

Metabolic syndrome (or syndrome X) is a clinical diagnosis characterised by the clustering (≥ 3) of the following CVD risk factors; abdominal obesity, elevated fasting concentrations of glucose and TAG, depressed high density lipoprotein (HDL) cholesterol and raised blood pressure (Grundy *et al.*, 2002; Grundy *et al.*, 2006). Patients diagnosed with metabolic syndrome confer the same clinical threat as those with T2DM (Ford, 2005) and are twice as likely to develop CVD between the next 5 -10 years compared to controls (Alberti *et al.*, 2009). There is convincing evidence to suggest these component risks occur at a heightened frequency in individuals with SCI; specifically increased central obesity (Gater, 2007), impaired fasting glucose/T2DM (Duckworth *et al.*, 1980; Bauman & Spungen, 2008) and dyslipidaemia (Bauman *et al.*, 1992), accelerating the trajectory to metabolic syndrome.

Whilst these criterion cut-points (Table 2.1) have been well established for the general population it is worth pointing out that a recent meta-analysis (Gilbert *et al.*, 2014) highlighted a unique lipid profile for individuals with SCI, primarily characterised by depressed HDL cholesterol. Compared with able-bodied controls no significant differences were found for TAG concentrations across fifty studies. A suggestion from this work was that more-specific CVD risk stratification guidelines are established for this population. However, in the absence of these SCI specific recommendations, general

targets for lipid and glycaemic markers are at present adequate (Kressler *et al.*, 2014). This is not the case for the standard categories used as surrogate measures of obesity. For example waist circumference (Ravensbergen *et al.*, 2014) and BMI (Laughton *et al.*, 2009) are not applicable for SCI, as such WC has been adjusted accordingly in Table 2.1. Furthermore, blood-pressure can pose a two-pronged problem in the SCI population dependent on the level of lesion. Individuals with a lesion ≥ T6 (where sympathetic nervous system is compromised; explained in section 2.3.1) often suffer from hypotension (Wecht *et al.*, 2015). Whereas, individuals with lower-level lesions experience similar hypertension issues as the general population (Bristow, 2013).

Table 2.1: Component risks for metabolic syndrome (*Adapted from* Kressler *et al.*, 2014).

Risk	Criterion
Increased (abdominal) obesity[a]	WC > 37 inches (94 cm)
Hypertriglyceridemia	≥ 1.7 mmol·L^{-1}
Hyperglycaemia	FPG ≥ 5.6 mmol·L^{-1}
Hypertension	Systolic ≥ 130 mm Hg and/ or diastolic ≥ 85 mm Hg
Reduced HDL-cholesterol	< 1.03 mmol·L^{-1} for men < 1.29 mmol·L^{-1} for women

WC waist circumference, FPG fasting plasma glucose

[a] *Adjusted for SCI based on (Ravensbergen et al., 2014)*

2.4.5. Chronic Inflammation

There is a 2 to 3 fold increase in levels of circulating inflammatory markers, indicative of systemic low-grade inflammation, in persons with SCI compared to those without (Frost *et al.*, 2005: Davies *et al.*, 2007; Gibson *et al.*, 2008). Of these circulating inflammatory markers, interleukin-6 (IL-6) and C-reactive protein (CRP) are measured in Chapter 6 of this thesis.

Interleukin-6

IL-6 is a polypeptide messenger substance involved in the cytokine cascade, which assists in the regulation of immune function, primarily activating leukocytes and is secreted locally by white adipose tissue, skeletal muscle and the liver. Mohamed-Ali *et al.,* (1997) suggested that in healthy human's adipose tissue contributes to approximately one third of circulating IL-6. It is perhaps pertinent to address that adipose tissue, besides its traditional role in energy storage, is composed of distinct cell types: mature adipocytes which represent 60-70 % of the total cell population, with the remainder being attributed to the stromal vascular fraction (SVF). The SVF contains immune cells such as macrophages and T lymphocytes (Thompson *et al.,* 2012). Obesity, whilst characterised by a higher adipocyte number (Spalding *et al.,* 2008), is also associated with increased macrophage infiltration (Weisberg *et al.,* 2003). It is plausible that these immune cells could be responsible for the majority of inflammatory cytokine secretions from adipose tissue (Fain, 2010). Furthermore, visceral adipose tissue exhibits a more pro-inflammatory state (Bouloumie *et al.,* 2005), as greater macrophage accumulation has been found in visceral adipose tissue (Cancello *et al.*, 2006). The increased likelihood of obesity, coupled with increases in the visceral adipose tissue depot following SCI, may explain the increase in chronic systemic inflammation reported in this population.

C-reactive protein

An elevated level of IL-6 in the systemic circulation also leads to an acute phase response whereby proteins, such as CRP are released from the liver (Moshage, 1997). CRP functions as a pro-inflammatory mediator, assisting in complement binding to damaged and foreign cells, along with stimulating macrophage phagocytosis. Evidence would suggest that CRP is the most accurate inflammatory marker to predict future risk of cardiovascular events (Schillinger *et al.,* 2003; Rutter *et al.,* 2004). This is most likely a result of its relatively long half-life compared to other inflammatory markers (Vigushin *et al.,* 1993).

Link to Atherosclerosis and Metabolic Syndrome

Although elevated chronic inflammation is not formally included among evidence-based metabolic syndrome components, its role in the development of atherosclerosis has been extensively characterised (Libby, 2002: Hansson, 2005: Libby, 2012). Historically, atherosclerosis was considered a cholesterol storage disease, as lipids are a main feature of atherosclerotic lesions (Hansson, 2005). A detailed discussion concerning the development of atherosclerotic lesions is outside the scope of this review. Simplistically when endothelial tissue becomes inflamed, due to infiltration and retention of low-density lipoprotein (LDL) cholesterol in the arterial intima (Skalen *et al.*, 2002; Leitinger, 2003), leukocytes are recruited to the area by the expression of adhesion molecules. Once the leukocytes become attached to the endothelium, pro-inflammatory cytokines provide a chemotactic stimulus, whereby T-lymphocytes join lipid-laden macrophages in the intima of evolving atherosclerotic lesions (Libby, 2002). As a result, elevated levels of inflammatory markers are detected in the systemic circulation and further contribute to the progression of atherosclerotic lesions.

A study of 129 men with SCI, free from infection and abstaining from use of anti-inflammatory drugs, found that CRP was associated with depressed HDL cholesterol (Liang *et al.*, 2008). It is possible that the aetiology of depressed HDL cholesterol in individuals with SCI is a result of the direct relationship between endothelial lipase (EL) and inflammatory markers (TNFα, IL-6 and CRP) (Hirata *et al.*, 2000; Paradis *et al.*, 2006). EL plays a role in the clearance of HDL cholesterol from the circulation, by catalysing the hydrolysis of HDL cholesterol phospholipids (Gilbert *et al.*, 2014). Furthermore, LPL and hepatic lipase have been shown to be down-regulated by TNFα and IL-6 (Hardardottir *et al.*, 1992; Mead *et al.*, 2002). Therefore, besides its direct role in the progression of atherosclerotic lesions, chronic inflammation has been linked with the metabolic syndrome (Yudkin *et al.*, 1999) and insulin resistance (Festa *et al.*, 2000; Huang *et al.*, 2008). Worryingly even modest subclinical elevations in IL-6 and CRP increase the risk of developing heart disease (Ridker *et al.*, 1997; Koenig *et al.*, 1999). In conjunction with adipose tissue expansion, other secondary complications following SCI such as pressure sores and acute symptomatic infections may explain elevated systemic concentrations of inflammatory cytokines compared to able-bodied controls.

Furthermore, it is likely that bladder management techniques (e.g. intermittent catheterization, indwelling catheter) contribute to increased UTI infections, further exacerbating the problem.

2.4.6. Dysregulated Secretion/ Action of Adipokines

In the mid -1990s, adipose tissue was recognised as an endocrine organ (Hotamisligil *et al.,* 1993; Zhang *et al.,* 1994), which significantly progressed researchers understanding of obesity. Adipose tissue secretes a number of hormones, collectively termed 'adipokines', which play a key role in regulating glucose metabolism and insulin sensitivity, as well as immunity and a variety of other physiological processes. Whilst they can act locally in an autocrine and paracrine manner, they're also capable of acting in an endocrine manner, eliciting effects on the rest of body (Balistreri *et al.,* 2010). The expression of a number of adipokines are markedly dysregulated with excess adiposity (Maury & Brichard, 2010), thereby contributing to metabolic complications. Considering the above body composition changes following SCI (section 2.3.2) it is perhaps unsurprising that various cross-sectional evidence has suggested altered levels of these adipokines in this population (Huang *et al.,* 2000; Maruyama *et al.,* 2008). Adipokines that will be measured in Chapter 6 will be described briefly below.

Leptin

Leptin (from the Greek *leptos;* thin) is a protein encoded for by the *ob* gene and was one of the first identified to be secreted by adipose tissue (Zhang *et al.,* 1994). Consequently, circulating leptin concentrations directly correlate with adipose tissue mass (Maffei *et al.,* 1995; Das, 2001). The primary role of leptin is to suppress food intake by inhibiting appetite and to stimulate increased energy expenditure by driving SNS activity (Scarpace *et al.,* 1997; Tang-Christensen *et al.,* 1999). It has actions centrally in the brain (e.g. hypothalamus) but also in a number of peripheral tissues (e.g. pancreas, liver and immune system). It could be argued that leptin secretion from adipocytes is a mechanism to prevent obesity. However, this notion has been challenged, as obesity is typically associated with high leptin levels (Ahima, 2008). As such a state of leptin resistance prevails whereby the neurons of obese patients develop a relative resistance to the effect

of leptin (Sahu, 2003). There are complex interactions between leptin and insulin (Ceddia *et al.*, 2002); they compete for the same signalling molecules (Baranova, 2008) and leptin impacts on insulin action in skeletal muscle (Rabe *et al.*, 2008), pancreatic β-cells and blood vessels (Seufert, 2004; Ronti *et al.*, 2006). Therefore increased leptin concentrations impair insulin sensitivity (Benomar *et al.*, 2005).

Wang *et al.*, (2005) suggested that the findings of increased serum leptin levels in individuals with SCI are irrespective of increased adiposity. The authors found men with SCI have significantly higher serum leptin concentrations compared to age and BMI-matched able-bodied controls. However, due to lower extremity muscular atrophy, BMI is not a sensitive measure to identify obesity in individuals with SCI (Laughton *et al.*, 2009). It is likely that the SCI group had a greater amount of FM for a relative BMI, which might have explained these findings. That said, Bigford *et al.*, (2012) demonstrated alterations in mouse hypothalamic adipokine gene expression and leptin signalling following chronic SCI. Leptin produces widespread sympathetic activation in various tissues (Haynes *et al.*, 1997) and activation of the SNS modulates leptin expression and secretion. Individuals with SCI ≥ T6 show decentralisation of the SNS (Section 2.3.1). Therefore with high level injuries, this interruption blocks any inhibitory effect of the SNS on leptin expression and secretion (Rayner & Trayhurn, 2001). Furthermore, Jeon, (2003) found that an intact SNS was required for the stimulatory effect of leptin on resting energy expenditure in persons with SCI. It is possible that SCI itself plays a role in disrupted adipokine secretion independent of increased adiposity.

Adiponectin

Adiponectin is a protein also primarily produced by adipocytes (Scherer *et al.*, 1995; Maeda *et al.*, 1996). In contrast to leptin, circulating adiponectin is decreased in obesity (Arita *et al.*, 1999) and patients with T2DM or CVD (Ouchi & Walsh, 2007). The mechanisms underpinning downregulated adiponectin production may involve the pro-inflammatory state (Bruun *et al.*, 2003) and abnormal hormonal milieu (Halleux *et al.*, 2001) associated with obesity. Adiponectin is best known as an important regulator of

insulin sensitivity. A review by Kadowaki *et al.*, (2006) stated adiponectin improves insulin sensitivity by i) AMP Activated Protein Kinase (AMPK) mediated reduction of hepatic gluconeogenesis, ii) increased skeletal muscle glucose transport and, iii) enhanced fatty acid oxidation in the liver and skeletal muscle, thereby reducing tissue TAG content. As such adiponectin has been implicated to an improvement in both hepatic and peripheral insulin sensitivity (Fasshauer & Paschke, 2003). This adipokine also has direct anti-inflammatory effects, such as inhibition of IL-6 and pro-inflammatory cytokines (TNFα and IFNɣ), while increasing production of anti-inflammatory cytokines, IL-10 and IL-1 receptor antagonist (Rajala & Scherer, 2003; Tilg & Moschen, 2006).

2.4.7. Summary

The pathophysiology of SCI, primarily inactivity and alterations in body composition, predisposes individuals to an increased likelihood of chronic disease and impaired metabolic control compared to able-bodied individuals. Various psychosocial and environmental barriers mean that it is difficult for individuals with SCI to engage in PA. Moreover, due to functional limitations as a result of the injury, exercise options are limited to the upper extremities. The exercise itself might also be less effective, as the smaller muscle mass engaged leads to reduced absolute oxygen flux and total fuel requirements. The current available evidence on PA levels in persons with SCI, albeit limited to a few studies, shows that most of this population is sedentary. Considering the independent role that PA has on metabolic health and inflammation, plus the modulation of energy balance and subsequently body composition, it is important to understand how it is quantified. This review will now focus on the components of energy expenditure, and the measurement of these in individuals with SCI.

2.5. COMPONENTS OF ENERGY EXPENDITURE

It is essential for the purpose of this review to first distinguish between PA and energy expenditure (EE). Total energy expenditure (TEE) can be partitioned into basal metabolic rate (BMR), Diet-induced thermogenesis (DIT) and physical activity energy expenditure (PAEE). Basal metabolic rate represents the energy required to maintain homeostasis and sustain the metabolic activities of cells and tissues. It is also the largest component of TEE, 80 to 56% for sedentary or very active persons, respectively (Landsberg *et al.*, 2009). An accurate estimate of BMR is not always possible as participants are required to sleep in a specifically designed respiration chamber (a calorimeter), where oxygen (O_2) uptake and carbon dioxide (CO_2) production can be measured. The literature tends to use BMR and resting metabolic rate (RMR) terminology interchangeably. Although, in reality, most studies have not measured BMR overnight in a respiration chamber due to equipment limitations. Therefore, the resting component of TEE will be referred to as RMR from here forward. RMR is influenced by body mass, specifically fat-free mass (Schofield, 1985), which, as eluded to earlier (Section 2.3.2) is reduced in persons with SCI. RMR is also regulated by thyroid hormones, with a minor contribution from the sympathetic nervous system which can also be disrupted in high level SCI. As such, it has been suggested that RMR is reduced by 14 – 27% in individuals with SCI compared to able-bodied controls (Buchholz *et al.*, 2003a).

Diet-induced thermogenesis (DIT) or thermic effect of food (TEF), reflects the energy expenditure associated with digestion and assimilation of food. This represents roughly 10% of TEE based on a standardised western diet of mixed macro-nutrients (Westerterp-Plantenga, 1999). Despite only representing a relatively small portion of TEE, DIT can vary according to the type of macronutrient consumed, Lipids: 0 – 3%, Carbohydrates: 5 – 10%, Proteins: 20 – 30%, (Tappy, 1996). Other factors may influence DIT, such as stimulation of the autonomic nervous system, hormones, PA and body composition (Volp *et al.*, 2011). We have previously mentioned how these factors can be modulated following SCI, which might explain why DIT was 3% less of total daily energy expenditure for males with SCI compared to non-injured controls when assessed in a respiratory chamber (Monroe *et al.*, 1998). It is generally accepted that central activation of the sympathoadrenal system is an essential component in stimulating nutrient-induced

thermogenesis. However, this might be altered in conditions such as SCI, whereby neural pathways between the central nervous system and peripheral sympathetic nerves are disrupted.

Physical activity energy expenditure (PAEE) represents the thermic effect of any movement produced by a skeletal muscle contraction which exceeds RMR (Westerterp, 2009). It could be suggested that PAEE is the most important component of TEE due to its high variability amongst free-living individuals and potential malleability. Currently, it is problematic to accurately translate human movement into units of PAEE owing to its complex and varied nature. This task is even more challenging in wheelchair users during free-living, attributable to atypical movement patterns and a lack of an appropriate criterion measure.

2.6. CRITERION MEASURES OF ENERGY EXPENDITURE

2.6.1. Direct Calorimetry

Directly measuring EE involves quantifying heat exchange between the human body and the environment. This represents the combustion of energy in the form of carbohydrate, protein or fat, through measuring heat released by the body as well as the water vapour released through respiration and from the skin (Schutz, 1995). Whilst highly accurate, it requires a participant to remain unaccompanied in a hermetically sealed, room-sized isolation chamber for 24 hours or more. Total energy expenditure over 24 hours was significantly lower in male SCI participants compared to age-matched non-injured controls (1870 ± 73 vs. 2376 ± 45 kcal·min^{-1}) (Monroe *et al.*, 1998). Ideally the chamber should be large enough to allow some degree of activity, but in reality this confinement will influence PAEE. Despite being considered a gold standard method, it is not widely used due to its large cost and high complexity. Therefore, this review will focus on more applicable measures.

2.6.2. Indirect Calorimetry

Indirect calorimetry measures the type and rate of substrate utilisation (Ferrannini, 1988), whereby energy metabolism is estimated from respiratory gas exchange measurements (oxygen consumption [VO_2] and carbon dioxide production [VCO_2]). Whilst an indirect measure, Seale *et al.*, (1990) observed that direct and indirect calorimetry were equivalent when using a whole room calorimeter. The indirect calorimetry method provides unique information, is non-invasive and more adaptable than direct calorimetry. Despite being over 100 years old, one of the most common indirect calorimetry methods, the Douglas bag technique (Douglas, 1911) is still referred to as the gold standard for measuring oxygen uptake in the laboratory (Gladden *et al.*, 2012). When best practice is adhered to this method has high reliability, CVs of 0.5% for both CO_2 and O_2 (Hopker *et al.*, 2012).

Technological advances, from the Douglas bag method to online systems, have enabled valid and reliable instantaneous breath-by-breath pulmonary gas exchange measurements (Carter & Jeukendrup, 2002). Whilst the Douglas bag technique is mainly confined to the laboratory, light-weight (600g) fully-portable equipment is now available that can continually measure gas exchange variables between 1-5 hours (Ainslie *et al.*, 2003). This equipment can be worn using a back-pack style harness and face mask. Although these portable systems have been shown to be reliable instruments for measuring respiratory gas exchange (Meyer *et al.*, 2001) and can be used outside of the laboratory, their short memory capacity and battery life make them impractical to use for an extended period. Furthermore, portable units may also acutely interfere with everyday habitual activities during free-living assessment.

2.6.3. Doubly Labelled Water

First reported for use in humans by Schoeller and Vansanten, (1982), the Doubly labelled water (DLW) technique is a method of measuring TEE in free-living humans. The DLW method is based on the principle of isotope dilution, and TEE is measured via estimating whole-body CO_2 production (Speakman, 1998). Participants orally ingest a dose of water enriched with stable isotopes of hydrogen (H^2) and oxygen (O^{18}), which diffuses

throughout the body over 2 – 6 hours and mixes with the more abundant forms of hydrogen (H^1) and oxygen (O^{16}) found in the endogenous body water pool. As energy is expended by the body, CO_2 and water are produced. Hydrogen is removed from the body via urination and sweating. O^{18} is also removed from the body via these routes, and is lost as CO_2 which is expelled via the lungs during exhalation. Consequently, with both isotopes being ingested simultaneously, their rate of elimination will differ as O^{18} will be eliminated at a faster rate than H^2 (Speakman, 2005). The disappearance rate of both isotopes is determined by measuring their concentrations in urine samples collected over a period of time (typically 7 – 14 days). The difference in the elimination rate of H^2 and O^{18} reflects the rate at which CO_2 is produced. EE can then be estimated using the Weir equation, assuming a mean respiratory quotient value of 0.85, indicative of a standard westernised diet (Bray, 1997; Speakman, 1998).

The DLW technique is considered the 'gold standard' in measuring TEE during free-living and has been used previously in persons with SCI (Tanhoffer *et al.*, 2012; Tanhoffer *et al.*, 2015). EE can be accurately reported during habitual daily routines over extended periods (7 – 14 days) without the interference of equipment attached to a participant. However, this method is not without its limitations. Minimal information regarding frequency, duration or intensity of activity can be obtained (Plasqui & Westerterp, 2007). This technique is also considerably expensive given the high cost of the stable isotopes and associated analyses which requires sophisticated equipment and trained personnel. It remains to be seen whether DLW can be classified as a criterion measurement for various clinical populations with abnormal fluid distributions, including adults with SCI. The DLW technique remains to be validated in wheelchair users. It is unclear whether the various assumptions for the prediction of EE hold true for clinical populations that use wheelchairs and/or might be suffering from secondary health complications. Researchers have shown that TBW and its distribution within the body is different for individuals with SCI compared to able-bodied controls (Cardus & McTaggart, 1984; Nuhlicek *et al.*, 1988). Inter-compartmental body-fluid distribution is also dependent upon posture (Maw *et al.*, 1995), which, in wheelchair users, is predominantly restricted to sitting and lying. Moreover, Frisbie (2004) noticed altered salt and water balance, along with retention of sodium in the sitting position amongst tetraplegic participants, which might have implications for osmotic gradients within the

body. As both O_2 and H_2 turnover is determined by water flow through the body, this might be altered for wheelchair users which could impact on the accurate prediction of EE using the DLW technique.

Fuel selection during upper body exercise is also different when compared to leg exercise at similar percentages of the mode-specific $\dot{V}O_2$ max. The energy yield from carbohydrate oxidation has been shown to be higher during arm than leg exercise (Tremblay *et al.*, 2009). Furthermore, Jacobs *et al.*, (2013) demonstrated a heavy reliance on carbohydrate across a wide range of intensities during arm crank ergometry (ACE) for individuals with paraplegia compared to able-bodied controls. These factors would increase the respiratory quotient and violate the assumption 0.85 used in the prediction of EE via the DLW technique. The practicality of this technique, which requires collection of repeated urine samples, might be limited in individuals who require catheters as a result of paralysis

2.7. PREDICTION OF ENERGY EXPENDITURE IN WHEELCHAIR USERS

As alluded to earlier it is not always feasible to use criterion methods to measure free-living EE. Researchers have endeavoured to develop user-friendly, unobtrusive and accurate methods to predict EE during free-living. The development of these methods usually involves a validation study using one of the criterion measures above. This section will provide a detailed review of the available prediction tools for wheelchair users and introduce the more recent advancements in wearable technologies in the field. As population-based studies vary substantially in their measurement objectives, we first outline common indicators of PA behaviour obtained using various prediction tools.

2.7.1. Common Measurable Physical Activity Outcomes

Whilst the quantitative assessment of PA using wearable monitors is predominantly focused on the measurement of energy expenditure (Butte *et al.*, 2012), it is important to refer to other common outcome measures obtained during the prediction of PA. Simplistically, PA monitors attached to the wheelchair can provide direct measurers of specific behaviours (e.g. distance travelled), similar to pedometers that capture steps per day in ambulatory cohorts. It is clear that PA is highly heterogeneous and there is no single outcome measure that captures all the relevant information about a given individual (Thompson & Batterham, 2013). Physical activity is a multidimensional construct comprised of four dimensions (a) duration, (b) frequency, (c) type, and (d) intensity. Activity counts from wearable devices capture raw movement signals and can be used to characterise both the duration and intensity of movement (Matthews *et al.*, 2012). Increasingly, more contextual information (e.g. location, type of behaviour) is being collected from logs or Global Positioning Systems (GPS). Common outcomes from methods used to predict PA are listed in Table 2.2.

The intensity dimension is an important determinant of the metabolic health benefits derived from PA in able-bodied populations (Haskell *et al.*, 2007). This can be captured by metabolic equivalents (METs) which are often used to express the energy cost of a physical activity as multiples of RMR. One MET is taken to be an oxygen uptake of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$, yet this is only applicable to able bodied individuals. This conventional MET value is not applicable to individuals with SCI due to the reduced RMR alluded to previously. To account for this Collins *et al.*, (2010) suggested that one MET for a person with SCI should be adjusted to 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$. Throughout this thesis we have expressed MET values relative to each participant's RMR, measured in the laboratory via indirect calorimetry.

Physical activity level (PAL) is often used to quantify an individual's daily PA, which is calculated as TEE/RMR, the variability is reflected in values ranging from 1.2 to 2.5 (Food and Agricultural Organization., 2004). Extremely low PAL (mean: 1.23) have been reported in non-ambulatory adolescents with cerebral palsy (Bandini *et al.*, 1991).

Buchholz *et al.*, (2003b) found relatively low PAL (1.46) in individuals with complete paraplegia, which was only slightly higher than the 1.40 suggested as the lower limit of the sedentary lifestyle range during an expert consultation on human energy requirements (Food and Agricultural Organization., 2004).

Table 2.2: Common estimates of behaviour obtained from physical activity monitors or questionnaires (Adapted from Matthews *et al.*, 2012).

Types of Estimates	Types of Summary Values	
	Absolute	**Relative**
Activity count-based measures	Total counts (counts per day)	Average counts (counts per minute per day)
Energy expenditure-based measures		
Total energy expenditure	Kilocalories/ kilojoules per day	Kilocalories/ kilojoules per min/hour monitored
Physical activity energy expenditure	Kilocalories/ kilojoules per day	Kilocalories/ kilojoules per hour monitored
Intensity-based measures		
Sedentary (<1.5 METs)	Hours per day	Percent wear/monitored time
Light (1.5 -2.9 METs)	Hours per day	Percent wear/monitored time
Moderate (3.0-5.9 METs)	Hours per day	Percent wear/monitored time
Vigorous (> 6.0 METs)	Hours per day	Percent wear/monitored time
Distance travelled	Metres per day	Metres per hour monitored

2.7.2. Self-report Measures

There are currently three predominant self-reported questionnaires that have been employed to measure the PA behaviour of people with a disability. However, as will be seen not all were developed and/or validated for use in manual wheelchair users. Below we describe each questionnaire before considering their strengths and limitations in respect to this population.

2.7.2.1. The Physical Activity and Disability Survey (PADS)

The PADS (Rimmer *et al.*, 2001) was one of the first questionnaires developed to measure the PA behaviour of people with a disability. The PADS was developed and validated for

a group with disabilities ranging from strokes to T2DM. The questionnaire contains four subscales that measure Exercise, Leisure time physical activity (LTPA), Household activity and Time indoors. For each subscale, the tool requests information regarding the activity type (e.g. aerobic, strength or flexibility), how many days a week the activity has been conducted and how many minutes per day. The PADS employs a semi-structured interview technique but has also been used as a questionnaire (Rimmer *et al.*, 2001). Subsequently the PADS was revised to contain six subscales; 1. Exercise, 2. LTPA, 3. General activity, 4. Therapy, 5. Employment/school, and 6. Wheelchair use. The score for the revised version of the PADS is calculated based on the time respondents spend doing the activities multiplied by an intensity rating of that activity. Each activity type has an assigned weighting (e.g. Aerobic = .3, strength = .2 and flexibility = .1). Higher scores represent more activity and negative scores can be achieved through sedentary behaviour.

2.7.2.2. The Physical Activity Scale for Individuals with Physical Disabilities (PASIPD)

The PASIPD (Washburn *et al.*, 2002) was adapted from the Physical Activity Scale for the Elderly (PASE) which was developed and validated by the same research group (Washburn *et al.*, 1993; Washburn *et al.*, 1999).

The final version of the PASIPD contains 13 questions and follows a similar format to that of the International Physical Activity Questionnaire (IPAQ) (Craig *et al.*, 2003). Respondents are requested to provide information about their leisure time activities (including walking and wheeling), household activity and work related activity conducted over the past 7 days. Categories available to respondents are never, seldom (1-2days/wk), sometimes (3-4 days/wk), or often (5-7days/wk). In addition, participants are asked to indicate the average amount of time in hours that they participated in each of the activities (<1hr, >1-2hr, 2-4hr, <4hr). The intensity of activity conducted is established by multiplying the average hours per day for each item by a standard MET value developed for healthy people. Scores are calculated by multiplying the average number of hours per day by the number of days per week. A single total score represents mean MET hr/day.

Alternatively, scores can be generated for five dimensions (Home repair/gardening, Housework, Vigorous Sport, Moderate Sport and Occupation).

2.7.2.3. The Physical Activity Recall Assessment for People with Spinal Cord Injury (PARA-SCI)

The PARA-SCI was specifically developed by Ginis and colleagues (2005) as a tool for people with SCI. The tool employs a similar format to that of the 7-day Physical Activity Recall (Sallis *et al.*, 1985). However, instead of recalling the activity conducted over the previous 7 days, participants are asked to recall the previous 3 days. The PARA-SCI measures the type, frequency, duration and intensity of PA. Specifically, the instrument is designed to capture LTPA (i.e. activity during free time) and lifestyle activity (i.e. daily activity that are routine such as household chores, hygiene and work). These two categories can also be combined to form a third cumulative activity score. Employing an interview technique, participants begin by recalling the activity conducted during the previous day, and an interviewer guides the participant through eight periods of the day (Morning routine, Breakfast, Morning, Lunch, Afternoon, Dinner, Evening and Evening Routine). A series of flow charts help the interviewer guide the participant through the periods of day with questions such as "What did you do after breakfast?". When an activity is identified, the number of minutes spent in that activity and whether it is LTPA or lifestyle activity is recorded. The participant also indicates the intensity of each activity as mild, moderate, heavy or nothing at all based on definitions provided. Once participants complete the first day, the interview continues to the preceding day. Scores are generated by calculating the mean number of minutes per day spent in mild, moderate, and heavy intensity LTPA and activities of daily living. Scores may be summed to generate total minutes of activity**.**

2.7.2.4. Physical Activity Log

Physical activity logs have also been used to measure activities of daily living and leisure time PA in wheelchair users (Warms *et al.*, 2008). Participants are asked to write down activities as they are performed or recall them at the end of a day. It is possible for these activities to be coded with EE values using the adapted PA compendium for wheelchair

users (Conger & Bassett, 2011) to estimate daily TEE. The compendium describes the energy cost of 63 wheelchair activities. However, this resource offers considerably less variety to code activities than the 821 specific activities included in the updated version of the compendium of physical activities for able-bodied individuals (Ainsworth *et al.*, 2011). The studies used to develop the compendium of wheelchair-related PA included subjects with diverse injury characteristics and, in some cases, had small sample sizes. Also, accurately recording PA behaviours using an activity log can be quite burdensome and the quality of information provided is perhaps compromised over prolonged periods (> 24 hours). There may be merit in using this approach as a reference value over short periods, but its use is perhaps limited as a self-report measure during free-living EE assessment and will not be discussed further.

2.7.2.5. Strengths and Limitations of Self-report Measures

Self-report PA questionnaires are cheap and easy to administer. Until recently the quantification of free-living PA in wheelchair users was reliant on outputs from self-report measures (Martin Ginis *et al.*, 2007; Buchholz *et al.*, 2009). However, the results, like other self-report measures, depend on the accuracy of the participants' memory and recall. It has been suggested that self-report measures are unable to adequately quantify the lower end of the PA continuum (Tudor-Locke & Myers, 2001; Shephard, 2003) and often lend themselves to recall bias, floor-effects (lowest score is too high for inactive respondents) and participant over-reporting (Sallis & Saelens, 2000). Besides these general limitations, specific issues pertaining to the administration of the three predominant questionnaires used to predict EE in this population are discussed below.

Questionnaire Administration

All three questionnaires were developed for disabled populations. However only the PARA-SCI was specifically developed and subsequently evaluated for people with SCI. The PASIPD was developed in people with both visual/auditory disabilities and people with locomotor/SCI while the PADS was developed for a group of T2DM and stroke patients. Therefore, one could argue that the content of questionnaires adopted previously fail to capture activities specific to the lifestyle of manual wheelchair users.

A distinguishing feature between the three questionnaires is the resource demand to complete each tool. The PASIPD was developed and designed to be completed independently as a questionnaire. In contrast, the PADS was designed as a semi-structured interview, although the tool has been used as a questionnaire (Rimmer *et al.*, 2001). Finally, the PARA-SCI was also designed as an interview based questionnaire that collects rich behavioural data. Thus the PARA-SCI is resource intensive because it was developed to be used in epidemiologic studies. For example, it can take between 20-45 minutes to complete, the cost of the interviewer needs to be considered and there is high participant demand. Ullrich *et al.*, (2012) also suggested that the use of the PARA-SCI might have limited application for other investigators, besides the developers, due to the exclusion of subjective appraisals and the technical complexity of interview administration. These limitations were acknowledged by the authors who subsequently developed a new questionnaire to address these limitations. The Leisure Time Physical Activity Questionnaire for People with Spinal Cord Injury (LTPAQ-SCI) (Martin Ginis *et al.*, 2012) is a brief (5 minutes) self-report questionnaire specifically designed for people with SCI that measures minutes of mild, moderate and heavy intensity LTPA performed over the previous 7 days. Therefore, the LTPAQ-SCI is not capable of measuring activity of daily living.

Reliability and Validity

The test-retest reliability of the three questionnaires has been tested, however, the PADS has had no reliability studies conducted in wheelchairs users or people with SCI. Therefore, it remains unclear whether the PADS can be reliably used as a measure of PA behaviour in this population. The test-retest reliability of the PASIPD was established in a study of 45 adult patients with a range of disabilities but it is noteworthy that only one participant had SCI (van der Ploeg *et al.*, 2007). Results revealed a test-retest reliability correlation of .77. Further, the internal consistency of the PASIPD has been shown to be moderate in a sample of people with SCI (Cronbach $\alpha = .63$) (de Groot *et al.*, 2010). The PARA-SCI is the only instrument to have tested its reliability in a sample solely consisting of people with SCI. To establish the test-retest reliability of the PARA-SCI, 102 people with SCI completed the instrument on two separate occasions a week apart

(Ginis *et al.*, 2005). Intra-class correlations revealed adequate to good test-retest reliability for the different activity intensities. However, moderate-intensity LTPA and heavy intensity lifestyle activity demonstrated poor levels of reliability (ICC = .45 and .56 respectively).

Establishing the validity of questionnaires is important in order to be sure that the tool effectively measures what it intends to (i.e. the activity of people using a manual wheel chair). In a study of 139 people with SCI, de Groot *et al.*, (2010) investigated the relationship between PASIPD scores and measures of wheelchair user skills and fitness. Results revealed that scores on the PASIPD distinguished between persons with tetraplegia and paraplegia as well as between those with long and short time since injury. However, scores on the PASIPD did not reveal differences in expected and hypothesized factors such as age, BMI and gender. In terms of comparing scores from the PASIPD with indicators of physical capacity, results revealed weak to moderate relationships. For example, PASIPD scores were positively related to scores on the manual muscle test (0.35), and $\dot{V}O_2$ max (0.25). De Groot *et al.*, (2010) suggested that the homogeneity of the sample (i.e. low scores on PASIPD) may provide some explanation for the low correlations. Manns and colleagues (2005) conducted a rare example of the PADS being employed to measure the PA behaviour of individuals with paraplegia. The aim of the study was to determine relationships between lifestyle factors including PA behaviour and components of metabolic syndrome in people with paraplegia. Results revealed a significant moderate relationship between scores on the PADS and, $\dot{V}O_2$ max (r = 0.45). However, equating self-report PA to fitness, rather than a criterion measurement (described above) may not be the most appropriate way to ascertain concurrent validity.

Results from validity studies indicate that of the three questionnaires, the PARA-SCI has the strongest relationships with criterion measures. During the development and evaluation of the PARA-SCI (Ginis *et al.*, 2005), criterion ($\dot{V}O_2$ reserve) values displayed a very large correlation with cumulative (LTPA plus lifestyle) activity data for total activity (r = 0.79). When data was coded for intensity of activity, large to very large positive correlations were seen for moderate-intensity (r = 0.63) and heavy-intensity (r = 0.88) activity. However, this relationship was weak and non-significant for low intensity

activities (r = 0.27) and consequently the PARA-SCI scores under-reported the amount of time spent doing activities of low intensity by 10%. Therefore, although these findings indicate some evidence of convergent validity, the results also point to the limitations of self-report measures.

Measuring Intensity

A distinguishing feature between the three disability questionnaires is how they gather information pertaining to the intensity of activity conducted. Failure to consider individual differences in PA intensity makes it difficult to detect relationships between lifestyle activities and health outcomes (Ginis *et al.*, 2005). The PADS employs a single item to examine the overall intensity of structured activity but doesn't assess the intensity of leisure time activities. One of the fundamental limitations of the PASIPD is the use of standard MET values as a measure of activity intensity regardless of the participant's level or type of disability. Further, the standard MET values employed were developed for healthy individuals. If MET values are to be used, it will be necessary to develop a new empirically based supplement to the compendium of PA appropriate for people with SCI (Lee *et al.*, 2010). The inability of the PASIPD and PADS to effectively measure intensity of activity prompted the development of the PARA-SCI. Subsequently, the authors of the PARA-SCI conducted a systematic and empirical process to develop definitions of three different exercise intensities (i.e. mild, moderate and heavy) specifically for people with SCI (Ginis *et al.*, 2005). The empirical development of intensity definitions suggest the PARA-SCI may be the most effective self-report questionnaire at measuring the intensity of PA in people with SCI. However, it should be noted that even with such a rigorous development of intensity definitions, the PARA-SCI is still dependent upon the accurate recall of behaviour. Research has also challenged the use of RPE as a valid psychophysiological index of perceived exertion in persons with SCI (Lewis *et al.*, 2007). This could have implications with the prediction of activity intensity using self-report measures in persons with disabilities, which could be influenced by secondary conditions such as chronic pain.

Objective sensors overcome these shortcomings of self-report by removing the subjective recall element. The next section of this review will now discuss the use of these objective sensors in wheelchair users.

2.7.3. Accelerometry

Accelerometer-based devices have commonly been used to quantify habitual free-living PA in able bodied cohorts (Plasqui *et al.*, 2005). Various studies have supported the utility of accelerometers to detect variability in activity levels in ambulatory populations with disabling conditions such as multiple sclerosis and rheumatoid arthritis (Khemthong *et al.*, 2006; Cervantes & Porretta, 2010). However, at present there is a lack of research focussing on the accurate prediction of physical activity levels using commercial movement sensors in manual wheelchair users. Accelerometers are capable of providing temporal information about the specific variables mentioned previously, such as the total amount, frequency, intensity and duration of PA (Westerterp, 2009). Two main varieties of accelerometers are used widely in PA research - uniaxial and increasingly tri-axial. Uniaxial accelerometers register movement in the vertical axis only, whereas tri-axial accelerometers register movement in the anteroposterior (X), mediolateral (Y) and vertical (Z) axes. During laboratory and free-living validation studies in able-bodied cohorts, it appears that the greater sensitivity of the tri-axial accelerometer to movement in three different planes leads to a better prediction of PAEE than uniaxial accelerometers. In a recent systematic review, (Van Remoortel *et al.*, 2012) reported a pooled *r* (95% CI) of 0.39 (0.16, 0.58) and 0.59 (0.45, 0.70) between PAEE estimates from uniaxial and tri-axial accelerometers, respectively, compared to PAEE measured from DLW.

Whilst a comprehensive description of the internal components of movement sensors is not within the scope of this review but excellently described elsewhere (Chen *et al.*, 2012), it is perhaps important to address how a physical measure is converted by a device into a signal/quantifiable value. Simply speaking, accelerometers contain transducers which convert one type of energy, e.g. movement (raw acceleration) which is difficult to quantify, to another (voltages). The secondary on-board processing step is data acquisition where the converted energy is transformed to a signal and processed in order to retain desirable parameters while discarding noise or movement artefacts.

Almost all commercially available movement sensors report their outcomes in counts per unit time or epoch. Counts derived from movement sensors are arbitrary units which are

commonly derived in three ways. First, summing the integral of the modulus of acceleration from each axis (Horner *et al.*, 2011), second, summing the integral of the route mean squared acceleration from each axis (Cook *et al.*, 2011) and third, summing the vector magnitude of acceleration from each axis. Band-pass filtering frequencies, utilised during the data acquisition stage to 'filter out' signals which are not likely to be representative of 'human movement', often differ between devices. Knowledge regarding digital signal processing filters has only recently become more available, as an obligation has been placed on device manufacturers to be more transparent in regards to their specific properties and functions. For example, the upper and lower bandwidth filters of 0.25 and 2.5 Hz of the GT3X+ (Actigraph, Fort Walton Beach, FL; used in Chapter 3 & 4) were designed for ambulation, based on the premise that acceleration frequencies arising from most human activities at the hip usually fall within this range. There is considerable variation in filter width amongst commercially available monitors on the market, the RT3 (Stayhealthy Inc., Monrovia, CA) and 3DNX (BioTel Ltd, Bristol, UK) have upper cut-off frequencies of 10 and 20Hz, respectively. Researchers have suggested it is advisable that accelerometer-based PA monitors should be able to measure accelerations with frequencies up to 20 Hz (Bouten *et al.*, 1997). It is clear that the band-pass filter plays a crucial role in determining the quality of the output from movement sensors (Chen *et al.*, 2012) and should be selected carefully dependent on anatomical wear location and the types of movements to be considered.

Despite enormous differences in signal processing and internal components, all accelerometers have similar fundamental properties defined by accuracy, precision, range and sensitivity and must be compared against criterion measurements (Chen *et al.*, 2012). These properties are particularly important in objective PA monitoring. Manufacturers have managed to ensure that the end user requirement for higher-resolution signals does not interfere with other practical issues such as size or functionality of the accelerometer. This has mainly been achieved through the introduction of microelectromechanical system (MEMS) transducers, currently the principle class of motion-detecting accelerometer due to their good sensitivity, small size, affordability and low power consumption (Chen *et al.*, 2012). Hence, these days, commercially available movement sensors are more compact, in that they are relatively unobtrusive and overall compliance in large population based studies has been shown to be high (Matthews *et al.*, 2012).

Other improvements such as an increased on-board memory capacity and extended battery life of newer generations of accelerometers permits extended monitoring periods of habitual PA with higher time resolutions.

2.7.3.1. Accelerometer Devices Attached to the Wheelchair

Researchers have tried attaching a custom data logger onto the wheel (Tolerico *et al.*, 2007) or a tri-axial accelerometer (Coulter *et al.*, 2011) to the frame of the wheelchair in order to capture certain mobility characteristics such as average speed and distance travelled. Whilst this approach is relatively unobtrusive, these devices offer limited information on the intensity of the activities performed. Conger *et al.*, (2014) tried to address this limitation by using hand rim propulsion power, and concluded that it can accurately and precisely measure EE based on the two variables being significantly correlated (r = 0.69). However, we contend that any device attached to the wheelchair cannot distinguish between self or assisted propulsion and cannot quantify activity out of the wheelchair. It is common for wheelchair users to have different chairs to participate in various sports, therefore a device attached to a single chair will fail to capture the moderate-vigorous-intensity activity of training or competitive match play situations. Due to these limitations we will primarily focus on body born movement sensors in this literature review. Recently the feasibility of using Global Positioning Systems (GPS) to measure PA has been explored (Duncan *et al.*, 2009). The major limitation of GPS is that units require a clear line of sight to four or more satellites, and hence can only measure outdoor PA, but even this becomes difficult when the line of sight is obstructed by heavy foliage or tall buildings (Stopher *et al.*, 2008).

2.7.3.2. Body-borne Accelerometers

Waist-mounted single-sensor devices, positioned within close proximity to an individual's centre of mass, have been the mainstay of activity monitoring in able-bodied cohorts, but instruments have also been placed on the upper arm (Welk *et al.*, 2007) and wrist (Reiterer *et al.*, 2008). The accuracy and precision (two fundamental properties of movement sensors) of single units worn on the waist can be limited for certain types of upright behaviours that have a low ambulatory component and may involve upper body work (Matthews *et al.*, 2012). The measurement error of waist mounted devices is

generally related to the inability to detect arm movements as well as static work (lifting, pushing, carrying loads). However, movement of wheelchair users is predominantly restricted to the upper body. Therefore, ambiguity remains as to the most appropriate anatomical location to offer improved sensitivity in order to estimate PAEE in this population. We attempt to address this issue in Chapters 3 and 4.

A summary of validation studies assessing the most appropriate anatomical wear location of accelerometers for wheelchair users is shown in Table 2.3. Previous studies have used different dependent variables ($\dot{V}O_2$ and EE), accelerometer devices (CSA, GT3X and RT3) and activity protocols (propulsion: wheelchair treadmill, ergometer, over ground, ACE and activities of daily living). The magnitude of correlations between accelerometer outputs and criterion measurements at the waist were large, r = 0.66 (Hiremath & Ding, 2011b) and r = 0.67 (Garcia-Masso *et al.*, 2014). Yet correlations were stronger for devices worn on the upper arm and wrist, ranging from r = 0.83 – 0.93 and r = 0.52 – 0.93, respectively (Table 2.3). The smaller correlation reported in the Washburn & Copay, (1999) study might be a result of the CSA uniaxial accelerometer offering reduced sensitivity.

Table 2.3: Summary of body-borne accelerometer validation studies in wheelchair users

Study	Sample[a]	Criterion measure	Activity protocol	Device/ outputs	Anatomical location	Results
(Washburn & Copay, 1999)	21 (9F). SCI (n=11), SB (n=7), other (n=3).	$\dot{V}O_2$ (Aerosport TEEM 1000)	Three timed pushes (slower than normal, normal, and faster than normal) over a rectangular indoor course	PAC from a CSA uniaxial ACC	Left wrist	r = 0.67, SEE = 4.99 ml·kg^{-1}·min^{-1}
					Right wrist	r = 0.52, SEE = 5.71 ml·kg^{-1}·min^{-1}
(Postma *et al.*, 2005)	10 SCI (3F) (Cervical to Lumbar)	video records analysed separately	Several ADL (propulsion, chores, sedentary activities) according to a standard protocol, in a semi-natural setting	Acceleration signals from an ULAM (6 ADXL202 biaxial ACC)	One sensor attached at each thigh and at each wrist, a two sensor attached over the sternum	Agreement for the detection of self-propelled propulsion was 92%; sensitivity 87% & specificity 92%. Mean overestimation in duration of propulsion by the ULAM was 3.9%
(Hiremath & Ding, 2011b)	24 SCI (5F) (T3-L4)	IC EE (COSMED K4b^2)	Resting and three activity routines; propulsion (performed on a WERG and flat tiled surface), ACE (20-40) and deskwork.	PAC from a RT3 tri-axial ACC and participant demographics Two prediction equations were developed (general equation and activity-specific) for the upper arm	Waist	r = 0.66, SEE = 1.38 kcal·min^{-1}
					Upper left arm	r = 0.83, SEE = 1.02 kcal·min^{-1}. Error was reduced to between 12.2 - 38.1% for the RT3 arm using activity-specific equations from 14.1 - 113.7% using the general equation.
					Combined	r = 0.84, SEE = 1.00 kcal·min^{-1}
(Kiuchi *et al.*, 2014)	6 SCI (C6 – T9)	IC EE (AR-1 Type-4)	Propulsion at 3 continuous speeds on a WT that elicited an RPE of 9 (2.5-3 km/hr), 11 (3.5-4.0 km/hr) & 13 (4.5-5.0km/hr) for 2 min	Tri-axial ACC with gyro sensor. Predicted EE was calculated by incorporating acceleration, angular velocity and participant demographics	Left wrist	R^2 = 0.86
					Right wrist	R^2 = 0.68
					Left upper arm	R^2 = 0.75
					Right upper arm	R^2 = 0.87

(Garcia-Masso *et al.*, 2014)	20 SCI (T4-S1)	$\dot{V}O_2$ (COSMED K4b^2)	10 activities which included ADL, transfers, ACE and propulsion that covered a wide range of exercise intensities.	GT3X (36 features extracted from the second-by-second acceleration signals were used as independent variables)	Non-dominant wrist.	r =0.86, MSE = 4.98 ml·kg^{-1}·min^{-1}
					Dominant wrist	r =0.86, MSE = 5.16 ml·kg^{-1}·min^{-1}
					Chest	r = 0.68, MSE = 10.41 ml·kg^{-1}·min^{-1}
					Waist	r = 0.67, MSE = 10.61 ml·kg^{-1}·min^{-1}
(Kooijmans *et al.*, 2014)	10 SCI (C4 – T12)	video records analysed separately by 2 independent reviewers	Comprehensive protocol representative of ADL in people with SCI (propulsion & ACE) and other activities that could be falsely detected, i.e. being pushed	Second-by-second vector counts from an ActiGraph GT3X+	Combination between one ACC attached to the wrist and another on the spokes of the wheelchair	Agreement for the detection of self-propelled propulsion was 85%; sensitivity 88% & specificity 83%. Disagreement between ACC output and video was largest for propulsion on a slope and very low speed on a WT, and being pushed whilst making excessive arm movements

ACC accelerometers, *ACE* arm crank ergometry, *ADL* activities of daily living, *EE* energy expenditure, *IC* indirect calorimetry, *SB* Spina Bifida, *SCI* spinal cord injury, *ULAM* upper limb activity monitor, $\dot{V}O_2$ oxygen uptake, *WERG* wheelchair ergometer, *WT* wheelchair treadmill.

[a] All-male participants unless stated otherwise

The message with regards to limb dominance is somewhat unclear. Washburn & Copay, (1999) found differences in the magnitude of correlations between the left and right wrist (r = 0.67 and r = 0.52, respectively). This discrepancy could be due to handedness (n = 20 right handed), but is most likely due to an increase in right wrist movement to negotiate four left-hand turns of a rectangular course. Kiuchi *et al.*, (2014) also found considerable variation during propulsion on a wheelchair treadmill, where the right upper arm and left wrist offered the strongest correlations (r = 0.93). However, this study had a relatively small sample size n = 6. In contrast, Garcia-Masso *et al.*, (2014) noticed no negligible difference in relationships between the dominant and non-dominant wrist (r = 0.86 vs r = 0.86) during a comprehensive activity protocol.

Considering the validity of a movement sensor based solely on the strength of its relationship to a criterion measure should be avoided as it does not indicate the agreement between the two variables (Bland & Altman, 2010). Correlations are also dependent on the range of the true quantity in the sample, if this is narrow then the correlation will be weaker than if it is wide. As the best practice guidelines for validating activity monitors (Bassett *et al.*, 2012) suggest evaluating devices over a wide range of activities of various intensities it is therefore likely that a high correlation will be observed. Staudenmayer *et al.*, (2012) recommended in a recent review on statistical considerations in the analysis of accelerometer data, that it is useful for researchers to report measurement error.

To date relatively few studies have attempted to develop and then cross validate regression equations specific to manual wheelchair users that are capable of accurately predicting EE/PAEE. Strath *et al.*, (2012) stated that additional monitor calibration studies are necessary to provide population specific algorithms for individuals with functional limitations. Hiremath & Ding, (2011b) attached an RT3 to the upper arm and waist, whilst attempting to develop and then evaluate two new EE prediction algorithms, one general and one activity specific, through the use of a *k*-fold cross validation technique. Absolute EE estimation errors for the RT3 worn at the arm ranged from 14.1% – 113.7% for the general equation. However, whilst EE estimation accuracy improved using the activity-specific algorithm, ranging from 12.2% to 38.1% these were drastically higher than those previously reported in ambulatory populations (Rothney *et al.*, 2008).

Estimation errors were highest for sedentary activities using the developed general equation, 114% and 52% for resting and deskwork, respectively. This may be explained by the outcome variable being total EE, which comprises RMR, DIT and PAEE. During sedentary activities, RMR represents the largest fraction of TDEE, as PAEE is negligible. Fundamentally, accelerometers measure movement and should therefore only be associated with the component of energy expenditure arising from skeletal muscle contraction-induced movements (PAEE). Furthermore, as previously discussed, common equations to predict RMR in the general population are inappropriate for individuals with SCI and have been shown to over-predict measured requirements by 5-32% (Buchholz & Pencharz, 2004). It is not surprising that body mass was a significant predictor in the general, and more specifically, resting and desk work activity specific equations developed by Hiremath & Ding (2011b). However, as body mass does not differentiate between metabolically active tissue (LM), which is reduced in the lower extremities of individuals with SCI, it is possible the high EE estimation error observed during sedentary activities may be a result of error in the calculation of the RMR component. Accelerometer variables such as activity counts in the X and Y axis were significant predictors of EE during propulsion and arm-ergometry, which suggests activity monitors worn on the arm may be sensitive to upper body movements and therefore the detection of PAEE during these tasks.

Realizing the limitations associated with waist mounted PA monitors in able-bodied populations, researchers have utilized multi-sensor arrays applied to different body segments. Swartz *et al.*, (2000) combined two Actigraph accelerometers (CSA) worn at the wrist and hip in order to determine whether EE prediction could be improved using a bivariate regression equation incorporating data from both sites. This resulted in a significant but yet minor improvement compared with a univariate regression equation using the hip alone, $R^2 = 0.34$ and $R^2 = 0.32$, respectively. However, in research conducted specifically on wheelchair users, combining data from these two sites did not yield a more accurate estimation of EE (Hiremath & Ding, 2011b). In some research and development labs, such as the Department of Rehabilitation Medicine and Physical Therapy in the Netherlands, accelerometers have been arranged in parallel arrays and positioned at various anatomical locations to monitor the types of activity being performed by postural identification. Such prototype PA monitors were developed to primarily target specific

population groups during rehabilitation, including amputees (Bussmann *et al.*, 1998) or inpatients with SCI (van den Berg-Emons *et al.*, 2008).

The upper limb activity monitor (ULAM) consists of six ADXL202 biaxial accelerometers attached at each thigh, and at each wrist and two sensors attached to the skin using medical tape at the sternum. Specificity, agreement and sensitivity for the detection of wheelchair propulsion were high, 92 (range, 85 – 98) %, 92 (87 – 96) % and 87 (76 – 99) %, across a standardized activity protocol consisting of several activities representative of daily living. Despite the relatively small sample size (n=10), the diversity of physical functioning within the SCI population appeared well represented. Hence the authors concluded that the results were externally valid for the majority of patients with SCI. The ULAM contains several wires which connect to a data recorder carried in a belt around the waist. The device has previously been used to assess PA during rehabilitation (van den Berg-Emons *et al.*, 2008), although the monitoring period was restricted to a relatively short duration (< 48 hours) as a result of a reduced memory capacity and battery life required to power the six accelerometers. This is not in keeping with advancements in the area of PA monitoring, where end user requirements for higher-resolution signals have led to the development of newer generations of activity monitors with greater storage capacity and battery life. Where possible monitoring of habitual PA during free-living should be of a longer duration. One week monitoring periods have routinely been used in previous research to provide a sufficiently large number of days to achieve intraclass correlations > 80%, whilst also providing the opportunity to sample behaviour on both week and week-end days (Matthews *et al.*, 2012). Bussmann *et al.*, (2009) found that wearing the ULAM does not systematically influence the amount of daily manual wheelchair propulsion assessed using a rotation counter attached to the wheel. However, the activity monitor was only worn for one day over the 7-day period, and even in this short duration, participants reported moderate burden measured via a questionnaire. Moreover, multiple-site monitors such as the ULAM are often not available outside the developing labs, and are expensive, making it difficult for researchers to cross validate devices or compare results between prototype designs. Kooijmans *et al.*, (2014) combined outputs from a GT3X+ accelerometer worn on the wrist and on the spokes of the wheelchair and found strong agreement for the detection of self-propelled propulsion being 85%, sensitivity 88% and specificity 83%. Whilst less

burdensome, disagreement between GT3X+ outputs and video was largest for propulsion on a slope and very low speed on a wheelchair treadmill, and being pushed whilst making excessive arm movements. It may be that physiological signals should be incorporated into the prediction of EE to improve accuracy.

2.7.4. Heart Rate

Heart rate (HR) has an advantage as a physiological variable as it increases linearly and proportionately with exercise intensity and thus oxygen uptake (Chen *et al.*, 2012). Keytel *et al.*, (2005) concluded that PAEE can be accurately predicted from HR with a great deal of accuracy after adjusting for age, gender, body mass and fitness. However, during lower intensity PA there is a weak relationship between HR and EE (Luke *et al.*, 1997). This is most likely due to small postural changes causing alterations in stroke volume, or that HR during low intensity PA is affected by external factors such as psychological stress, stimulants, ambient temperature, dehydration and illness (Achten & Jeukendrup, 2003).

There are a number of ways to use HR data to predict EE, one of the most promising being the flex-HR method (Ainslie *et al.*, 2003), which has previously been used in individuals with SCI (Hayes *et al.*, 2005; Tanhoffer *et al.*, 2012). This method involves monitoring HR at rest and during an incremental exercise test which permits the development of an individual HR-$\dot{V}O_2$ calibration curve. The flex-HR is determined as the mean of the highest HR at rest and the lowest HR observed during light intensity activity. In order to calculate EE during the monitoring period, HR values recorded below the flex-HR assume that the participant is at rest and RMR is used to estimate EE. For values above the flex-HR the individual HR-$\dot{V}O_2$ curve is used to predict EE. Despite recent research into the use of various HR indexes (Coutinho *et al.*, 2014) and artificial neural networks (Garcia-Masso *et al.*, 2014) in the prediction of $\dot{V}O_2$ in individuals with SCI, it is clear that the accurate prediction of EE using HR is heavily reliant on individual calibration. This consideration is perhaps even more important in this population, taking into account the aforementioned cardiovascular changes post SCI. Hayes *et al.*, (2005) found that the variance in measured EE was considerably improved using an individual calibration (55%) compared to HR alone (8.5%).

2.7.5. Multi-sensor Devices; the Incorporation of Acceleration and Physiological Signals

New multi-sensor technologies, which include the combination of physiological parameters and accelerometry, have great potential for increased accuracy in assessing PAEE as they incorporate and minimize the strengths and weaknesses of HR and accelerometry alone. The Actiheart (Cambridge Neurotechnology Ltd, Papworth, UK) integrates an accelerometer and heart rate monitor into a single-piece movement monitor. The Actiheart (AHR) unit has been described in detail previously (Brage *et al.*, 2005), along with the detailed branched modelling technique it utilizes to estimate PAEE through the combination of heart rate and accelerometer counts (Brage *et al.*, 2004). Studies have supported the utility of combined HR and accelerometer devices to accurately estimate PAEE during treadmill walking and running in adults (Brage *et al.*, 2005), and in activities of low-to-moderate-intensity in a laboratory setting (Thompson *et al.*, 2006). However, the validity of the Actiheart in estimating PAEE remains to be established in wheelchair users, and this will be determined in Chapter 5.

The use of multi-sensor devices has mostly been limited to laboratory based validation of the SenseWear ® Armband (SWA), a commercially available monitor that is designed to be worn on the upper arm, a preferential anatomical location for the prediction of PAEE/EE in wheelchair users. This device incorporates dual-axis accelerometry and physiological measures such as heat flux, galvanic skin response and temperature to predict EE. More detailed components and specifications of this activity monitor have been described elsewhere (Chen *et al.*, 2012). Researchers from the department of Rehabilitation Science and Technology at the University of Pittsburgh, through various conference proceedings (Hiremath & Ding, 2009) and journal publications (Hiremath & Ding, 2011a; Hiremath *et al.*, 2012), have described the reduction in prediction error from this device for predicting EE in this population (Table 2.4). It is clear that the general manufacturer's model utilised by the SWA device, is unable to accurately estimate EE as it does not typically consider the types of physical movements performed by manual wheelchair users. It is possible that as wheelchair propulsion and arm-ergometry were not included in the predefined activity categories of the SWA device, that these activities

were misclassified into a more strenuous type of PA, leading to the observed overestimation of EE.

With the development of specific EE prediction equations, based on activities common in the lives of wheelchair users, the SWA's accuracy has been improved (Hiremath *et al.*, 2012). Activity specific models encompassed sensor data, demographic data and customized data derived from the sensor. Using the same activity protocol as their previous studies, the authors developed prediction models using a training group of 36 participants and evaluated these on a validation group (n = 9). Both developed prediction models performed significantly better than the proprietary algorithms of the manufacturer's model. Generalized and activity specific models underestimated EE with relatively small biases -2.3 ± 31.7% and -4.9 ± 20.7%, respectively, whereas the general manufacturer equation over predicted by 55.3 ± 56.1%. Looking solely at mean percentage difference can be misleading. It would appear that the general model has a smaller overall bias, but this is likely a product of under and overestimations from different activities cancelling each other out. This is evident when looking at the larger SD associated with the general compared to the activity specific model. Another alternative is to look at mean absolute percentage differences, which were 59.2%, 24.7% and 16.8% for the manufacturer's model, general model and activity-specific model, respectively (Hiremath *et al.*, 2012). These findings provide encouragement for the use of multi-sensor activity monitors with new prediction models developed specifically for individuals with SCI.

Table 2.4: Summary of multi-sensor device validation studies in wheelchair users

Study	Sample[a]	Criterion measure	Activity protocol	Device and location	Results
(Hiremath & Ding, 2011a)	24 SCI (5F) (T3-L4)	IC EE (COSMED K4b^2)	Resting and three activity routines; propulsion (performed on a WERG and flat tiled surface), ACE (20-40) and deskwork.	Estimated EE from **RT3** tri-axial ACC worn on the **waist**	R_S=0.72 for all activities (lowest for propulsion; R_S=0.44, highest for deskwork; R_S=0.66). EE estimation errors ranged from 22.0 to 52.8%. Poor ICCs 0.64 (<0.75)
				Estimated EE from **Sensewear** worn on the **upper arm** (manufacturer's model)	R_S=0.84 for all activities (lowest for deskwork; R_S 0.65, highest for propulsion; R_S=0.76). EE estimation errors ranged from 24.4 to 125.8%. Poor ICCs 0.62. Neither device is an appropriate tool for quantifying EE
(Hiremath *et al.*, 2012)	45 (8F) (C4–L4)	IC EE (COSMED K4b^2)		Estimated EE from **Sensewear** worn on the **upper arm (manufacturer's model)**	r = 0.75 (P < 0.001). ICCs 0.64 (P < 0.001). MAE = 2.0 kcal·min^{-1} (59.2%)
				Estimated EE from **Sensewear** worn on the **upper arm (SCI general model for all activities)**	r = 0.74 (P < 0.001). ICCs 0.72 (P < 0.001). MAE = 0.9 kcal·min^{-1} (24.7%)
				Estimated EE from **Sensewear** worn on the **upper arm (activity-specific model)**	r = 0.88 (P < 0.001). ICCs 0.86 (P < 0.001). MAE = 0.6 kcal·min^{-1} (16.8%)
(Conger, 2012)	14 (3F). SCI (n=7) SB (n=4) AMP (n=2) Charcot-Marie-Tooth (n=1)	IC EE (Oxycon Mobile)	5 different wheeling activities preformed for 8 min interspersed with at least 3 min rest. Level surface (4.5, 5.5 & 6.5 km/h), wheeling on a rubberised 400 m track (5.5 km/hr) & wheeling on a sidewalk course at a S-S speed	**Actical** on right **wrist**	No sig. differences between criterion method and Actical EE (± 9 – 25%)
				Sensewear on right **upper arm**	The SenseWear sig. overestimated EE during wheelchair propulsion (+ 30 - 80%)
				Sensewear using **wheelchair specific equation** (Hiremath and Ding, 2012)	The wheelchair specific equation improved EE prediction error, but this was still elevated during higher intensity activities (+27-43%)

ACC accelerometers, *ACE* arm crank ergometry, *EE* energy expenditure, *IC* indirect calorimetry, *SB* Spina Bifida, *SCI* spinal cord injury, *WERG* wheelchair ergometer. [a] All-male participants unless stated otherwise.

Furthermore, even when using the generalised SCI specific prediction equation, the SWA tended to overestimate EE (27 to 43%), whereas a wrist-mounted accelerometer accurately predicted EE (9 to 25%) during wheelchair propulsion (Conger, 2012). Also, a recent free-living study using DLW demonstrated that the SWA was unable to detect variation within-individual EE during voluntary increases in PA in individuals with SCI (Tanhoffer *et al.*, 2014). The advantage of incorporating physiological variables in EE estimation is that they address the shortcomings of accelerometry alone, and capture physiological strain associated with behaviours that produce similar acceleration profiles but have a different energy cost, such as changing gradient or load carriage (Lamonte & Ainsworth, 2001). To date there is limited available data on the validity of activity monitors in quantifying EE during wheelchair propulsion over differing gradients. It is clear that proprietary algorithms used by the SWA overestimate metabolic rate, but interestingly, previous research noted an increase in this overestimation and variability when gradient was elevated rather than when speed was increased (Davis *et al.*, 2010). During a treadmill protocol that included variable speeds over a flat gradient, coefficients of determination between indirect calorimetry and SWA EE ranged from 0.65 – 0.82. In contrast, when a constant treadmill velocity ($2km \cdot hr^{-1}$) was employed with variable gradients the coefficients of determination were much lower, in the range of 0.34 – 0.58. It would appear that even additional physiological variables are unable to assist with a more accurate prediction of EE during propulsion over differing gradients.

Ultimately, the calculation of EE by the SWA device is determined by proprietary algorithms which utilizes upwards of twenty possible output parameters including heat flux, galvanic skin response and temperature. Researchers should have access to these underlying equations. At present it is unclear how each parameter contributes to the prediction of EE in this device. Research has demonstrated disturbances in thermoregulatory responses that are proportional to the level and completeness of SCI lesion, reflecting the amount of sympathetic nervous system available for sweating and blood redistribution (Petrofsky, 1992). Tetraplegics display considerable thermal dysregulation due to the complete absence of sweating capacity. Price & Campbell (2003) also demonstrated that upper arm skin temperature was significantly higher for tetraplegics when compared to paraplegics over 60 minutes of prolonged wheelchair exercise in warm conditions. These issues could have profound implications for using this

technology in the prediction of EE in individuals with SCI, especially those with higher level lesions.

2.7.6. Summary

There is no shortage of research aiming to improve the prediction of PA in able-bodied individuals. Whilst this area has seen a great deal of progress over recent years, due to technological advancements and new data processing strategies, the use of movement sensors in diverse populations is lagging behind. The development of tools specific to wheelchair users would help researchers better understand the link between PA and metabolic health in this population. This is of primary importance in individuals with SCI, who exhibit lower levels of self-reported PA and an increased risk of chronic disease. As such there is now a renewed impetus to translate progress in measuring PA in able-bodied populations to wheelchair users, with the aforementioned techniques (self-report, physiological signals, accelerometry and multi-sensor devices) displaying varying degrees of success.

Due to the limitations with self-report measures (Section 2.4.1.5) and accelerometers attached to the wheelchair (Section 2.4.3.1), this thesis aims to focus on the development of new wearable technologies. Most of the previous studies have assessed predicted EE against a criterion rather than PAEE. In some cases it is plausible that the use of prediction equations for RMR, which are not suitable for individuals with disabilities, introduce error in the estimation of EE, particularly during sedentary and low-intensity activities. Despite the generation of various prediction models there is a lack of research in the area where these equations have been cross-validated. Some of the laboratory protocols adopted previously, lack a sufficient range of activities, and certain wheelchair propulsion tasks such as additional weight and changes in gradient have also been over looked. It is hoped that this thesis will address some of these limitations. The potential of using raw acceleration signals from devices (pre-processing) has recently been advocated by subject matter experts (Bassett *et al.*, 2012) but is yet to be assessed in wheelchair users. Also, the AHR device which is widely used to measure free-living PAEE in able-bodied individuals (Turner *et al.*, 2010; Betts *et al.*, 2014), could offer promise in the prediction of PAEE in wheelchair users, as it minimises the limitations of using HR or accelerometry alone.

2.10. THE IMPACT OF PHYSICAL ACTIVITY ON METABOLIC CONTROL, INFLAMMATION AND FITNESS

More often than not SCI leaves muscles completely paralysed below the level of injury, or with insufficient strength, resistance to fatigue, or motor control to support safe and effective training. Consequently, the modes of exercise available to individuals with SCI are limited to the upper extremity, such as arm crank ergometry or wheelchair propulsion. We have limited our discussion of the potential benefits of PA to studies examining upper body exercise, although research has also assessed the impact of lower extremity functional electrical stimulation (FES) (Hjeltnes *et al.*, 1998; Mohr *et al.*, 2001; Jeon *et al.*, 2002; Griffin *et al.*, 2009) and body weight supported treadmill training (Phillips *et al.*, 2004). These exercise modalities were deemed unsuitable for Chapter 6 of this thesis, based on numerous practical limitations: i) significant resources required; expensive equipment, lift apparatus and manpower ii) limited applications for use in the home due to cost and space. Furthermore, FES or neuromuscular electrical stimulation (NMES) is not possible for all individuals with SCI (Deley *et al.*, 2015; Gorgey *et al.*, 2015). For example, persons with preserved lower extremity sensations, since higher intensities required to produce movements might be painful, or persons with lower extremity osteoporosis, who may be susceptible to fractures as a result of strong/prolonged muscle spasms (Hartkopp *et al.*, 1998).

The focus of this section is to discuss findings in the context of chronic paraplegia, in keeping with the study population of Chapter 6. One of the criticisms of previous training studies conducted in this population has been the heterogeneity of participants, making it difficult to tease out responses to exercise. As such, exercise interventions using solely tetraplegic participants have not been cited in this section.

2.10.1. Epidemiological Studies

There is strong evidence from large scale epidemiological studies in able-bodied populations that increased levels of PA, assessed using objective measurement devices, are associated with reduced metabolic risk (Healy *et al.*, 2008; O'Donovan *et al.*, 2013; Loprinzi & Ramulu, 2013; Barreira *et al.*, 2014; Philipsen *et al.*, 2015). Despite the comparatively small sample sizes, the available cross-sectional evidence for these associations in persons with SCI has been summarised in Table 2.5. Out of these seven studies, one objectively measured PA (Nooijen *et al.*, 2012). However, the data collection period only consisted of two consecutive weekdays. Matthews *et al.*, (2002) suggested that ≥ 4 days of monitoring should be encouraged, along with the inclusion of weekend days to take into account potential differences in weekday to weekend activity patterns. One of these seven studies also used an unspecified questionnaire, which had not previously been validated for use in this population (Jones *et al.*, 2004). Nevertheless, whilst conflicting for certain outcomes and predominantly relying on self-report measures, the available evidence seems to suggest that PA is beneficial in improving metabolic control (Table 2.5).

Table 2.5: Description of cross-sectional studies evaluating the association between various PA outcomes and biomarkers of CVD risk

Author	Participants	Method of PA assessment	Statistical analysis	Outcome measures		
				Sig. Association	**Trend[a]**	**No Association**
(Jones *et al.*, 2004)	20, 9 PARA, 11 TETRA, *TSI*; 10.3 ± 1.8 yr *Age*; 16 – 52 yr	**Unspecified questionnaire**, not validated for SCI (PA min/wk)	Pearson correlation coefficients	- 2 hr post OGTT glucose (r = -0.59; P < 0.01), - 2 hr post OGTT insulin (r = -0.79; P < 0.01), - HDL-C (r = 0.46; P < 0.05), - TC/HDL (r = -0.49; P < 0.05), - body fat % (r = -0.60; P < 0.01), - Trunk FM (r = -0.58; P < 0.01)	- Fasting glucose (r = -0.40)	Fasting insulin
(Manns *et al.*, 2005)	22 PARA, *TSI*; 17 ± 9 yr *Age*; 39 ± 9 yr	**PADS** (arbitrary units of PA)	Partial correlation coefficients	- FG (r = -0.525; P < 0.05), - HDL-C (r = 0.625; P < 0.01), - $\dot{V}O_2$ peak (r= 0.636; P < 0.01)	- 2 hr post OGTT glucose (r = -0.344), - Fasting insulin (r = -0.397), - HOMA-IR (r = -0.429), - Total body fat (r = -0.365)	2 hr post OGTT insulin, TAG, IL-6, CRP, function
(Hetz *et al.*, 2009a)	75 (14F), 38 PARA, 37 TETRA *TSI*; 14.9 ± 10.6 yr *Age*; 42.4 ± 11.8 yr	**PARA-SCI** (participation in ADL)	GLM; controlled for LTPA and covariates	↑ time spend engaged in mobility ADLs was associated with; - ↓ LDL-C (P = 0.001) - ↓ TC (P = 0.005)		HDL-C, TAG or WC
(Buchholz *et al.*, 2009)[b]	28 (6F) Inactive SCI, 11 PARA, 17 TETRA *TSI*; 16.5 ± 10.0 yr *Age*; 41.1 ± 11.4 yr 28 (6F) Active SCI, 19 PARA, 9 TETRA *TSI*; 12.6 ± 10.0 yr *Age*; 42.6 ± 13.0 yr	**PARA-SCI** (participation in LTPA)	Participants were dichotomized into 2 groups; performing ≥ 25 or 0 min·day^{-1} LTPA. Diff. between groups were evaluated using 1-tailed *t*-tests	Active compared to Inactive group; - ↓ BMI (22.4 ± 4.8 vs. 29.0 ± 4.4, P = 0.002), - ↓ WC (83.5 ± 13.0 vs. 98.2 ± 11.9 cm), - ↓ SYS BP (117.6 ± 18.2 vs. 135.6 ± 29.8 mm Hg)	Active compared to inactive group: - ↓HDL (1.15 ± 0.20 vs. 1.31 ± 0.34 mmol·L^{-1}, P = 0.14, d = -0.57), - ↓ CRP (0.12 ± 0.50 vs 0.50 ± 0.46 mg·L^{-1}, P = 0.07, d = 0.79), - ↓ % FM (25.5 ± 10.6 vs. 31.4 ± 8.4, P = 0.14, d = 0.62)	Fasting glucose, Fasting insulin, HOMA-IR, TC, LDL-C, TAG, DIA BP

(Matos-Souza *et al.*, 2013)	30 Sedentary SCI, 15 PARA, 15 TETRA *TSI*; 7.7 ± 0.9 yr *Age*; 31.7 ± 1.3 yr 30 Active SCI, 13 PARA, 11 TETRA *TSI*; 9.4 ± 1.1 yr *Age*; 29.1 ± 1.2 yr	**Self-report**; Sedentary participant enrolled from outpatient clinic. Active participants were competitive athletes. Training load 11.2 ± 1.3 hr/wk for 4.3 ± 0.5 yr	Diff. between sedentary and active groups were evaluated by one-way ANOVA, kruskal-Wallis and GLM; adjusted for relevant covariates	↓TAG in physically active compared to sedentary group (75 ± 44 vs 89 ± 68 mg/dL, P < 0.05)		BMI, Fasting glucose, LDL-C, HDL-C, CRP, BP
(Nooijen *et al.*, 2012)	30, 14 PARA, 16 TETRA *TSI*; recently injured, rehab setting *Age;* 42 ± 15 yr	**Objectively assessed** using the **ULAM** over 48 hr period (% dynamic activities per day)	Multilevel regression analysis to determine longitudinal relationship between PAL and outcome measures	↑ activity associated with; - ↑ $\dot{V}O_2$ peak and PO peak (P < 0.01), - ↓ TAG (P < 0.01) - TC/HDL ratio (P < 0.05)		TC, HDL-C, LDL-C
(Flank *et al.*, 2014)	134 (31F), All PARA *TSI*; 18.5 ± 12.3 yr *Age*; 47.8 ± 13.8 yr	Questionnaire adapted from **PADS** and **PASIPD**, content validity and reliability was deemed good prior to use (PA min per day)	Participants were dichotomized into 2 groups, performing ≥ mod/vig. PA per day, or not. Diff. between groups were evaluated by Mann-Whitney U tests	DIA BP was lower (P < 0.007) with ≥ 30 min·day^{-1}, and this difference persisted even after adjusting for age.	PA ≥ 30 min·day^{-1} had a tendency to positively influence BMI (P = 0.053).	Fasting glucose, TC, HDL-C, LDL-C TAG, LDL-C/HDL-C ratio

BP; blood pressure, DIA; diastolic, FM; fat mass, GLM; general linear model, OGTT; oral glucose tolerance test, PARA; paraplegic, PO; power output, SYS; systolic, TAG; triglyceride, TC; total cholesterol, TETRA; tetraplegic, TSI; time since injury, WC; waist circumference.

[a] Non-significant but moderate association (r > 0.30) or medium effect size (d > 0.50)

[b] Outcome data displayed is only for PARA participants

2.10.2. Physical Activity Intervention Studies on Persons with a Spinal Cord Injury

These cross-sectional studies do not indicate cause and effect. For example, it is possible that increased PA is an indication that a person is in good health, rather than PA itself actually causing good health. Moreover, these studies are also susceptible to systematic bias and confounding variables. As such we will now discuss the role of PA in the context of exercise interventions with pre-post study designs.

2.10.2.1. Effect of Exercise on Functional Capacity

From the selection of upper body exercise studies presented in Table 2.6, mean $\dot{V}O_2$ peak increased by 18% and maximal workload increased by 23%. Studies where TSI was not reported were excluded from this average, as well as participants with acute SCI, as it is likely functional capacity would have increased due to the upper extremities not being accustomed to upper body exercise. Improvements due to training can be classified as central (or systemic) and peripheral (or local) adaptations. Devillard *et al.*, (2007) speculated that central adaptations to upper body exercise in individuals with SCI might be limited due to the smaller muscle mass used, being insufficient to elicit 'volume loading' of the heart in order to maximally stress central haemodynamic mechanisms. Volume loading is potentially reduced as a result of i) impaired sympathetic outflow, ii) reduced ability for peripheral vasoconstriction of non-exercising tissues, and iii) increased potential for blood pooling (Davis *et al.*, 1987). Peripheral adaptations to training, such as vascular remodelling in order to minimise disruptions in whole-body homeostasis during exercise, lead to increased $\dot{V}O_2$ peak and mechanical efficiency. The skeletal muscles subjected to training become more vascularised, with an increase in the number of arterioles and capillary density improving the delivery of O_2 to the working muscles. Other adaptations to endurance training include an increase in the oxidative capacity of the skeletal muscle through mitochondrial biogenesis and altered substrate metabolism (Hawley *et al.*, 2015). These changes increase the efficiency of energy utilization and functional capacity. Over time, such adaptations may also contribute to improved human health.

Table 2.6: Review of upper extremity training interventions on functional capacity ($\dot{V}O_2$ Peak and power) in persons with SCI

Author	Participant Characteristics				Exercise Intervention Characteristics					Outcome	
	n =	Lesion level	Age (yr)	TSI (yr)	Intensity	Time (min)	Frequency (times per wk)	Type of Exercise	Duration (wk)	$\dot{V}O_2$ Peak	Power
(Knutsson *et al.*, 1973)	10	C5-L1	N/A	N/A	HR = 140 – 180 b·min^{-1}	≈ 25	4 - 5	Int. ACE	6		↑ 41%
(Nilsson *et al.*, 1975)	12	C6-T12	23-46	N/A	HR_{max}	18	3	Int. ACE	7	↑ 12%	↑ 31%
(Miles *et al.*, 1982)		Mult.	18-33	N/A	80-95% HRR	30	3	Int. WERG	6	↑ 26%	↑ 31%
(Taylor *et al.*, 1986)	10	PARA	16 - 55	1 - 32	80% HR_{max}	30	5	Cont.	8	↑ 12%	
(Yim *et al.*, 1993)	11	T8-T12	24-49	6 – 48 mo	3 × 10 min + 5 min rest > 3km·hr	30	3	Int. WERG	5	↑ 19%	
(Hooker & Wells, 1989)	6	C5 – T7	26 – 36	4 mo - 19	50 - 60% HRR	20	3	Cont. WERG	8	↑ 10%	↑ 24%
	5	C5 – T9	23 - 36	2 - 19	70 - 80% HRR					↑12%	↑ 13%
(Midha *et al.*, 1999)	12	Mult.	22 - 58	4 -29	177W. Target HR; 90% age predicted max	20 - 30	2 – 3	Cont. WERG	10	↑26%	
(Duran *et al.*, 2001)	13	PARA	15 - 38	2 – 120 mo	40 - 80% HR_{max}	120	3	Combination of strength, mobility and aerobic training	16		↑ 22% MTP
(Nash *et al.*, 2001)	5	PARA	34 - 43	4.8 ± 1.4	Power: 400 kpm every 3 min until $\dot{V}O_2$ peak	45	3	Combination of resistance and Int. ACE	3 mo	↑ 30%	↑ 30% MTP
(Tordi *et al.*, 2001)	5	PARA	18 - 40	~ 2	1 min 80% MTP	30	3	Int. WERG	4	↑ 19%	↑ 28% MTP

(Bougenot *et al.*, 2003)	10	T6 – L5	21 - 55	1 - 30	1 min at 100% MTP, 4 min at VT	45	3	Int. WERG	6	↑ 16%	↑ 20% MTP
(de Groot *et al.*, 2003)	3	T3 - L1	50 - 54	61 – 225 days	40 - 50% HRR	60	3	Int. ACE	8	↑17%	↑ 24% MTP
	3	C5 - L1	20 - 38	43 – 175 days	70 - 80% HRR					↑ 50%	↑ 59% MTP
(Hicks *et al.*, 2003)	34	C4 – L1	19 - 65	1 - 24	70% HR max	15 - 30	2	Cont. ACE	36		↑ 81% Submax. PO
(El-Sayed & Younesian, 2005)	5	PARA	31 ± 3	N/A	60 - 65% $\dot{V}O_2$ peak	30	3	Cont. ACE	12	↑ 9%	↑ 10%
(Rosety-Rodriguez *et al.*, 2014)	9	≤ T5	20 - 35	4 - 5	50 - 65% HRR	20 - 30	3	Cont. ACE	12	↑10%	

ACE; arm crank ergometry, Con; continuous training, HR; heart rate, HRR; heart rate reserve, Int; interval training, MTP; maximal tolerated power, PARA; paraplegic, VT; ventilator threshold, WERG; wheelchair ergometry.

2.10.2.2. Effect of Exercise on Metabolic Health and Inflammation

Although physical inactivity is common among individuals with SCI, it has been established that PA has beneficial effects on physical capacity and cardiovascular fitness (Table 2.6). A growing, but low quality, body of evidence is beginning to emerge that PA improves metabolic health, primarily fasting lipid profiles (Table 2.7). However, there is a paucity of research to address the impact of exercise/PA on body composition, systemic inflammation, adipokines and insulin resistance/sensitivity. Currently this evidence remains insufficient to provide unified PA recommendations specific to the SCI population (Carlson *et al.*, 2009). Inconsistencies could be caused by the considerable variation in participant populations, the techniques used to assess outcome measures and the training programs themselves. Most studies had small sample sizes (n = 3 – 34) and used a heterogeneous sample of participants. For example, SCI level (C4 – L5, other conditions responsible for wheelchair use), severity (complete, incomplete) and TSI (43 days – 32 years) all varied considerably. It is highly likely, based on functional differences, that training adaptations will vary between acute/chronic and tetraplegic/paraplegic SCI. Although men are more likely to sustain SCI, studies showed a considerable selection bias, reflected by more male participants. Where female participants were included, no reference was made to stage of menstrual cycle, which can have profound implications on insulin sensitivity and fat oxidation (Pulido & Salazar, 1999; Lundsgaard & Kiens, 2014).

Exercise interventions varied substantially, with little consistency with regards to frequency (2 – 3 times per week), intensity (40 – 80% HRR), or duration of sessions (18 – 120 min). Whilst the selection of intervention studies presented here is limited to upper body exercise, the mode of exercise (ACE, WERG) and type (interval, continuous) is also different. Furthermore, the duration of training programs were relatively short (8 – 16 weeks). It is possible that interventions of this length are not long enough to impart consistent and measurable impacts to metabolic health. Particularly if participants were healthy at baseline. For example, exercise may have greater potential for therapeutic benefits among individuals with a higher risk for metabolic disorders at baseline than those with a normal risk profile. Little credence has been given to this, except for Bakkum

et al., (2015) who quoted the amount of participants with metabolic syndrome at baseline and follow-up. Also, participants were only eligible for this study if classified as inactive via the PASIPD at baseline. Most exercise intervention studies were pre-post, lacking a control group. Only Rosety-Rodriguez *et al.*, (2014) used a true control group to compare the effects of the intervention.

Whilst OGTTs were used in two out of the seven cross-sectional studies (Table 2.6), fasting measures were primarily used to assess glucose tolerance and insulin sensitivity in upper extremity exercise interventions (besides the HOMA-CIGMA test used by de Groot *et al.,* 2003). It has been suggested 87% of patients with classifiable T2DM would have been missed if diagnosis relied solely on the fasting plasma glucose concentration, rather than 2-hr OGTT time-point (Bauman & Spungen, 2008). Thus, it is important to perform provocative dynamic testing. A review on the effect of exercise on metabolic disorders requested by the Consortium for Spinal Cord Medicine recommended that higher-quality RCTs with well-defined cohorts would offer the most reliable knowledge to the current evidence base for PA and metabolic health in this population (Carlson *et al.*, 2009). They also suggested that baseline PA behaviour and other important psychosocial/quality of life measures be addressed. Hence Chapter 6 was proposed, in keeping with these recommendations, to better understand the benefits of upper body exercise in persons with chronic SCI.

Table 2.7: Description of upper limb exercise studies with carbohydrate, lipid, adipokine and inflammatory- related outcomes in persons with SCI.

Author	Study Design	Participant Characteristics	Intervention		Outcome Measures	
					Change	**No Change**
(Hooker & Wells, 1989)	Pre-post parallel group ACE INT	6 (3F), 5 PARA, 1 TETRA, *TSI;* 4 mo - 19 yr *Age;* 26 - 36 yr	*Frequency*: 3 x wk *Time*: 20 min *Duration*: 8 wks	Low-intensity (50 - 60% HRR)		TC, TAG, LDL-C, HDL-C
		5 (2F), 3 PARA, 2 TETRA, *TSI;* 2 - 19 yr *Age;* 23 – 36 yr		Moderate-intensity (70 - 80% HRR)	**↓ TAG** (96 ± 28 to 78 ± 18 mg/dL; P ≤ 0.10), **↑ HDL-C** (39 ± 11 to 47 ± 8 mg/dL; P ≤ 0.10), **↓ LDL-C** (137 ± 26 to 116 ± 5 mg/dL; P ≤ 0.10)	TC
(Midha *et al.*, 1999)	Pre-post WAFT training program	12 (1F), 7 PARA, 3 TETRA, 1 stroke, 1 Amp. *TSI;* 4 - 29 yr *Age;* 22 -58 yr	*Frequency*: 2 - 3 x wk, *Time*: sessions ceased at target HR of 90% age predicted max (20 - 30 min) *Intensity*: 177W *Duration*: 10 wks		**↓ TC** (185 ± 42 to 170 ± 32 mg/dL; P = 0.04)	Fasting glucose, TAG, HDL-C, body mass, WC
(Duran *et al.*, 2001)	Pre-post; mobility, strength and aerobic Ex.	13 (1F), All PARA *TSI;* 2 - 120 mo *Age;* 15 - 38 yr	*Frequency*: 3 x wk *Time*: 120 min *Intensity*: 40 - 80% HRmax *Duration*: 16 wks			HDL-C, LDL-C, body mass, % body fat
(Nash *et al.*, 2001)	Pre-post ACE INT (with a focus on resistance)	5 PARA *TSI;* 4.8 ± 1.4 yr *Age;* 34 - 43 yr	*Frequency*: 3 x wk, *Time*: 45 min *Intensity*: Power output 400 kpm every 3 min until $\dot{V}O_2$ peak *Duration:* 3 mo		**↓ LDL-C** (118 ± 22 to 88 ± 30 mg/dL; P = 0.05)	Non-significant ↓TC and TAG. Non-significant ↑ HDL-C

(de Groot *et al.*, 2003)	Pre-post parallel group ACE INT	3 (2F), All PARA *TSI;* 61 - 225 days *Age;* 50 - 54 yr	*Frequency*: 3 x wk, *Time*: 60 min, *Duration*: 8 wks	Light-intensity (40 - 50% HRR)		TC, HDL-C, LDL-C, TAG. Non-significant improvement in IS (56%, measured via HOMA-CIGMA)
		3, 2 PARA, 1 TETRA *TSI;* 43 - 175 days *Age;* 20 - 38 yrs		High-intensity (70 - 80 % HRR)	**↓TAG** (-31%), **↓ IS** (-33%, measured via HOMA-CIGMA)	TC, HDL-C, LDL-C
(El-Sayed & Younesian, 2005)	Pre-post, ACE INT	5 PARA *TSI;* N/A *Age;* 31 ± 3 yr	*Frequency*: 3 x wk *Time*: 30 min *Intensity*: 60-65% VO2 peak *Duration*: 12 wks		**↑ HDL-C** ($P < 0.05$)	TC, TAG
(Rosety-Rodriguez *et al.*, 2014)	RCT, ACE INT (mod. INT and CON)	17 (9 INT, 8 CON) ≤ T5 *TSI;* 4 - 5 yr *Age;* 20 - 35 yr	*Frequency*: 2 x wk *Time*: 20 - 30 min (+10-15 min warm up) *Intensity*: 50 - 65% HRR *Duration*: 12 wks		**↓WC** (98.1 ± 6.6 to 94.4 ± 6.3 cm; $P = 0.046$), **↓ Leptin** (9.6 ± 2.7 to 7.5 ± 2.4 ng/mL; $P < 0.05$), **↓ TNFα** (23.3 ± 5.6 to 20.6 ± 5.2 pg/mL; $P < 0.05$), **↓ IL-6** (6.7 ± 2.2 to 4.1 ± 1.9 pg/mL; $P < 0.05$)	Adiponectin
(Bakkum *et al.*, 2015)	Parallel group RCT, ACE INT (hybrid Ex group not displayed)	10 (1F), 7 PARA, 3 TETRA TSI; 9 - 30 yr Age; 30 - 63 yr	*Frequency*: 2 x wk *Time*: 18 - 32 min *Intensity*: 65 - 75% HRR *Duration*: 16 wks		**↓ WC** (Δ -2.5 ± 1.0 cm; $P = 0.03$); **↓ Fasting insulin** (Δ -14.3 ± 4.0 pmol·L^{-1}; $P = 0.01$); **↓ HOMA-IR** (Δ -0.5 ± 0.2; $P = 0.02$)	Fasting glucose, TAG, HDL-C, Visceral adiposity, CRP, IL-6, BP.

ACE; arm crank intervention, BP; blood pressure, CON; control group, INT; intervention group, HRR; heart rate reserve IS; insulin sensitivity, PARA; paraplegic, RCT; randomised controlled trial, TAG; triglyceride, TC; total cholesterol, TETRA; tetraplegic, TSI; time since injury, WC; waist circumference.

Upper Body Exercise Training and Insulin Sensitivity: Potential Mechanisms

To our knowledge the potential mechanisms underpinning these improvements in metabolic health have not been directly assessed in upper body skeletal muscle. However, for insulin sensitivity (our primary outcome measure in Chapter 6) it is likely these improvements are congruent with those reported in the able-bodied population or during lower extremity FES training studies in persons with SCI. Acute exercise presents a major challenge to whole-body homeostasis; prolonged training therefore results in cellular and systemic adaptations that function to minimize further widespread disruptions (Hawley *et al.*, 2014). An acute bout of exercise increases glucose uptake into skeletal muscle, via an insulin-independent increase in GLUT-4 translocation to the plasma membrane, mediated in part by AMPK (Zierath, 2002; Hawley & Lessard, 2008). AMPK is a fuel-sensing enzyme, activated in response to the increased cellular AMP: ATP ratio during acute exercise (Frosig *et al.*, 2004)

Repeated PA results in prolonged 'insulin sensitizing' effects due to increased expression and/or activity of key signalling proteins, such as AMPK, involved in the regulation of glucose uptake and fatty acid oxidation (Fujii *et al.*, 2000; Richter & Ruderman, 2009; Hawley *et al.*, 2014). AMPK itself plays a key role in the adaptive response of skeletal muscle to moderate-intensity exercise training by the regulation of key genes associated with metabolic flux and its ability to alter muscle fuel reserves (Winder *et al.*, 2006; McGee & Hargreaves, 2010). Furthermore, expression and activity of GLUT-4 is increased in skeletal muscle in response to FES training in individuals with SCI (Hjeltnes *et al.*, 1998), and regular aerobic exercise training in able-bodied individuals (Ivy, 1997; Short *et al.*, 2003). As such, these adaptations could explain improvements in insulin sensitivity reported in previous studies in persons with SCI (Table 2.7).

2.11. OVERVIEW OF EXPERIMENTAL WORK

The aim of this thesis was to address the impact of PA on the metabolic health and wellbeing of persons with SCI. A rigorous approach was taken to develop a method capable of accurately predicting PAEE in wheelchair users. This involved ascertaining the mechanical reliability of a widely used tri-axial accelerometer (GT3X+) and investigating its human validity during an outdoor wheelchair propulsion protocol (Chapter 3). The next step was to compare outputs (physical activity counts vs. raw acceleration) from wearable devices (GT3X+ vs. GENEActiv) during a robust and controlled treadmill protocol (Chapter 4). Considering the widespread use of multi-sensor devices in the able-bodied population, a subsequent study was conducted to determine whether the combination of acceleration and physiological signals offered an improvement in the prediction of PAEE in wheelchair users (Chapter 5). On completion of this method development, a randomised controlled trial was conducted to assess the impact of home-based moderate-intensity exercise on human metabolic health, body composition, inflammation and functional capacity in individuals with SCI (Chapter 6). Compliance to the intervention was monitored using the PA monitoring devices validated in preceding Chapters.

CHAPTER 3: INFLUENCE OF ANATOMICAL PLACEMENT AND MECHANICAL RELIABILITY OF THE GT3X+ ACCELEROMETER IN THE PREDICTION OF PHYSICAL ACTIVITY ENERGY EXPENDITURE IN MANUAL WHEELCHAIR USERS

3.1. INTRODUCTION

The effects of regular PA on the health and wellbeing of persons with a SCI remains poorly characterised. This is despite CVD now being the leading cause of mortality in individuals with SCI and occurring earlier in the lifespan in comparison to able-bodied controls (Garshick *et al.*, 2005). Individuals with SCI show an abundance of elevated CVD risk factors in comparison to matched able-bodied counterparts (Bauman & Spungen, 1994; Lavis *et al.*, 2007). The positive contribution of regular PA on these CVD risk factors and the maintenance of weight balance is well documented and broadly accepted in ambulatory individuals (Kesaniemi *et al.*, 2001). Results of self-reported PA monitoring in individuals with SCI (Ginis *et al.*, 2010a) suggest that reduced PA may play a role in the progression of these risk factors. However, little is known regarding specific components or patterns of PA that are required to derive protection from chronic diseases and improve metabolic health in manual wheelchair users. Therefore, objective measures of PA are required to inform future research efforts and this broader health agenda.

Free-living PA is inherently difficult to measure with precision. This becomes even more problematic within a heterogeneous group such as manual wheelchair users where, despite movement being restricted to the upper body, differential levels/completeness of SCI lesions result in highly variable movement patterns. Improved assessment of habitual PA would permit: appropriate cross-sectional comparisons, allow researchers to comment on the efficacy of behaviour change interventions and potentially inform PA guidelines (Brage *et al.*, 2005). The limitations of self-report measures have been outlined in Chapter 2. Considering these limitations and the impracticality of direct observations and indirect calorimetry during free-living assessment, other unobtrusive objective measurement tools

are needed that can be used to characterise the association with PA and metabolic health, particularly among cohorts where these conditions are more prevalent.

Accelerometers are commonly used to quantify free-living PA (Plasqui *et al.*, 2005). Over the past decade Actigraph has released several models, including the most recent GT3X+, with higher-resolution signals, greater data storage capacity and increased battery life (John & Freedson, 2012). This model remains to be validated in specific cohorts with differing movement patterns, such as manual wheelchair users. The logical first step in the development of an objective accelerometer based tool to assess PAEE is to assess its basic mechanical reliability. Various mechanical apparatus have been used to assess the reliability of previous generations of the Actigraph, such as turntables (Metcalf *et al.*, 2002) and rotating wheel setups (Brage *et al.*, 2003) for the initial CSA model and hydraulic shaker tables for newer generations (Esliger & Tremblay, 2006; Silva *et al.*, 2010; Santos-Lozano *et al.*, 2012). These are advantageous as investigators can maintain precise control over experimental conditions and simultaneously expose multiple monitors to a wide range of accelerations. Therefore any variability is exclusively intrinsic to the accelerometer (Esliger & Tremblay, 2006), and researchers can shift their attention to identifying and minimizing biological variation such as anatomical positioning.

Waist mounted monitors have been shown to under-estimate energy expenditure by 24% in manual wheelchair users with SCI (Hiremath & Ding, 2009). It is not surprising that manufacturers energy expenditure prediction algorithms developed based upon activity counts generated at the waist during ambulation are unsuitable to derive PAEE of manual wheelchair users. When Hiremath & Ding, 2011b, examined the correlations between raw activity counts from a RT3 tri-axial accelerometer and criterion energy expenditure measured by a portable metabolic cart, the counts on the upper arm demonstrated a better correlation (R^2 = 0.70 vs. 0.44) with the criterion energy expenditure compared to the waist. This observation identifies the arm as a potential location to yield better prediction accuracy and reduced error and also highlights the need for the development of specific algorithms to predict PAEE in manual wheelchair users.

To our knowledge, there are no published studies on the influence of anatomical placement on the validity of a GT3X+ accelerometer to determine PAEE in manual

wheelchair users. The aims of this study were twofold. Firstly, to assess the validity and reliability of the GT3X+ accelerometer during mechanical testing along each orthogonal axis within the physiological range of human movement. Secondly, to evaluate the effect of anatomical positioning of the GT3X+ accelerometer on the relationship between physical activity counts (PAC) and criterion PAEE during a range of representative activities in manual wheelchair users. We hypothesise that due to considerable improvements in manufacturing and design that the GT3X+ would display large intra and inter-unit reliability when subjected to a robust acceleration protocol on a multi-axis shaker table (MAST rig). We also hypothesise that due to altered movement patterns in wheelchair users, wearing a GT3X+ on the waist will result in a weaker relationship between PAC and criterion PAEE compared to devices attached on the upper arm and wrist.

3.2. METHODS

3.2.1. Accelerometer

The GT3X+ activity monitor (Actigraph, Pensacola, FL, USA) records time-varying accelerations within the dynamic range of ± 6 g, and contains a solid state tri-axial accelerometer sensitive to movement along three axes: anteroposterior (X), mediolateral (Y) and vertical (Z). The GT3X+ activity monitor is compact (dimensions: 4.6 cm x 3.3 cm x 1.9 cm), lightweight (19 grams), and can easily be worn at multiple locations on the body. Each unit is powered by a rechargeable lithium ion battery and has a memory of 512 MB. Approximately forty days of PA data can be recorded when sampling at a frequency of 30 Hz; although the battery would need recharging after thirty days. To quantify the amount and frequency of human movement, accelerometer outputs are digitized via a twelve-bit-analogue to digital converter (A/DC) and passed through Actigraph's proprietary digital filtering algorithms. In order to eliminate any acceleration noise outside of the normal human activity frequency, digitized signals pass through low (0.25 Hz) and high (2.5 Hz) band width filters (John & Freedson, 2012). The GT3X+ records time-varying accelerations at a user-defined sampling frequency ranging from 30 Hz to 100 Hz, these are then converted to arbitrary units called 'physical activity counts' (PAC). These are calculated through summing the change in raw acceleration values measured during a specific interval of time, or 'epoch'. Unlike previous models such as

the GT1M, the desired epoch length can be selected by the end user (1-s to 240-s) following rather than prior to data collection.

3.2.2. Multi-axis Shaker Table

All reliability testing was conducted using a Multi-axis shaker table (MAST-9720, Instron Structural Testing Systems Ltd, High Wycombe, UK). The MAST-9720 is powered via three vertical, one horizontal and two lateral hydraulic actuators and is calibrated regularly to an accuracy of 0.1 *g* (Figure 3.1).

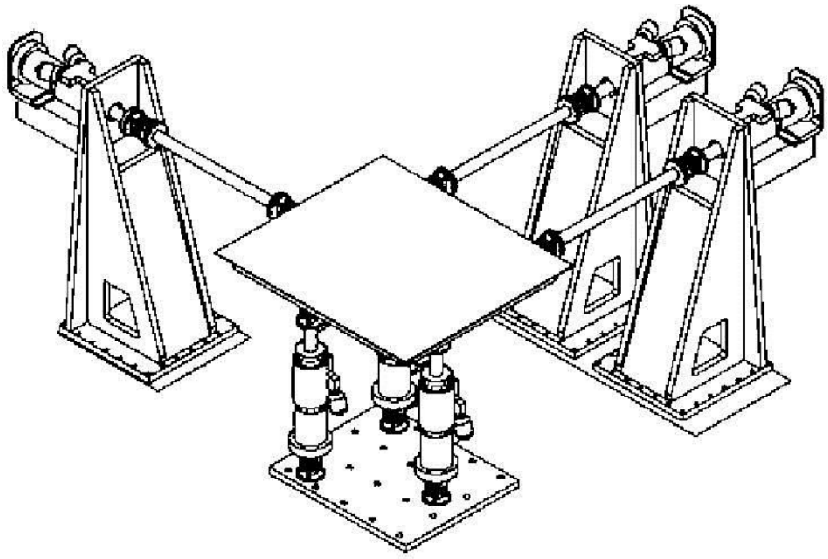

Figure 3.1: Schematic of the MAST 9720 *(Taken with permission from Horner, 2012)*

3.2.3. Experiment 1- Mechanical Testing

The MAST testing conditions were restricted by the maximum displacement amplitude of the horizontal actuator (approx. 62.5 mm), which limited maximum acceleration to 1.5 *g*. With the limitations of the MAST rig, a similar testing schedule to that used by Horner *et al.*, (2011) was developed that comprised various acceleration conditions (Table 3.1) to replicate a range of physiological movements. These were applied to the units by manipulating the frequency of oscillation and displacement amplitudes. The majority of humans movements tend to fall between 0.3 and 3.5 Hz (Sun & Hill, 1993), and maximum angular velocities of the forearm during the drive phase in elite wheelchair racers has a frequency component of 3.6 Hz (Wang *et al.*, 2008). The conditions selected produced similar PAC to those recorded by a GT3X+ device worn on the wrist during wheelchair

propulsion ranging from light to moderate-intensity PA based on metabolic equivalent values. In a number of conditions acceleration was kept constant, allowing for an independent assessment of the effect of frequency on count magnitude. Conversely, frequency was also kept constant whilst acceleration of the aluminium mounting plate was manipulated to independently assess the effect of acceleration on accelerometer output. The units were subjected to these testing conditions using a sinusoidal oscillation procedure which was pre-programmed using the MASTs dedicated software (RS Replay, Instron Structural Testing Systems Ltd).

All ten GT3X+ units to be used in subsequent human testing were initialized at a sampling frequency of 30 Hz via a computer interface. Prior to testing, a trial run was conducted without the accelerometers, to ensure the hydraulics were functioning at an optimum operating temperature. Then each GT3X+ unit was attached to a piece of angle iron 2 cm apart using double-sided floor tape (DS Scrim 306/250, Tape Range distributors Ltd, UK). Each GT3X+ unit was mounted firmly and securely to prevent accelerometer misalignment. The angle iron was then attached to the aluminium alloy mounting plate of the MAST. As only the horizontal actuator was used during this protocol the angle iron was rotated after each test schedule so that the horizontal motion of the MAST corresponded to displacement along the *x*, *y* and *z* axes of the GT3X+ (Figure 3.2). The testing schedule was repeated in all three axes. Each individual condition was maintained for seventy seconds. After completion of the testing schedule and when the MAST rig was safely parked the accelerometers were removed and downloaded using dedicated software (Actilife 6, Pensacola, FL, USA) and exported to Microsoft Excel in a comma-separated value (c.s.v.) file format for further analysis. The activity counts were summated into 5-s epochs. The first and last 10-s were excluded to ensure only steady state values were included in the analysis. Each condition was reduced to 50-s long, with the mean of the 10 remaining values expressed as counts per 5-s (Counts $5 \cdot s^{-1}$).

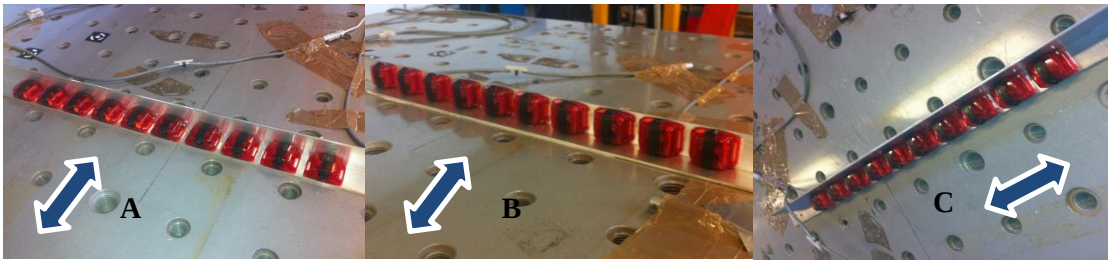

Figure 3.2: *Multi-axis shaker table set up along the Z (A), Y (B) and X (C) axis.* The arrow represents the direction of oscillation by the horizontal actuator

3.2.4. Experiment 2- Human Validity

Ethics approval was granted by the University of Bath Research Ethics Approval Committee for Health (REACH) and informed consent was obtained from each participant. Fifteen manual wheelchair users (mean ± SD, age: 36 ± 11 years, time since injury: 15 ± 17 years, body mass: 70 ± 12 kg,) visited the Centre for DisAbility Sport and Health (DASH) human physiology laboratory on one morning following an overnight fast (> 10 hrs). Participants were asked to refrain from performing any strenuous PA 24 hrs prior to trials. The medical condition responsible for regular use of a wheelchair was nine SCI (paraplegic), one fibromyalgia, one complex regional pain syndrome and two participants with Spina Bifida. Two able-bodied participants were included in the analysis; both were familiar with wheelchair propulsion having played wheelchair basketball >1 year. Time since injury (TSI) was self-reported based on when the medical condition was first diagnosed by a clinician.

Mass of the wheelchair and participants was recorded to the nearest decimal place using platform wheelchair scales (Detecto ® BRW1000, Missouri, USA). The wheelchair, along with participants shoes were weighed separately and subtracted from the total mass of the participant plus wheelchair to derive an accurate body mass as recommended (Clasey & Gater, 2007). Participants transferred from their wheelchair into a supine position on a physiotherapy bed with their feet placed in dorsal flexion and head positioned in the Frankfurt plane. Length was measured with the participant barefoot in centimetres to the nearest decimal place, along the left side of the body using a non-elastic

tape measure (Lufkin, US). If spasticity occurred then participants were segmented by joint and limb length measured accordingly.

Resting metabolic rate (RMR) was estimated by indirect calorimetry from four 5-min expired air samples collected in Douglas Bags (Hans Rudolph, MO, USA) in accordance with best practice (Compher *et al.*, 2006). Each Douglas bag was fully evacuated prior to gas collection. The obtained samples were passed through tubing containing anhydrous calcium sulphate (Drierite, Cole-Parmer Instrument Co. Ltd, London, UK) to remove water vapour from the samples. Respiratory gases were measured using a paramagnetic oxygen (O_2) and an infrared carbon dioxide (CO_2) gas analyser (Series 1400, Servomex Ltd., Sussex, UK). The analyser was calibrated within less than one hour of each test with references gases of known composition within the physiological range (British Oxygen Company, UK). The volume of expired air was determined using a dry gas meter (Harvard Apparatus, Kent, UK) and temperature was measured using a digital thermometer (model C, Edale Instruments, Cambridge, UK). All values were corrected to reflect standard temperature and pressure. These processes allowed the volume of inspired air and subsequent $\dot{V}O_2$ to be calculated using the Haldane transformation (Haldane, 1912). An average of three stable values (within 100 kcal·day^{-1}) was accepted as RMR.

Activity Protocol

The activity protocol consisted of wheelchair propulsion at varying velocities anti-clockwise around an outdoor athletics track and simulated deskwork. This created a controlled research environment but, importantly, outside of the laboratory, where energy expenditure is more likely to reflect that of daily wheelchair propulsion. Each activity lasted for 6-min, interspersed with 5-min recovery periods. Throughout the activity protocol three GT3X+ units were worn, one on the right wrist (using a Velcro wrist strap positioned over the dorsal aspect of the wrist midway between the radial and ulnar styloid processes), one on the upper arm (using a small elastic belt positioned on the lateral surface of the arm midway between the acromion process and lateral epicondyle of the humerus) and one on the waist (positioned above the right hip along the anterior axillary line). The devices were initialised with a sampling frequency of 30 Hz.

In addition participants also wore a portable metabolic system (COSMED K4b^2, Rome, Italy) and a Polar T31 heart rate monitor (Polar Electro Inc., Lake Success, NY, USA). The K4b^2 analyser unit was placed on the chest in a harness with battery pack on the participants back (Total weight ~ 1.5 kg). A rubber face mask (Hans Rudolf, Shawnee, USA) of appropriate size was fitted carefully to the face and checked for leaks prior to each test. Expired gases pass through a flow meter and are channelled down a permapure sampling line into the analyser unit where the fractions of O_2 and CO_2 in expired air are measured. Metabolic data was retrieved and analysed using associated software (Cosmed 9.0, Rome, Italy). Oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were used to estimate energy expenditure ($kcal \cdot min^{-1}$) of each activity, using indirect calorimetry (Weir, 1949). Prior to use the K4b^2 was calibrated according to manufacturer's instructions. The K4b^2 has been shown to be both reliable and valid (Duffield *et al.*, 2004; McLaughlin, 2001), and has also been used previously to measure criterion EE in persons with SCI (Hiremath & Ding, 2011a; Garcia-Masso *et al.*, 2013). The Polar T31 heart rate monitor was firmly secured on the chest using an elastic strap and ultrasound gel was applied to the electrodes to improve the connection. The heart rate transmitted by the polar T31 was captured by a wireless receiver module connected to the K4b^2.

The wheelchair propulsion activities included four conditions 2, 4, 6 and 8 $km \cdot hr^{-1}$, which were counterbalanced to prevent order and carryover effects using a Latin Square design. During deskwork participants were asked to type out a script. Participants only completed trials that they felt comfortable/competent with. Real time speed feedback was provided via a GPS cycle computer (Garmin ® EDGE 500, Garmin Ltd, Southampton, UK) placed where visible in the participants lap. After direct correspondence with the manufacturer this GPS device is accurate to within 15 metres 95% of the time. However, under normal conditions accuracy improves to within 5 – 10 metres. No attempt was made to standardise wheelchair variables, although tire pressure and chair characteristics were recorded, participants used their everyday wheelchair. As alluded to elsewhere (Washburn & Copay, 1999), differences in these variables, such as chair weight, would be reflected in oxygen uptake values.

3.2.5. Statistical Analyses

Experiment 1- Mechanical Testing

The mean ± SD activity PAC output was calculated for each unit in each condition and each axis (330 in total). The coefficient of variation (CV_{intra}) was calculated from the replicate 5-s epochs within each condition to assess intra-unit reliability. This is a noteworthy distinction of our design compared to previous research in the field of intra-unit reliability analyses, which tends to focuses on within-unit between trial variability (Horner *et al.*, 2011). However, we adopted an approach similar to that of Esliger & Tremblay, (2006) in order to remove any trial effects which may increase variability (i.e. more technological error). Secondly, coefficients of variation (CV_{inter}) for each axis during each condition were determined. Additionally, intra-class correlation coefficients (ICCs) with a two-way random-effects model for absolute agreement were calculated.

A Spearman's rank correlation coefficient (R_s) was used to determine the criterion-related validity between PAC from the GT3X+ and the MAST acceleration. Paired *t*-tests were conducted to assess the independent effect of acceleration when frequency was held constant at 2 Hz on PAC output across units. A Repeated-measures ANOVA was conducted to assess the independent effect of frequency on PAC output across units when acceleration was held constant at 9.81 $m \cdot s^{-2}$. Where significance was found ($P < 0.05$), bonferroni corrections were applied to *post hoc* tests where multiple comparisons were considered.

Experiment 2- Human Validity

A priori power calculation revealed a sample size of 15 was necessary in order to detect an *r* of 0.67 using a one-tailed test with an $\alpha = 0.05$ and power = 0.95. This calculation was based on data from (Washburn & Copay, 1999). The $K4b^2$ and activity monitors were synchronised prior to use. Breath-by-breath $K4b^2$ data was interpolated into 1-s intervals for all tests. Individual $\dot{V}O_2$ and $\dot{V}CO_2$ breath values that were > 3 SDs from the mean were removed (Lamarra *et al.*, 1987). Final data sets were then averaged over a 2-min

period. Physical activity counts from the GT3X+ were summated into 60-s epochs. Assuming that Dietary-induced thermogenesis was negligible (i.e. participants were fasted) resting metabolic rate (kcal·min^{-1}) was subtracted from total energy expenditure measured by the K4b^2 to generate PAEE for each activity. Comparisons between the 'criterion' measurement of PAEE [Total energy expenditure (TEE) – RMR] and activity monitors were made between 03:30 and 05:30 (*mm:ss*) of each activity.

Pearson product moment correlation coefficients (*r*), coefficients of determination (R^2) and linear regressions were conducted to assess the association between the criterion and PAC from the GT3X+ accelerometers at each anatomical position during wheelchair propulsion. Using the generated regression equations an analysis of agreement was conducted for each anatomical location using Bland and Altman plots to calculate absolute bias and 95% limits of agreement (LoA). Standard Error of the Estimate (SEE) was also calculated for each correlation. Statistical significance was set at a *priori* of $\alpha < 0.05$. All analyses were performed using IBM® SPSS® Statistics 20 for Windows (IBM, Armonk, NY, USA).

3.3. RESULTS

3.3.1. Experiment 1- Mechanical Testing

Overall mean ± S.D activity counts across all eleven testing conditions for all devices was 497 ± 2.4, 497 ± 2.0 and 496 ± 2.4 counts 5·s^{-1} for the z, y and x axes respectively. Intra-unit reliability (CV_{intra}) values, displayed as mean and 95% confidence intervals (lower – upper), were 0.9% (0.7 – 1.2), 0.7% (0.5 – 0.9) and 1.0% (0.7 – 1.2) for the z, y, and x axes, respectively (Table 3.1). Irrespective of the axis, the highest and lowest CV_{intra} values corresponded to condition one (0.06 *g*; 0.5 Hz) and five (1.0 *g*; 2.0 Hz), respectively. We also considered the between trial intra-unit reliability, which were higher than within-trial results, these were 1.5% (0.8 – 2.2), 1.5% (0.7 – 3.1) and 1.7% (0.8 – 2.5) for the z, y and x axes, respectively (mean, 95% upper and lower confidence intervals).

Table 3.1: Description of the acceleration and frequency conditions used during the mechanical testing schedule and within-trial intra- and inter-unit CV values

Condition	Amplitude	Frequency	Acceleration	Intra-unit CV			Inter-unit CV		
				Axis			Axis		
	(m)	(Hz)	(*g*)	Z	Y	X	Z	Y	X
1	0.063	0.5	0.06	4.4% (3.4 - 5.4)	2.5% (2.1 - 3.0)	4.7% (3.5 - 5.9)	5.2% (4.4 - 6.0)	4.7% (4.1 - 5.4)	5.0% (4.0 - 6.0)
2	0.063	1.0	0.25	0.9% (0.7 - 1.1)	0.5% (0.3 - 0.7)	0.8% (0.7 - 1.0)	1.6% (1.3 - 1.9)	0.9% (0.8 - 1.0)	1.1% (0.9 - 1.3)
3	0.055	1.5	0.50	0.4% (0.3 - 0.4)	0.3% (0.3 - 0.4)	0.5% (0.3 - 0.7)	1.8% (1.7 - 2.0)	1.9% (1.7 - 2.0)	3.3% (3.0 - 3.5)
4	0.031	2.0	0.50	0.5% (0.3 - 0.6)	0.6% (0.3 - 0.8)	0.4% (0.4 - 0.5)	1.4% (1.3 - 1.5)	1.2% (1.0 - 1.4)	1.8% (1.7 - 1.9)
5	0.062	2.0	1.00	0.2% (0.2 - 0.3)	0.2% (0.1 - 0.3)	0.2% (0.2 - 0.3)	1.1% (1.0 - 1.1)	1.4% (1.3 - 1.5)	1.0% (1.0 - 1.1)
6	0.040	2.5	1.00	0.3% (0.2 - 0.4)	0.3% (0.1 - 0.5)	0.4% (0.2 - 0.5)	2.5% (2.3 - 2.6)	2.7% (2.6 - 2.8)	4.1% (3.9 - 4.2)
7	0.016	4.0	1.00	1.6% (1.2 - 2.1)	1.5% (1.1 - 1.8)	1.5% (1.1 - 2.0)	2.9% (2.6 - 3.2)	5.3% (5.0 - 5.6)	3.6% (3.2 - 4.0)
8	0.035	3.0	1.25	0.5% (0.4 - 0.7)	0.3% (0.2 - 0.5)	0.3% (0.2 - 0.5)	3.9% (3.7 - 4.1)	3.5% (3.5 - 3.6)	3.4% (3.2 - 3.5)
9	0.025	3.5	1.25	0.7% (0.6 - 0.8)	0.6% (0.4 - 0.8)	0.6% (0.5 - 0.7)	1.0% (0.8 - 1.2)	1.7% (1.7 - 1.8)	1.4% (1.3 - 1.6)
10	0.060	2.5	1.50	0.2% (0.2 - 0.3)	0.3% (0.2 - 0.3)	0.3% (0.2 - 0.3)	1.7% (1.7 - 1.8)	0.9% (0.8 - 0.9)	1.8% (1.7 - 1.8)
11	0.023	4.0	1.50	0.7% (0.5 - 0.9)	0.7% (0.6 - 0.8)	0.8% (0.6 - 1.0)	2.0% (1.9 - 2.2)	2.3% (2.2 - 2.5)	2.8% (2.6 - 2.9)
	Overall mean			***0.9% (0.7 - 1.2)***	***0.7% (0.5 - 0.9)***	***1.0% (0.7 - 1.2)***	***2.3% (2.1 - 2.5)***	***2.4% (2.2 - 2.6)***	***2.7% (2.4 - 2.9)***

Data is displayed as mean and 95% confidence intervals (lower - upper)

The ICCs for activity counts across all conditions were 1.0 for each axis (all $P < 0.001$). The mean variability between units was 2.5% (CV_{inter}) across all conditions for all units in each axis and ranged from 1.0 – 5.2%, 0.9 – 5.3% and 1.0 – 5.0% for z, y and x axes, respectively (Table 3.1).

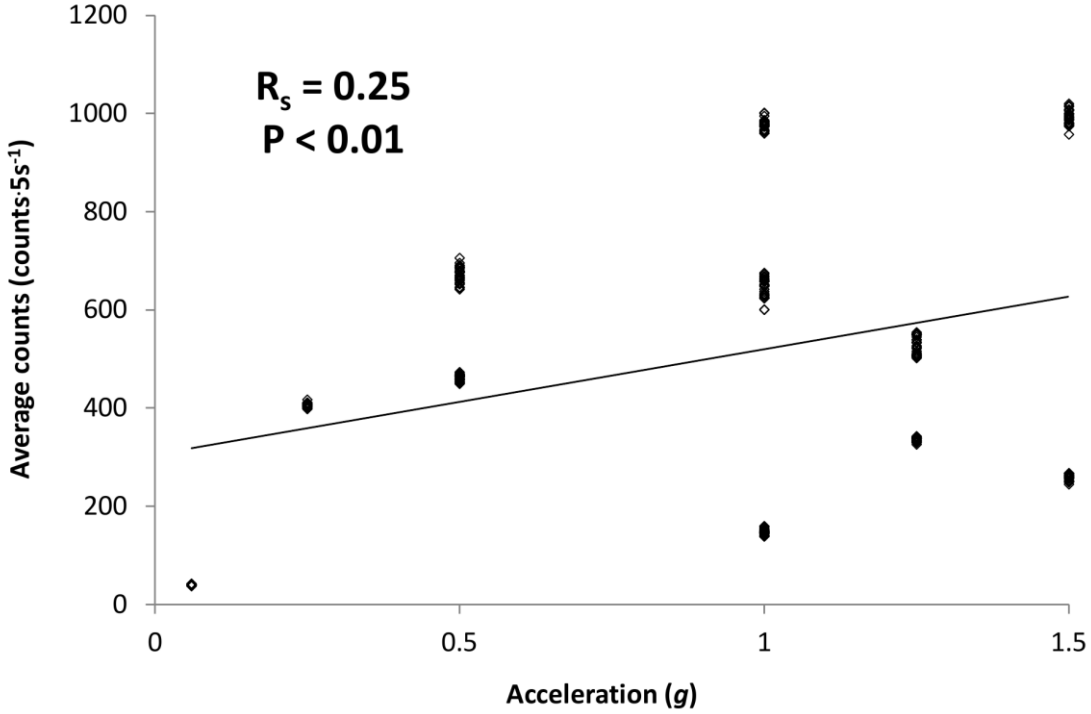

Figure 3.3: Relationship between count magnitude and MAST rig acceleration ($n = 660$)

Figure 3.3 demonstrates a significant weak positive linear relationship ($R_s = 0.25$, $P < 0.01$) when PAC output across all eleven conditions from each axis for all units are displayed together ($n = 660$). Holding the frequency of oscillation of the mounting plate of the MAST constant at 2 Hz and increasing acceleration lead to a significant increase in PAC (0.5 g = 462 ± 2 counts 5·s^{-1}, 1.0 g = 977 ± 2 counts 5·s^{-1}, $P < 0.01$) (Figure 3.4). However, holding acceleration constant at 9.81 m·s^{-2} and manipulating the frequency of movement had counter-intuitive results; interestingly increasing movement frequency resulted in a significant decrease in PAC (2 Hz = 977 ± 2 counts 5·s^{-1}, 2.5 Hz = 644 ± 2 counts 5·s^{-1}, 4 Hz = 147 ± 2 counts 5·s^{-1}, $P < 0.01$) (Figure 3.5).

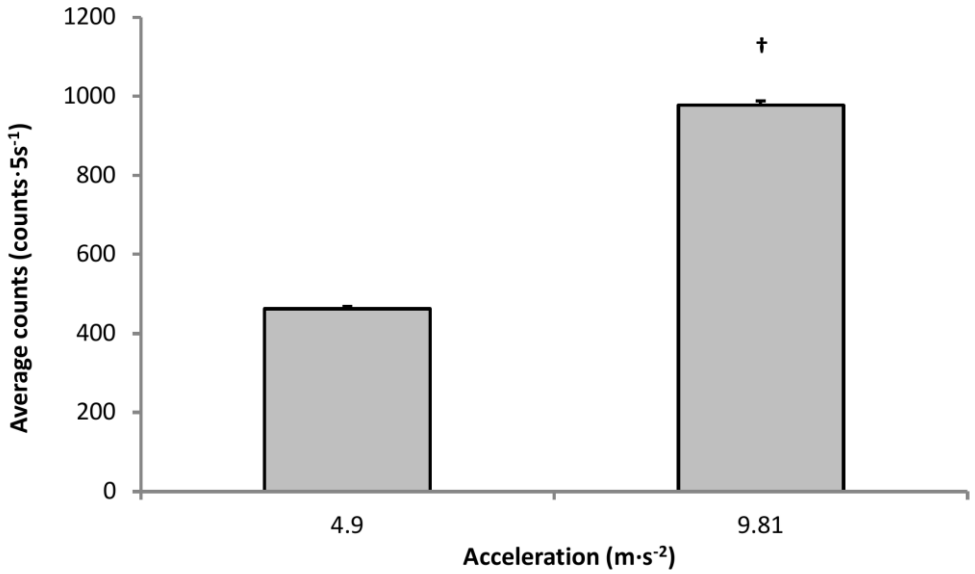

Figure 3.4: Effects of acceleration on count magnitude (Frequency held constant at 2 Hz). *† Significant difference (P < 0.01)*

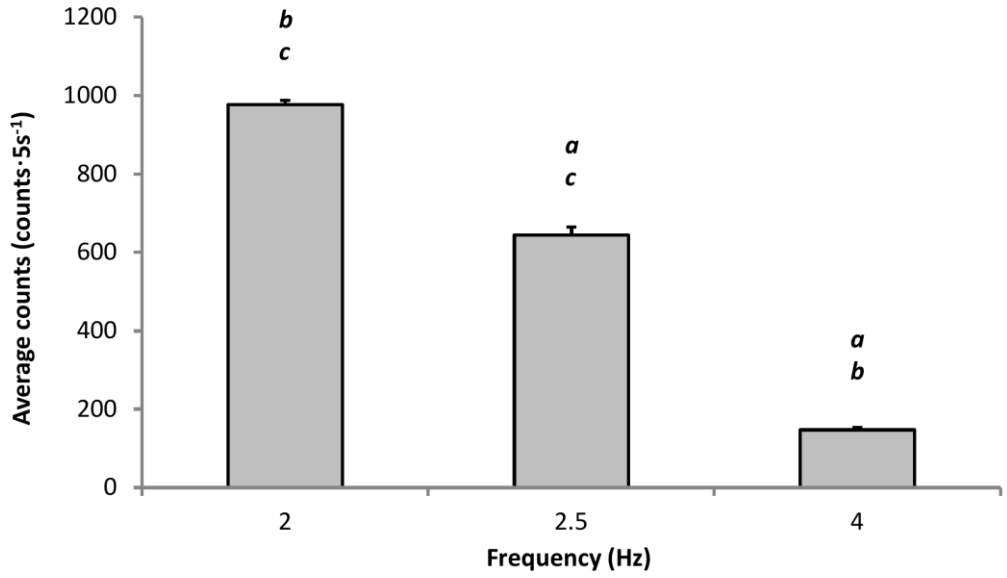

Figure 3.5: Effects of frequency on count magnitude (acceleration held constant at 9.81 $m \cdot s^{-2}$)

[a] *significantly different to 2 Hz*

[b] *significantly different to 2.5 Hz*

[c] *significantly different to 4 Hz*

3.3.2. Experiment 2- Human Validity

Criterion PAEE (kcal·min^{-1}), heart rate and GT3X+ count output data at each anatomical location all increased from the deskwork task to higher propulsion velocities (Table 3.2). Calculated metabolic equivalents (METs) from dividing $\dot{V}O_2$ for each activity by individuals $\dot{V}O_2$ determined at rest, suggests that deskwork and 2 km·hr^{-1} were on average light intensity activities, 4 - 6 km·hr^{-1} were moderate-intensity activities, whereas propulsion at 8 km·hr^{-1} was considered vigorous.

The relationships between criterion PAEE estimated by the K4b^2 and predicted PAEE derived from activity counts from each device are presented as scatter plots in Figure 3.6 (a-c). Physical activity counts from each anatomical location were significantly ($P < 0.01$) associated with PAEE (waist; r = 0.73, upper arm; r = 0.87, wrist; r = 0.93). This relationship remains linear when assessing wheelchair propulsion separately (wrist; r = 0.90). The SEE for each correlation was 1.45, 1.05, and 0.80 kcal·min^{-1} for the waist, upper arm and wrist respectively. The linear regression equations for devices worn at each anatomical location are shown in equations 1–3.

$$PAEE_{waist} = (0.001151 * \text{Physical activity counts}\cdot\text{min}^{-1}) + 1.265318 \quad \text{(Eq. 1)}$$

$$PAEE_{upperarm} = (0.000392 * \text{Physical activity counts}\cdot\text{min}^{-1}) + 0.048896 \quad \text{(Eq. 2)}$$

$$PAEE_{wrist} = (0.000222 * \text{Physical activity counts}\cdot\text{min}^{-1}) - 0.068073 \quad \text{(Eq. 3)}$$

Figure 3.7 (a–c) further illustrates the difference between the criterion PAEE and the predicted PAEE through the use of Bland and Altman plots displaying the mean difference and 95% limits of agreement (LoA). Using the generated regression equations the absolute bias ± 95% LoA values were 0.0 ± 2.82 kcal·min^{-1}, 0.0 ± 2.03 kcal·min^{-1} and 0.0 ± 1.55 kcal·min^{-1} for the waist, upper arm and wrist, respectively.

Table 3.2: GPS velocity, criterion PAEE, PAC at each anatomical location, calculated METs, HR, and number of participants per trial for each activity (mean ± SD)

Activity	Garmin velocity ($km \cdot hr^{-1}$)	$K4b^2$ PAEE ($kcal \cdot min^{-1}$)	Physical activity counts ($counts \cdot min^{-1}$)			MET $K4b^2$	Heart rate ($b \cdot min^{-1}$)	n
			Upper arm	Waist	Wrist			
Desk	-	0.26 ± 0.25	30 ± 38	1 ± 3	362 ± 182	1.3 ± 0.3	73 ± 14	15
2 $km \cdot hr^{-1}$	2.6 ± 0.4	1.26 ± 0.41	5748 ± 1399	644 ± 757	8192 ± 2209	2.3 ± 0.4	96 ± 19	12
4 $km \cdot hr^{-1}$	4.0 ± 0.3	2.41 ± 0.94	7098 ± 2168	841 ± 643	11712 ± 3313	3.5 ± 1.1	105 ± 17	15
6 $km \cdot hr^{-1}$	5.6 ± 0.6	3.74 ± 1.00	8477 ± 2054	1803 ± 1347	17105 ± 4271	4.7 ± 1.2	125 ± 23	13
8 $km \cdot hr^{-1}$	7.1 ± 0.7	5.92 ± 1.89	12459 ± 5042	2880 ± 1421	25599 ± 4522	6.4 ± 2.1	149 ± 22	9

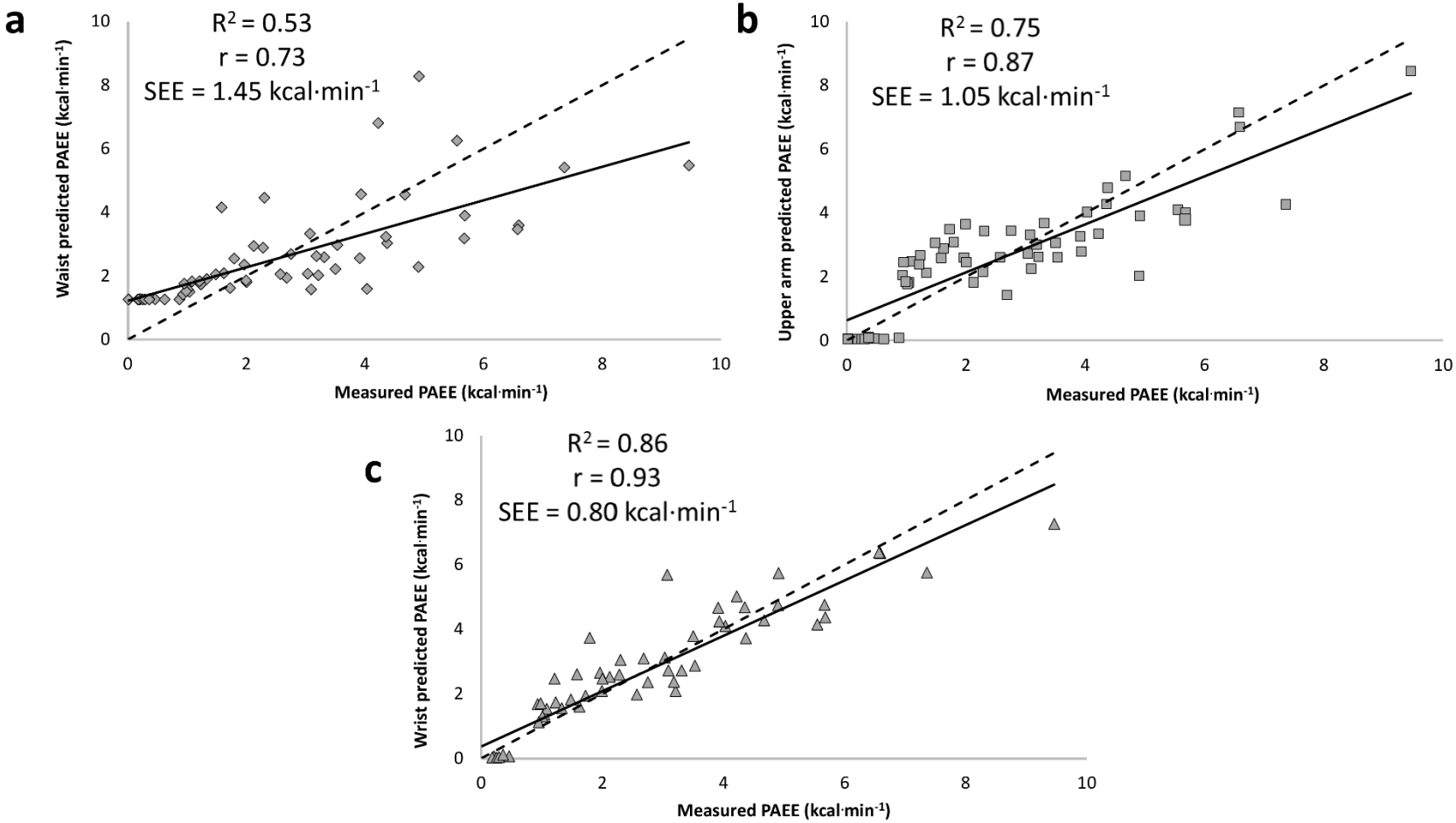

Figure 3.6: Scatterplots showing the relationship between predicted PAEE from the waist (a), upper arm (b) and wrist (c) against criterion PAEE. The *Straight line* represents the models best fit, and the *dotted line* indicates the line of identity.

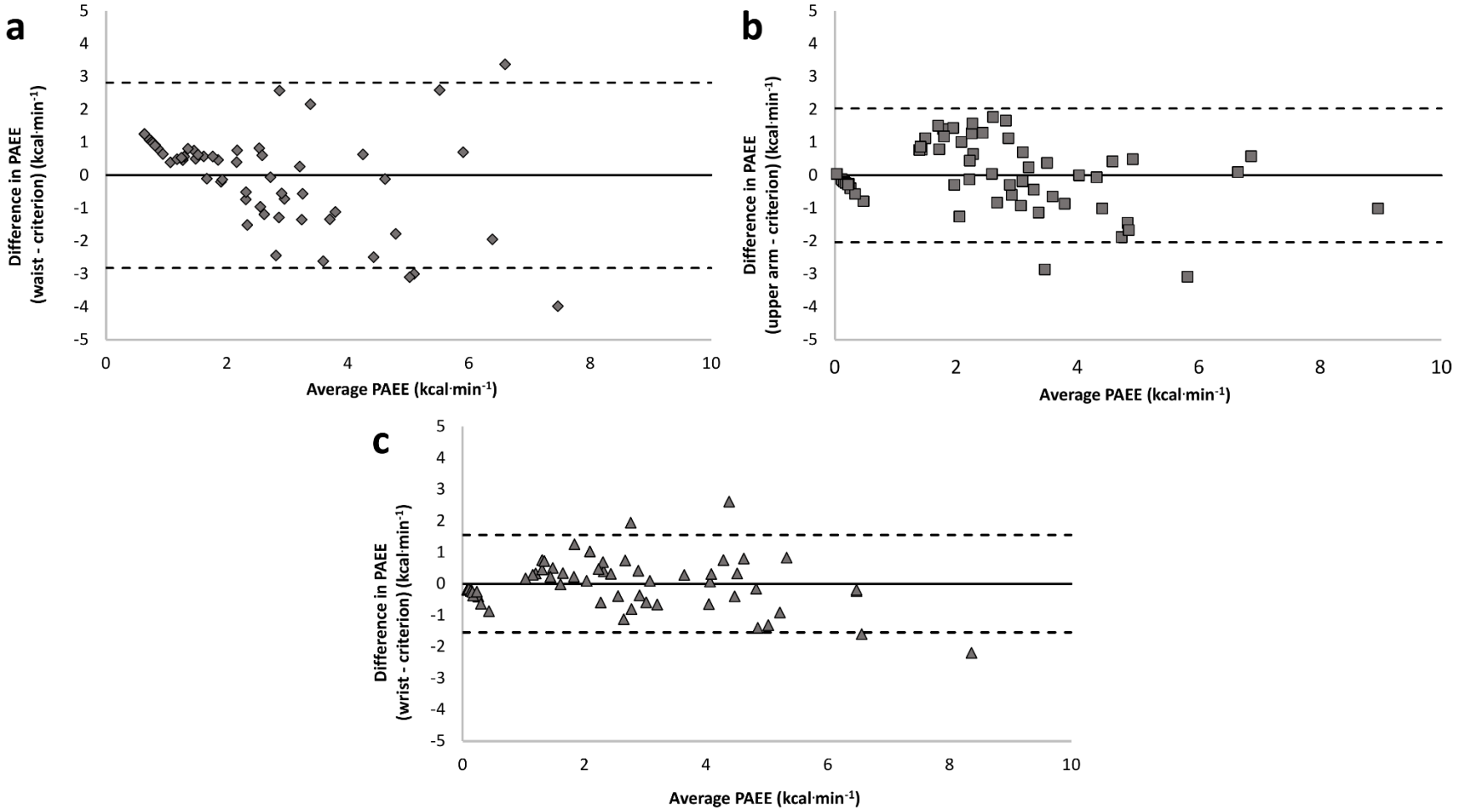

Figure 3.7: Bland- Altman plots for the criterion and estimated PAEE using regression equations developed at the waist (A), upper arm (B), and wrist (C).

3.4. DISCUSSION

Of the three anatomical locations considered in this study the results indicate that the wrist provides the most valid prediction of PAEE in manual wheelchair users. The accelerometer worn on the wrist explained the highest amount of variance and displayed the lowest random error. Using a schedule that comprised eleven test conditions of various frequencies and accelerations the GT3X+ demonstrated excellent reliability, with mean intra and inter-unit coefficients of variation of 0.9% and 2.5% respectively. To our knowledge this is the first study to assess the mechanical reliability and validity of the newest generation Actigraph GT3X+ accelerometer and assess the validity of its use in manual wheelchair users.

3.4.1. Experiment 1- Mechanical Testing

The majority of previous mechanical reliability studies have focused on older generations of the Actigraph accelerometer, of which the GT1M displays the next best reliability compared to the GT3X+ (CV_{intra} = 2.9% and CV_{inter} = 3.5%) (Silva *et al.*, 2010). Considering the aforementioned software and component improvements, such as switching to micro-electro-mechanical system (MEMS) transducers which have greater sensitivity, it is not surprising that newer generations display improved intra and inter-unit reliability. The older generations of the Actigraph accelerometers contained piezoelectric transducers, which were typically fitted manually during manufacturing by experienced technicians (Chen & Bassett, 2005). Intuitively this might explain the increased inter-unit variability with older models. Older generations (7164 model) have also demonstrated large inter-unit variation (> 100%) at lower accelerations (< 1 $m \cdot s^{-2}$) (Brage *et al.*, 2003). Although not of the same magnitude, our results also indicate poorer inter-unit reliability during the lowest frequency and acceleration condition (5%). However, a recent study assessing the inter-unit reliability of the GT3X model reported a mean CV_{inter} of 60.2% across a range of accelerations, and was > 149.4% when units were oscillated at 1.1 Hz (Santos-Lozano *et al.*, 2012). This is disconcerting especially considering the improvements with the newer generation GT3X+ are mostly cosmetic and we have displayed acceptable inter-unit reliability, only three out of the 33 conditions tested displayed $CV_{inter} \geq 5$ %. These variances could be explained via differences in the

protocol, whereby Santos-Lozano *et al.*, (2012) included a condition outside the range of human motion (10 Hz) contributing to the higher overall mean CV_{inter}. The authors also used a smaller scale vibration table as opposed to a MAST rig, it is unclear whether the vibration table was separate to the electric motor in order to minimise the mechanical vibration as advocated previously (Esliger *et al.*, 2011). Moreover, we believe there is an error in the calculation of accelerations used in the Santos-Lozano *et al.*, (2012) study. They cite a 1.1 Hz cite of orbit, a 0.04 m radius of orbit and claim this yields an acceleration of 1.087 g's. Using the standard equation for tangential acceleration (Eq. 4) we calculate the acceleration for this condition as 0.194 g's.

$$a = 4\pi^2 f^2 r \qquad \text{(Eq. 4)}$$

In our study the ICC observed across testing conditions were high and concurred with those reported for other available accelerometers (Powell *et al.*, 2003; Horner *et al.*, 2011) and previous generations of Actigraph (Brage *et al.*, 2003). If inter-unit reliability is poor then it becomes difficult to distinguish whether the variability in PA during free-living monitoring between participants is solely attributed to variations in behaviour or inherent to the accelerometer. The GT3X+ demonstrated poor validity when compared to criterion acceleration of the MAST rig (Figure 3.3). The weak relationship of R_s= 0.25 between 0.06 and 1.5 *g* is well below that of most industry standard PA monitoring accelerometers. The GENEA and 3DNX PAC outputs are both strongly related to acceleration during a mechanical set up with correlations of r = 0.97 and r = 0.99, respectively (Esliger *et al.*, 2011; Horner *et al.*, 2011). In the older 7164 model Actigraph, Brage *et al.*, (2003) unequivocally stated that count output is only proportional to acceleration if frequency is held constant, implying that some form of frequency-dependent filter exists. This would also appear to hold true for the newest generation GT3X+, supported by our counter-intuitive findings of decreased PAC as frequency of oscillation is increased whilst acceleration was held constant. Brage *et al.*, (2003) developed and then employed a frequency based correction factor which when applied to Actigraph counts restores linearity improving the relationship from r = 0.69 to r = 0.94. Most of the current accelerometers on the market use band-pass filters to extract acceleration signals within certain frequency ranges while discarding those that are not likely to be representative of 'human movement'. Outputs from other accelerometers including the Actical (Esliger &

Tremblay, 2006) and RT3 (Powell *et al.*, 2003) have also been shown to be dependent on movement frequency in a mechanical setup.

3.4.2. Experiment 2- Human Validity

Hiremath & Ding, (2011a) advocated the importance of keeping the accelerometer device constant but manipulating its anatomical positioning to determine the most appropriate placement of an accelerometer to capture PAEE in manual wheelchair users. Our results indicate that of the three anatomical locations considered, a wrist-mounted accelerometer provides the most valid prediction of PAEE during outdoor wheelchair propulsion. This is the first study to assess the validity of the GT3X+ accelerometer in this population and to evaluate the accuracy of specifically developed algorithms capable of predicting PAEE.

Accurate measurement of habitual PAEE is a prerequisite to determine the link and establish dose-response relationships between PA and health (Strath *et al.*, 2005). Surprisingly, relatively few studies have tried to evaluate monitoring tools among wheelchair users (Washburn & Copay, 1999; Warms & Belza, 2004). Washburn & Copay, (1999) found PAC from the older generation uniaxial CSA accelerometer worn on the wrist had a moderate relationship (left wrist, $r = 0.66$, right wrist $r = 0.52$, $P < 0.01$) with oxygen uptake during wheelchair propulsion at three velocities. Warms & Belza, (2004) observed low to moderate relationships ($r = 0.30 – 0.77$, $P < 0.01$) between activity counts from an Actiwatch containing an omnidirectional accelerometer and self-reported PA. Whilst these results suggests than an accelerometer located on the wrist is a suitable measure of PAEE for individuals with SCI, the Warms & Belza, (2004) study is only able to confer the concurrent validity of wrist Actigraphy against a self-report measure of activity intensity and frequency. The higher correlation ($r = 0.93$) observed between activity counts at the wrist and PAEE in this current study might be due to the direct comparison against a criterion measurement of PAEE rather than a self-report measurement; or the inclusion of more than three propulsion velocities and an activity of daily living of low intensity, combined with using a tri-axial accelerometer offering greater sensitivity.

A similar relationship was observed at the upper arm (r = 0.87) compared to previous research using a RT3 tri-axial accelerometer (r = 0.83) (Hiremath & Ding, 2011b). It is perhaps pertinent to address some methodological differences here, as the authors compared activity counts against total energy expenditure (including RMR and Dietary Induced Thermogenesis), not PAEE as measured in the present study. Total energy expenditure (TEE) and PAEE should not be equated (Tudor-Locke & Myers, 2001). It is a noteworthy distinction that accelerometers are only capable of detecting movement and should therefore only be associated with the component of energy expenditure arising from skeletal muscle contraction-induced movements.

Furthermore, PA monitoring devices (e.g. Actiheart) use demographic characteristics such as body mass to predict RMR and determine TEE. Common equations to predict RMR in the general population are inappropriate to use for individuals with SCI and have been shown to over-predict measured requirements by 5-32% (Buchholz & Pencharz, 2004). Considering RMR is the largest component of TEE, particularly in sedentary individuals (Volp *et al.*, 2011), it is possible that error observed with the prediction of TEE by these devices in manual wheelchair users maybe a result of the algorithms used to determine RMR not being suitable for individuals with SCI.

Moreover, whilst the previous studies made no attempt to control for individual variations in RMR, they also only reported correlations and made no attempt to develop regression equations capable of accurately predicting PAEE. This study attempted to build on this by assessing the degree of error associated with the generated equations for PAC at each anatomical location. The mean bias for each location was negligible. However, these findings should be viewed with caution. As the development of the regression equations to predict PAEE and subsequent evaluation was carried out on the same sample of participants, there is a tendency for the evaluation statistics to be biased and can often be overly optimistic (Staudenmayer *et al.*, 2012). Therefore, we appreciate that further work

is required to cross-validate these equations on an independent sample of wheelchair users.

Although, considering the primary aim of this study was to identify the best anatomical location to capture PAEE, analysing our results this way can offer an insight into the spread of random error. For example, visual inspection of Figure 3.7a indicates a considerable degree of heteroscedasticity using the prediction equation at the waist. Thus this anatomical location displayed increased random error as the intensity of activity increased. Despite the wrist displaying the narrowest 95% LoA (Figure 3.7c: ± 1.55 $kcal \cdot min^{-1}$), it is advisable, when more studies have been published in the area, that the academic community produce a consensus statement addressing the clinical limits of PA assessment in this population. However, in combination with the highest association to the criterion measurement and lowest SEE reported, these data suggests that the wrist is the most appropriate anatomical location to quantify PAEE in manual wheelchair users. With movement restricted to the upper limbs in manual wheelchair users, the most distal anatomical location seemingly offers improved sensitivity to the detection of PAEE during wheelchair propulsion.

Actigraph PAC have been shown to peak at approximately 10 to 12 $km \cdot hr^{-1}$ when running and plateau thereafter when worn at the hip in ambulatory subjects (John *et al.*, 2012). Knowledge regarding digital signal processing filters has only recently become more available, as an obligation has been placed on device manufacturers to be more transparent with regards to their specific properties and functions. The GT3X+ has half power frequencies of 0.5 Hz and 2.5 Hz, taken from the device manual it could be misleading that movements within these limits are measured full scale while those outside of it are not registered at all. Larger bandwidth filters could allow physiologically unrelated vibrations or noise to be included in the signal. Conversely overly aggressive frequency dependent filtering can lead to erroneous measurements of human movements, and cause the previously observed plateau effect (Ried-Larsen *et al.*, 2012). However, a plateau effect was not observed when worn at the wrist for speeds up to $8km \cdot hr^{-1}$, yet the study cannot conclude whether a plateau phenomenon exists above this propulsion speed.

Only nine out of fifteen (two of which were able-bodied) participants were able to complete the 8km·hr^{-1} propulsion speed. Considering wheelchairs user have been shown to achieve minimal amounts of strenuous activity during free-living (Warms & Belza, 2004), if a plateau effect does exist it may negligibly affect the accuracy of monitoring PAEE in this population.

A limitation of this study is the relatively small sample size and considerable variation within subjects based on the diversity of disabilities included. However, this diversity may be considered beneficial, as the assortment of propulsion techniques captured improves the external validity of the regression equations, making them more suitable for the wider wheelchair user population. Once we removed the two occasional wheelchair users from the analysis this had a negligible effect on the relationships observed between PAEE and PAC at the wrist (All data: $r = 0.93$, regular wheelchair users only: $r = 0.92$), consequently, we see value in taking a more generic approach. Also, despite the diversity of the population, the amount of unexplained random error is relatively small. The inclusion of a diverse range of subjects is in accordance with best practice recommendations for PA validation studies (Bassett *et al.*, 2012). Future studies should assess the validity of the GT3X+ for predicting PAEE during more complex representative daily activities performed by manual wheelchair user to determine whether band-pass filtering processes may affect the sensitivity of the GT3X+ to quantify sedentary behaviours or detect vigorous intensity activities above a certain threshold. The devices' utility to accurately assess PAEE during free living also needs to be explored. The associated equations, which are generated, require cross-validation using an independent sample of representative participants. Furthermore, mechanical testing was conducted over a limited range of accelerations (0.06 – 1.5 *g*), using simple single axis movements, which do not cover the entire dynamic range of the GT3X+ device (± 6 *g*) or the complete range within which physiologically relevant movements can occur (Bhattacharya *et al.*, 1980). Actigraph have assured us that, based on comprehensive testing during manufacturing, their GT3X+ devices are stable over time. Future studies should undertake a more comprehensive testing schedule across the devices entire dynamic range, for longer durations (e.g. > 6h) and potentially during more complex 3-dimensional movements, to determine simulated performance over longer durations.

In conclusion, we have shown excellent intra-and inter-unit reliability of the GT3X+. Whilst the uni-dimensional mechanical test data are useful in evaluating the devices mechanical reliability, it is important to remember that the GT3X+ is an accelerometry-based PA monitor. Our applied data from human testing suggests that the GT3X+ is a valid tool for predicting PAEE. Of the three anatomical locations considered, a wrist-mounted accelerometer provides the most accurate prediction of PAEE in manual wheelchair users during outdoor propulsion. However the poor validity when compared to criterion acceleration during mechanical testing and counter-intuitive findings of decreased PAC with increased frequency of oscillation could be an issue with monitoring PAEE in wheelchair users. Therefore, we recommend that the human validity of the GT3X+ device be compared to another tri-axial accelerometer device, which is not subjected to on-board bandwidth filtering processes, during a comprehensive laboratory activity protocol.

CHAPTER 4: DEVICE COMPARISON AND DEVELOPMENT/ VALIDATION OF SPECIFIC ALGORITHMS FOR THE PREDICTION OF PHYSICAL ACTIVITY ENERGY EXPENDITURE IN MANUAL WHEELCHAIR USERS

4.1. INTRODUCTION

The positive contribution of regular physical activity (PA) to weight balance, metabolic regulation and cardiovascular fitness is well documented and broadly accepted in the able-bodied population (Haskell *et al.*, 2007). Epidemiological studies concerning the impact of PA on health in wheelchair users with SCI have been limited to assessing associations between subjective reports of activities of daily living (ADL) (Hetz *et al.*, 2009a) or leisure time physical activity (LTPA) (Buchholz *et al.*, 2009) and chronic disease risk factors. To date, despite the aforementioned limitations, quantifying free living PA among wheelchair users has mostly been restricted to self-report measurements.

The PA monitoring literature has evolved rapidly, particularly in able-bodied populations, yet there is a paucity of research focussing on the use of activity monitors to predict physical activity energy expenditure (PAEE) in certain populations, including manual wheelchair users. Broadly speaking, various devices used previously to determine PA in persons that use wheelchairs have distinct limitations, which have been eluded to in chapter 2. For example despite being unobtrusive, a tri-axial accelerometer attached to a wheelchair (Coulter *et al.*, 2011) is unable to distinguish between self or assisted propulsion and is also unable to quantify any activity out of the wheelchair, or during stationary arm crank ergometry exercise. Monitors attached on the waist near the participants' centre of mass, as advised by manufacturers for use in able-bodied cohorts, have been shown to under-estimate energy expenditure by 24% in wheelchair users (Hiremath & Ding, 2009). Chapter 3 indicated that the anatomical placement location is critical to accurately estimate PAEE. It is perhaps not surprising due to restricted patterns

of movement that a tri-axial accelerometer worn on the wrist explains more of the variance in PAEE, resulting in the lowest random error compared to the waist.

The technological advancements in the field of PAEE assessment have stimulated the development of sensitive tri-axial accelerometers, capable of storing higher resolution raw, unfiltered acceleration signals, with increased memory capacity for capturing data over prolonged periods of time (Intille *et al.*, 2012). Previous work validating objective PA monitoring tools in wheelchair users have only reported accelerometer outputs as arbitrary count values. The GENEActiv device gives raw acceleration values, reporting signal vector magnitude (SVM) in *g*-seconds ($g \cdot s^{-1}$). This device is not subject to on-board manufacturer-defined band pass filters and hence does not demonstrate the plateau phenomenon of the GT3X+ observed previously during mechanical testing (Chapter 3). Furthermore, it remains to be established whether fluctuations in criterion PAEE during wheelchair propulsion over differing gradients or during load carriage can be detected by accelerometer outputs at the wrist. Therefore, the aim of the present study was to assess the validity of two commonly used accelerometer devices, at two different anatomical locations, for the prediction of PAEE in wheelchair users in a controlled laboratory environment. It was hypothesised that the use of raw acceleration signals might lead to an improved prediction of PAEE in wheelchair users.

4.2. METHODS

Ethics approval was granted by the University of Bath Research Ethics Approval Committee for Health (REACH) and written informed consent was obtained from each participant. Seventeen (n = 17) male manual wheelchair users visited the Centre for DisAbility Sport and Health (DASH) human physiology laboratory on one morning following an overnight fast. As in Chapter 3 participants were asked to refrain from vigorous exercise for 24 h. Ten of the participants had complete paraplegia with lesion levels ranging from T1 to L4. Other conditions responsible for use of a wheelchair included Spina Bifida (n = 3), Cerebral Palsy (n = 1) and Scoliosis (n = 1). A bilateral lower limb amputee (n= 1), who was considered a regular wheelchair user (>70% of

locomotion manual wheelchair propulsion) and an able-bodied wheelchair basketball player (n = 1) who was also familiar with wheelchair propulsion (> two years) were also included in the analysis. Chapter 3 demonstrated that the inclusion of numerous disabilities had no measurable impact on the prediction of PAEE in wheelchair users. Other research has also included participants with various aetiologies responsible for wheelchair use when assessing methods to predict EE in this population (Conger *et al.*, 2014). If anything, this approach provides a robust model for the assessment of PAEE in the broader wheelchair user population and the inclusion of a diverse range of participants is in accordance with best practice recommendations for PA validation studies (Bassett *et al.*, 2012).

Time since injury (TSI) was self-reported based on when the medical condition was first diagnosed by a clinician. Height and body mass were measured using the same methods described in chapter 3. Resting metabolic rate (RMR; $kcal \cdot day^{-1}$) was measured in a semi-recumbent position in accordance with best practice (Compher *et al.*, 2006) using a TrueOne® 2400 computerized metabolic system (ParvoMedics, Salt Lake City, UT). Blood pressure (mmHg) was also measured using an automated blood pressure monitor (Boso Medicus Prestige, Bosch + Sohn, Germany) following RMR. Three readings were taken, with a minutes rest between each measurement, and the mean value was calculated.

Waist and hip circumference (cm) were measured in duplicate to the nearest 0.1cm, with participants lying flat on a hard physiotherapy bed, using a metallic tape measure (Lufkin, US). Waist circumference was measured at the midway point between the lowest rib and the iliac crest. The tape was passed underneath the small of the participants back and positioned horizontally across the waist, with the reading made at the end of gentle expiration. Hip circumference was measured horizontally around the widest portion of the buttocks. For both circumference measurements, the participants were lying with feet close together and arms at sides with the tape snug around the body. Skinfold thickness (mm) at 4 upper body sites (biceps, triceps, subscapular, suprailiac) were also measured in duplicate using a set of skinfold calipers (Holtain Ltd, Crymych, UK); with the mean value calculated. Where duplicate measurements differed by more than 5% at each site a third measurement was taken and the median value was calculated.

4.2.1. Activity Protocol

Following the measurement of RMR and anthropometric assessment, participants performed an activity protocol, which consisted of wheelchair propulsion and a folding clothes task, representative of an activity of daily living. Participants continuously untangled t-shirts placed on a desk, then neatly folded and stacked them. Wheelchair propulsion took place on a wheelchair adapted treadmill with necessary safety features and stabilising arm (HP Cosmos Saturn 250/100r, HaB International Ltd, UK). A counterbalanced approach for randomly assigning the order of activities was not utilised in this study based on observations from Chapter 3. Even with five minutes of recovery in between activities, a considerable carryover effect in oxygen uptake ($\dot{V}O_2$) and heart rate (HR) was observed. Therefore, each activity was assigned in order of intensity and lasted for six minutes interspersed with four minute recovery periods. Wheelchair propulsion on the adapted treadmill included eight trials 3 $km \cdot hr^{-1}$, 4 $km \cdot hr^{-1}$, 5 $km \cdot hr^{-1}$, 6 $km \cdot hr^{-1}$ & 7 $km \cdot hr^{-1}$ on a 1% gradient. Following a ten minute rest, participants propelled at 4 $km \cdot hr^{-1}$ on a 1% gradient with 8% of body mass added to the chair in a rucksack and 4 $km \cdot hr^{-1}$ on a 2% and 3% gradient.

4.2.2. Instrumentation and Assessment of Energy Expenditure

The GT3X+ activity monitor (Actigraph, Pensacola, FL, USA) has been described in chapter 3. The technical specifications of the GENEActiv tri-axial device (GENEActiv, Activinsights, Cambridge, UK) are described beneath (Table 4.1) and has been explained in more detail elsewhere (Esliger *et al.*, 2011). The original prototype GENEA (not the commercially available, developed GENEActiv device) has displayed excellent technical reliability (CV_{intra} = 1.4%, CV_{inter} = 2.1%) and validity compared to criterion MAST acceleration (r = 0.98, $P < 0.001$) (Esliger *et al.*, 2011). The technical reliability is comparable to that observed for the GT3X+ during mechanical testing in chapter 3. Furthermore, outputs from the GENEActiv are non-proprietary SI units (raw acceleration) as opposed to arbitrary physical activity counts.

Table 4.1: Comparison of the technical specifications for the GT3X+ and GENEActiv devices

Device	Dimensions: Length x Width x Height (mm)	Weight (g)	Piezosensor Orientation	Dynamic Range (*g*)	Frequency Range (Hz)
Actigraph GT3X+	46 x 33 x 19	19	Tri-axial	± 6 *g*	0.25 – 2.5
GENEActiv	43 x 40 x 13	16	Tri-axial	± 8 *g*	-

Throughout the activity protocol two GT3X+ units were worn, one on the right wrist (W, using a Velcro wrist strap positioned over the dorsal aspect of the wrist midway between the radial and ulnar Styloid processes) and one on the right upper arm (UA, using a small elastic belt positioned on the lateral surface of the arm midway between the acromion process and lateral epicondyle of the humerus). Two GENEActiv accelerometers were also worn; one distal to the GT3X+ on the right W and one on the posterior aspect of the midpoint on the right UA, securely fixed to the skin over the triceps brachii using a 10 cm^2 patch of tape (Hyperfix self-adhesive dressing retention tape, Smith & Nephew Healthcare Ltd., UK). The GENEActiv and GT3X+ devices were both initialised with a sampling frequency of 30Hz.

Continuous gas exchange measurements were collected during each activity, using a TrueOne® 2400 computerized metabolic system, calibrated according to manufacturer's instructions prior to use. Fractions of oxygen and carbon dioxide were measured via a paramagnetic oxygen analyser and an infrared, single beam, single wave-length carbon dioxide analyser, respectively. Metabolic data was retrieved and analysed using associated software (TrueOne® metabolic software, Salt Lake City, UT). $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) were used to estimate EE ($kcal \cdot min^{-1}$) of each activity, using indirect calorimetry. The TrueOne® provides accurate, precise and reliable results for the measurement of gas exchange variables (Bassett *et al.*, 2001; Crouter *et al.*, 2006). A Polar T31 HR monitor (Polar Electro Inc., Lake Success, NY, USA) was also worn during each activity as described in chapter 3. Peak oxygen uptake ($\dot{V}O_2$ peak) was determined at the end of the activity protocol using a continuous, progressive intensity test on an

electrically braked arm crank ergometer (Lode Angio, Groningen, Netherlands). A cadence of 75 rpm was encouraged throughout and a starting intensity of 35 W was typically chosen, although this was based on the participants training history. The resistance was increased by 14 W every three minutes until the point of volitional exhaustion (~ 9 – 12 min). The criteria for the attainment of a true $\dot{V}O_2$ peak measurement was; (1) a peak RER value ≥ 1.1, (2) a peak heart rate ≥ 95 % of age-predicted maximum (200 $b \cdot min^{-1}$ minus chronological age) (Goosey-Tolfrey, 2007) and an RPE = 20. Each participant met at least two of these criteria.

4.2.3. Statistical Analyses

An *a priori* power calculation revealed a sample size of fifteen was necessary, using the same study as in chapter 3. Activity monitors were synchronised prior to use. Breath-by-breath data was exported into Microsoft Excel from the TrueOne® metabolic software and averaged over the final two minutes of each activity. Assuming that dietary-induced thermogenesis was negligible (participants came into the laboratory following a 10-hr overnight fast) resting metabolic rate ($kcal \cdot min^{-1}$) was subtracted from total energy expenditure (TEE) measured by the TrueOne® 2400 computerized metabolic system to generate PAEE for each activity. Comparisons between the 'criterion' measurement of PAEE [TEE – RMR] and activity monitors were made between the final two minutes of each activity.

Data Modelling

GT3X+ and GENEActiv units were downloaded using ActiLife software (Actigraph, Pensacola, FL, USA) and GENEActiv PC software (version 1.2.1, Activinsights, Cambridge, UK), respectively. Data was exported to Microsoft Excel in a time and date stamped comma-separated value (c.s.v.) file format. Physical activity counts ($counts \cdot min^{-1}$) from the GT3X+ and Signal vector magnitude (SVM_{gs}) data from the GENEActiv were summated into 60-s epochs. Activity counts ($counts \cdot min^{-1}$) from the GT3X+ and raw acceleration values ($g \cdot min^{-1}$) from the GENEActiv were then averaged over the final two minutes of each activity. Physical activity energy expenditure prediction models were

developed using corresponding data from each task for each device at each location, using linear regression analysis. The dependent variable was PAEE (kcal·min^{-1}) during the final two minutes of each task (that is, 171 values in total). The independent variables included accelerometer outputs, i.e. counts·min^{-1} and $SVM_{g\text{.min-1}}$ for the GT3X+ and GENEActiv, respectively. Pearson product moment correlation coefficients (*r*) and coefficients of determination (R^2) statistics were conducted to assess the association between the criterion PAEE and outputs from each device at each location. Standard Error of the Estimate (SEE) was also calculated for each correlation.

Error Statistics

When the development and evaluation of predictive models are conducted on the same participants, subsequent evaluation statistics tend to be biased and are often overly optimistic (Staudenmayer *et al.*, 2012). Hence, there is a need to cross-validate generated prediction equations using an independent sample; this can be achieved by using a 'split sample' approach whereby half of the participants are used for developing the models and half for cross-validation. However, it is not always feasible to utilise this 'split sample' approach when sample sizes are small, a common occurrence when working with disabled populations due to challenges with participant identification and recruitment (Yilmaz, 2006). This problem was overcome by developing the estimation algorithm on all but one of the participants and then evaluating it on the 'held-out' participant by calculating the PAEE prediction error. This process was repeated where each participant acted as the held-out participant and the mean of all the error evaluations were calculated. This procedure is a 'leave-one-out cross validation' described in more detail elsewhere (Hastie, 2009).

The comparison statistics involved calculating the mean absolute error (MAE) and mean signed error (MSE) for each activity, the later will be displayed graphically using modified Bland and Altman plots. Considering it is likely the absolute error of estimation will increase with exercise intensity (Staudenmayer *et al.*, 2012), error of estimate data will also be presented as a percentage. A two-way mixed model ANOVA was performed on the raw data to determine differences between criterion PAEE and predicted PAEE. Where a significant interaction effect was observed, a Ryan-Holm-Bonferroni Stepwise Adjustment was applied to *post hoc* tests where multiple comparisons were considered.

This was to identify the specific activities in which there were significant differences between the criterion and predicted PAEE. Statistical significance was set at *a priori* of $\alpha < 0.05$. All analyses were performed using IBM® SPSS® Statistics 20 for Windows (IBM, Armonk, NY, USA).

4.3. RESULTS

Demographic and anthropometric characteristics of the participants are described in Table 4.2. Criterion PAEE ($kcal \cdot min^{-1}$) and accelerometer outputs at each anatomical location are displayed in Table 4.3. Four [SCI (T1 and T2); n=2 Cerebral Palsy; n=1 and Scoliosis; n=1] and two participants (T1 and Cerebral Palsy) were unable to complete the $7km \cdot hr^{-1}$ propulsion speed and $4km \cdot hr^{-1}$ (3% gradient) tasks, respectively. PAEE, HR and rating of perceived exertion (RPE) increased with increasing velocity of wheelchair propulsion and during steeper gradients. Calculated metabolic equivalents (METs) from dividing $\dot{V}O_2$ for each activity by individual $\dot{V}O_2$ determined at rest, suggests that all the propulsion trials besides $3km \cdot hr^{-1}$were on average considered as moderate-intensity activities, whereas folding clothes and propulsion at $3km \cdot hr^{-1}$ were light-intensity activities.

Table 4.2: Demographic and anthropometric characteristics of the participants

Variable	**Mean ± SD**	**Range (lowest – highest)**
Age (years)	36 ± 10	19 - 50
Body mass (kg)	71.6 ± 10.6	53.4 – 87.5
Time since injury (years)	15 ± 14	2- 50
Total skinfold from 4 sites (mm)	48.5 ± 20.3	24.6 – 110.9
Waist-hip ratio	1.0 ± 0.1	0.8 – 1.1
Blood pressure (mmHg)		
Systolic	133 ± 18	108 - 174
Diastolic	84 ± 16	62 - 116
RMR ($kcal \cdot day^{-1}$)	1571 ± 254	1201 - 2152
$\dot{V}O_2$ peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	27.0 ± 8.0	16.7 – 41.1

Note: Able-bodied participant was not included in Time since injury

Table 4.3: Measured PAEE, accelerometer outputs at each anatomical location, calculated METs, heart rate, RPE and number of participants per trial for each activity (mean ± SD)

Activity	Measured PAEE (Kcal·min^{-1})	Physical activity counts·min^{-1}		SVM (g·min^{-1})		MET (calculated)	Heart rate (b·min^{-1})	RPE	n
		GT3X+-UA	GT3X+-W	GENEActiv-UA	GENEActiv-W				
Resting	0.0 ± 0.0	46 ± 57	119 ± 151	30 ± 16	46 ± 24	1.0 ± 0.0	65 ± 12	-	17
Folding clothes	1.1 ± 0.2	3843 ± 1235	8905 ± 1885	121 ± 22	296 ± 66	2.0 ± 0.3	85 ± 15	8 ± 2	17
3 km·hr^{-1}	1.9 ± 0.4	7008 ± 1751	8806 ± 1973	330 ± 78	529 ± 125	2.7 ± 0.4	90 ± 13	9 ± 2	17
4 km·hr^{-1}	2.4 ± 0.6	7056 ± 1761	10283 ± 2569	421 ± 110	708 ± 220	3.2 ± 0.6	97 ± 20	10 ± 3	17
5 km·hr^{-1}	3.1 ± 1.0	7100 ± 1405	12066 ± 4382	492 ± 127	898 ± 353	3.8 ± 0.8	114 ± 23	12 ± 3	17
6 km·hr^{-1}	4.2 ± 1.7	7615 ± 1422	14918 ± 5500	618 ± 154	1170 ± 491	4.7 ± 1.2	130 ± 33	14 ± 3	17
7 km·hr^{-1}	4.7 ± 0.9	8602 ± 1898	16367 ± 5492	701 ± 151	1244 ± 355	5.1 ± 0.8	136 ± 26	14 ± 3	13
4 km·hr^{-1} (+ 8% of body mass)	2.5 ± 0.7	7151 ± 2091	10193 ± 2718	397 ± 106	667 ± 240	3.4 ± 0.6	111 ± 20	10 ± 3	17
4 km·hr^{-1} (2% gradient)	3.2 ± 0.8	7477 ± 1891	10934 ± 3503	455 ± 109	760 ± 276	3.9 ± 0.7	119 ± 24	12 ± 3	17
4 km·hr^{-1} (3% gradient)	4.0 ± 0.9	7852 ± 1785	11439 ± 2686	512 ± 121	830 ± 223	4.6 ± 0.9	128 ± 22	13 ± 4	15

4.3.1. Data Modelling

The associations between criterion PAEE measured by the TrueOne® 2400 computerized metabolic system and predicted PAEE derived from accelerometer outputs from each device are presented as scatter plots in Figure 4.1. Physical activity counts from the GT3X+ were significantly ($P < 0.01$) associated with PAEE (UA; $r = 0.68$, W; $r = 0.82$), as were raw acceleration outputs from the GENEActiv (UA; $r = 0.87$, W; $r = 0.88$). The SEE for the correlations were 1.16 and 0.91 kcal·min^{-1} for the GT3X+ worn at the UA and W, 0.77 and 0.75 kcal·min^{-1} for the GENEActiv worn at the UA and W. The linear regression equations using activity counts from the GT3X+ (Eq. 1 & 2) and raw acceleration outputs from the GENEActiv (Eq. 3 & 4) for each location are shown beneath.

$PAEE_{UA}$ = (0.000372 * Physical activity counts·min^{-1}) + 0.291708 Eq. 1

$PAEE_{W}$ = (0.000245 * Physical activity counts·min^{-1}) + 0.132379 Eq. 2

$PAEE_{UA}$ = (0.006260 * SVM g·min^{-1}) + 0.139778 Eq. 3

$PAEE_{W}$ = (0.003210 * SVM g·min^{-1}) + 0.392209 Eq. 4

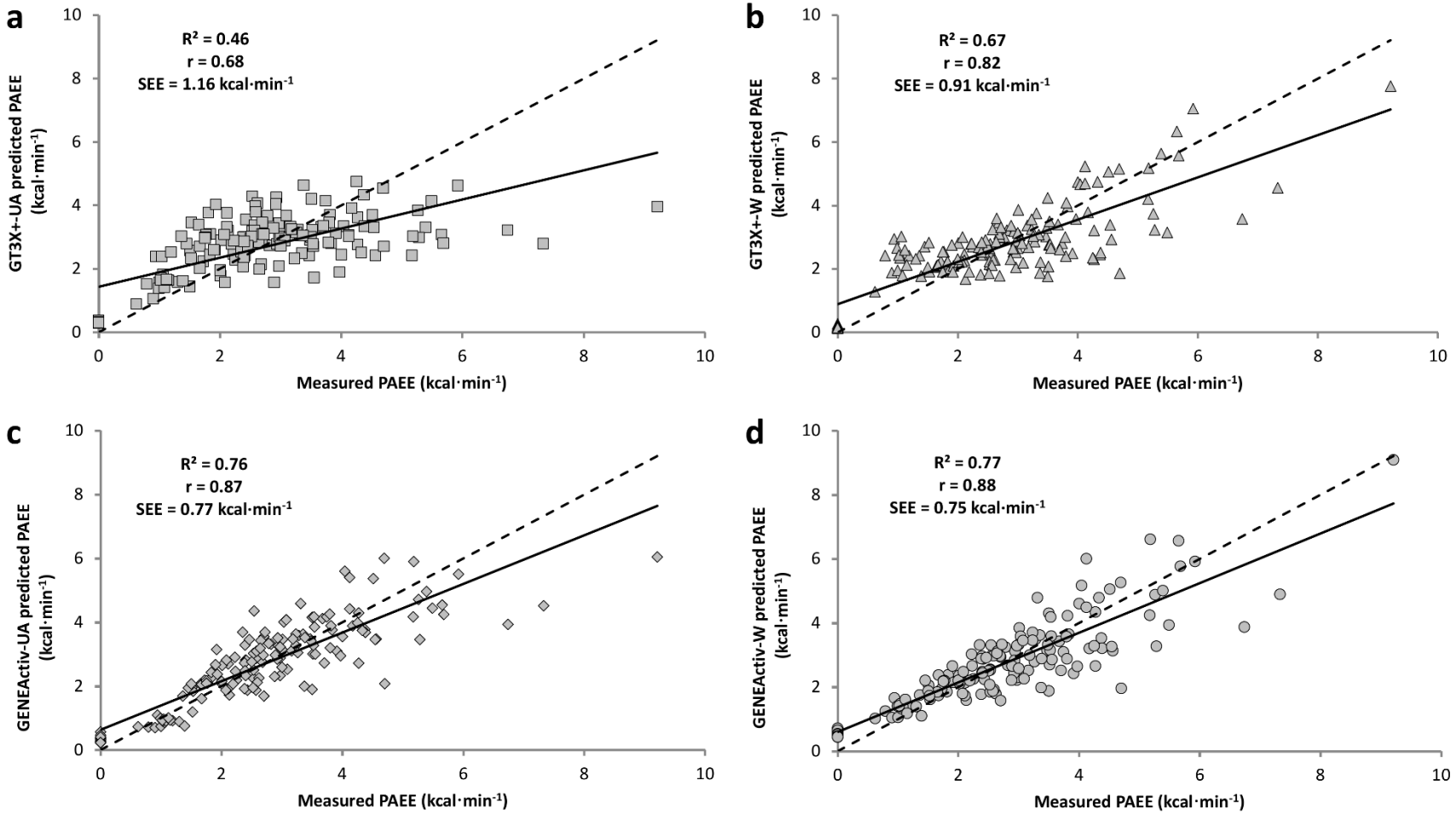

Figure 4.1: Scatterplots showing the relationship between criterion and predicted PAEE for the GT3X+-UA (a), GT3X+-W (b), GENEActiv-UA (c) and GENEActiv-W (d). The *straight line* represents the models best fit, and the *dotted line* indicates the line of identity

4.3.2. Error Statistics

Modified Bland and Altman plots illustrate overall percentage error of estimate [± 95 % limits of agreement (LoA)] between criterion PAEE and predicted PAEE derived from the developed linear regressions; 15 ± 87%, 14 ± 97%, 3 ± 49% and 4 ± 50% for the GT3X+-UA, GT3X+-W, GENEActiv-UA and GENEActiv-W, respectively (Figure 4.2). The GT3X+-W significantly ($P < 0.05$) over-predicted propulsion at 3km·hr^{-1} (mean ± SD; 25 ± 27%), as does the GT3X+-UA (62 ± 48%) and GENEActiv-UA (20 ± 22%). Both the GT3X+-W (-23 ± 24%) and GENEActiv-W (-20 ± 24%) significantly under-predicted PAEE during propulsion at 4km·hr^{-1} on a 3% gradient. The GT3X+-UA, GT3X+-W and GENEActiv-W over-predicted PAEE during a simulated folding clothes task by 64 ± 50%, 122 ± 51% and 29 ± 26%, respectively, whereas the GENEActiv-UA significantly under-predicted PAEE (-14 ± 18%). All monitors significantly over-predicted PAEE during rest by 0.31, 0.16, 0.32 and 0.54 kcal·min^{-1} for the GT3X+-UA, GT3X+-W, GENEActiv-UA and GENEActiv-W, respectively.

Table 4.4 shows the MAE and mean absolute percentage difference between the criterion and estimated PAEE. Absolute PAEE estimation errors varied from 19 to 66% for the GT3X+-UA, 17 to 122% for the GT3X+-W, 15 to 26% for the GENEActiv-UA and 17 to 32% for the GENEActiv-W. The aetiology responsible for wheelchair use was evaluated to see if it impacted on the fit of the model during our leave-one-out analysis. No trend with regards to increased mean absolute error for various aetiologies was observed. There was no relationship between wheelchair experience, TSI was used as a surrogate for this, and error. Furthermore, looking specifically at participants with paraplegia, there was no relationship between level of SCI lesion (indicative of function) and magnitude of error.

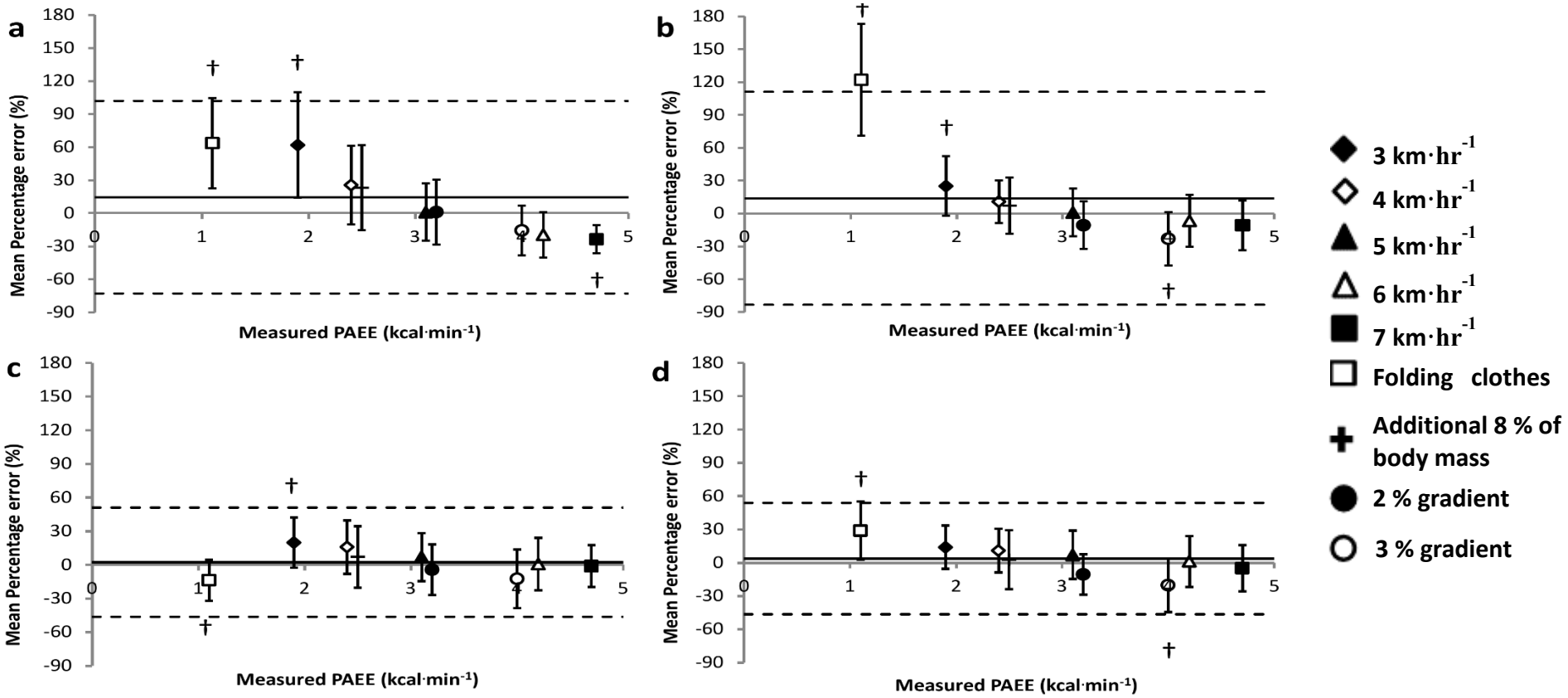

Figure 4.2: Modified Bland and Altman plots displaying error of estimated PAEE expressed as a percentage for GT3X+-UA (a), GT3X+-W (b), GENEA-UA (c) and GENEA-W (d) for each activity. *The solid line indicates overall percentage error of estimate. The dotted lines indicate the upper and lower 95% LoA. † Indicates significant difference ($P \leq 0.05$) from the criterion PAEE*

Table 4.4: Mean absolute error (MAE; kcal·min^{-1}) and Mean absolute percentage error of predicted PAEE using generated linear regression equations for each monitor at each location

Activity	MAE (kcal·min^{-1})				Mean absolute percentage error (%)			
	GT3X+-UA	GT3X+-W	GENEActiv-UA	GENEAcitv-W	GT3X+-UA	GT3X+-W	GENEActiv-UA	GENEAcitv-W
Resting	0.31 ± 0.05	0.16 ± 0.07	0.32 ± 0.11	0.54 ± 0.08	-	-	-	-
Folding clothes	0.66 ± 0.41	1.24 ± 0.46	0.21 ± 0.17	0.32 ± 0.19	63.7 ± 41.0	122.0 ± 51.3	18.9 ± 12.2	32.1 ± 22.0
3 km·hr^{-1}	1.15 ± 0.65	0.48 ± 0.33	0.46 ± 0.27	0.34 ± 0.22	66.1 ± 41.6	28.0 ± 23.7	25.8 ± 14.7	19.1 ± 14.2
4 km·hr^{-1}	0.86 ± 0.57	0.42 ± 0.24	0.52 ± 0.45	0.42 ± 0.29	35.9 ± 24.7	18.4 ± 12.3	21.9 ± 18.3	17.9 ± 13.5
5 km·hr^{-1}	0.67 ± 0.84	0.54 ± 0.43	0.61 ± 0.42	0.60 ± 0.42	19.3 ± 16.6	17.1 ± 12.9	18.9 ± 11.3	18.8 ± 12.2
6 km·hr^{-1}	1.14 ± 1.53	0.90 ± 0.81	0.87 ± 1.02	0.74 ± 0.75	21.7 ± 18.1	19.7 ± 14.1	17.3 ± 15.0	17.5 ± 14.4
7 km·hr^{-1}	1.13 ± 0.72	0.92 ± 0.84	0.73 ± 0.51	0.79 ± 0.67	23.6 ± 13.0	18.7 ± 16.0	15.2 ± 9.7	16.5 ± 12.8
4 km·hr^{-1} (+ 8% of body mass)	0.96 ± 0.61	0.52 ± 0.31	0.59 ± 0.33	0.55 ± 0.31	38.0 ± 22.9	21.5 ± 14.5	24.1 ± 14.0	22.6 ± 12.9
4 km·hr^{-1} (2% gradient)	0.81 ± 0.83	0.64 ± 0.51	0.56 ± 0.56	0.54 ± 0.46	22.9 ± 17.7	19.9 ± 13.1	16.6 ± 15.4	16.7 ± 12.2
4 km·hr^{-1} (3% gradient)	0.95 ± 0.96	1.19 ± 0.95	1.01 ± 0.80	1.16 ± 0.81	21.4 ± 16.5	28.0 ± 18.0	24.3 ± 14.8	27.6 ± 14.5
All activities	**0.86 ± 0.82**	**0.69 ± 0.63**	**0.58 ± 0.56**	**0.59 ± 0.51**	**35.3 ± 30.8**	**33.0 ± 39.5**	**20.4 ± 14.3**	**21.0 ± 15.1**

4.4. DISCUSSION

Of the two accelerometers considered in this study, these data indicate that the GENEActiv device worn on either the upper arm or wrist provided the most valid (mean percentage error 3 & 4% for the upper arm and wrist, respectively) prediction of PAEE. For the GT3X+, as alluded to in Chapter 3, the most appropriate anatomical location was on the wrist. There was a negligible difference in the strength of associations and error statistics for the GENEActiv device worn on the upper arm or wrist. Seemingly, incorporating raw acceleration signals as opposed to 'arbitrary' physical activity counts into linear regression models for the prediction of PAEE offered an improvement in the error of estimation for PAEE in wheelchair users (Figure 4.2; Table 4.3).

Considering physical inactivity has been associated with a cluster of metabolic abnormalities (Biolo *et al.*, 2005), it is surprising that relatively few studies have attempted to investigate the use of movement sensors in a population where self-report measures suggest that PA is substantially reduced. Despite employing some complex statistical modelling methods, previous studies have tended to use arbitrary 'count' values in the prediction of EE (Washburn & Copay, 1999; Garcia-Masso *et al.*, 2013) and also adopted a small selection of activities in their validation protocol (Hiremath & Ding, 2009; Hiremath & Ding, 2011a; Hiremath & Ding, 2011b). The current study aimed to improve our understanding of accelerometer outputs and the prediction of PAEE in wheelchair users by incorporating raw acceleration values into linear regression models. Furthermore, participants performed a comprehensive wheelchair propulsion protocol which consisted of various velocities and gradients whereby the validity of these devices were assessed.

Previous research has provided encouragement for the wrist as the preferred anatomical location for previous generations of Actigraph accelerometers to predict $\dot{V}O_2$, explaining 44% (Washburn & Copay, 1999) and 74% (Garcia-Masso *et al.*, 2013) of the variability in $\dot{V}O_2$, respectively. Off-the-shelf activity monitors incorporating manufacturer's proprietary equations are unable to accurately predict EE in wheelchair users (Hiremath

& Ding, 2011b; Hiremath & Ding, 2011a). As such, validation studies in this area have attempted to develop new predictive models. Washburn & Copay, (1999) generated a simple linear equation using counts·min^{-1} from the uniaxial CSA accelerometer over three propulsion velocities. Improvements in this prediction can be seen in the Garcia-Masso *et al.*, (2013) study, which used the GT3X tri-axial device and the acquisition of 1-s epochs to permit a feature extraction process which was incorporated into more complex multiple linear modelling (MLM). Chapter 3 demonstrated associations of $r = 0.93$ and $r = 0.87$ between counts·min^{-1} from the newest generation GT3X+ worn at the wrist and upper arm and PAEE during outdoor wheelchair propulsion. One of the strengths of the present study was the controlled laboratory protocol adopted, being more comprehensive, including five extra activities, smaller increments in velocity (1km·hr^{-1} compared to 2km·hr^{-1}) and various treadmill gradients. Consequently, weaker associations were observed between GT3X+ physical activity counts with criterion PAEE at the wrist and upper arm of $r = 0.82$ vs. $r = 0.68$. However, correlations between raw acceleration values expressed as SVM in g·minute^{-1} from the GENEActiv and criterion PAEE were similar to our previous field-based observations, at $r = 0.88$ and $r = 0.87$ for the wrist and upper arm, respectively. The GENEActiv-W has previously demonstrated excellent validity in able-bodied populations, displaying similar correlations to ours during a series of semi-structured laboratory and free living activities (left wrist vs. $\dot{V}O_2$, $r = 0.86$) (Esliger *et al.*, 2011).

Another strength of this present study was the comparison of two widely used accelerometry-based technologies to quantify PAEE. Specifically, by holding the anatomical location constant, variations in the strength of the relationships and error of estimate are inherent to the differences in the internal components, on-board filtering processes and outputs of each device (Chen & Bassett, 2005). To discard noise or movement artefacts unlikely to be representative of 'human movement', the GT3X+ has upper and lower bandwidth filters of 0.25 and 2.5Hz. These filters were designed for ambulation, based on the premise that acceleration frequencies arising from most human activities at the hip usually fall between this range. Bailey *et al.*, (2014) demonstrated that processed activity counts from a GT3X+ worn on the wrist are capable of distinguishing between tasks where upper extremities were used more intensively (e.g folding towels) than less intensively (e.g. writing). Whilst this protocol consisted of a comprehensive

selection of upper extremity ADLs, no comparison was made to a PAEE criterion measurement, preventing the assessment of PAEE error. It is possible that these aforementioned filters are not suitable to capture movements at the wrist of wheelchair users. As mentioned in chapter 3, the GT3X+ has half power frequencies of 0.5 Hz and 2.5 Hz. This doesn't mean that movements within these limits are measured full scale while those outside of it are not registered at all, but in fact a scaling filter is applied. Therefore, certain movements which have frequency components that are measured full scale, might register greater PACs, which could explain the sizeable over-estimation of 122% during the folding clothes task. This brings doubt into whether the GT3X+ is a suitable device to be worn at the wrist to measure PAEE associated with ADLs during free-living in wheelchair users.

However, excluding the folding clothes task from the analysis reduced the mean percentage error of estimate for the GT3X+-W to 0.4% during wheelchair propulsion at various speeds and gradients. Outputs from the GENEActiv are raw acceleration signals per unit time or epoch and are not subject to a tight bandwidth filter which may influence the prediction of PAEE at the wrist during certain activities. Whilst the GT3X+, and other commercially available monitors have the capability to report raw acceleration, the most common and easily accessible outputs from these devices are counts, which are influenced by the amplitude and frequency of acceleration. Physical activity counts have been shown to vary across devices and even within generations of the same type of device (Ried-Larsen *et al.*, 2012). It is possible that the band-pass filtering and reporting of accelerometer outputs using 'arbitrary' units, which lack physical meaning, may be responsible for the differences in the error of estimation between the two devices (Figure 4.2; Table 4.4). As processing of raw data from the GT3X+ and other devices becomes available as standard then researchers can start to adopt an end-user practitioner approach to assessing the application and efficacy of these devices in the future.

Another explanation for the differences in associations for the two devices at the upper arm could be due to slight variations in their anatomical positioning and method of affixation. The GT3X+-UA worked loose during two trials, although these data were removed from subsequent analyses. It is possible that the secure attachment of the

GENEActiv-UA provided by the medical tape minimised any movement inherent with the elastic belt of the GT3X+-UA. Whilst predictive models for the GENEActiv at the upper arm and wrist offer negligible bias in error prediction statistics and both under/over-predicted PAEE during three activities, the feasibility of attaching the GENEActiv to the upper arm during free living might be limited. Whereas the device worn on the wrist has a constant position, securely attached over the styloid processes of the radius and ulna (worn like a watch). From a practical perspective, the GENEActiv worn on the wrist would be the preferred device/location for the accurate prediction of PAEE in wheelchair users. Accelerometers worn on the wrist are well tolerated and unobtrusive in this population and intuitively should not interfere with regular PA levels during free-living monitoring.

Considering the validity of an accelerometer based solely on the strength of its association to a criterion measure should be avoided as it does not indicate the agreement between the two variables (Bland & Altman, 2010). Correlations are also dependent on the range of true quantity in the sample, seeing as our protocol had a wide selection of wheelchair propulsion velocities and gradients it is perhaps not surprising that this current study reported strong associations. A recent review on statistical considerations in the analysis of accelerometer data (Staudenmayer *et al.*, 2012) advocated that it is useful for researchers to report measurement error. Mean percentage error of estimate (±SD) for the GT3X+-UA and GT3X+-W was 15 ± 45% and 14 ± 50%, compared to 3 ± 25% and 4 ± 26% for GENEActiv-UA and GENEActiv-W, respectively. Whilst our generated linear regression models for the GENEActiv demonstrated a relatively small bias, looking at MSE can be misleading as it is likely that under and over-estimations from different tasks cancel each other out.

An alternative is to look at mean absolute percentage error. Mean absolute percentage error ranged from 19 – 66%, 17 – 122%, 15 – 26% and 17 – 32% for the GT3X+-UA, GT3X+-W, GENEActiv-UA and GENEActiv-W, respectively. Previous research (Hiremath & Ding, 2011b) attempted to develop new prediction models, using general and activity specific equations for an RT3 tri-axial accelerometer worn on the arm. The authors generated MLM's using a training group of 19 participants and evaluated their

performance on a smaller validation group (n = 4). The range of mean absolute percentage error using the general equation was 14 – 114% during an activity protocol that involved propulsion on a dynamometer, tiled floor and arm-ergometer exercise. This was similar to that of the GT3X+-W (17 – 122%). When looking solely at wheelchair propulsion, resting and deskwork using the activity specific equations, the mean absolute percentage error was reduced to 26% (Hiremath & Ding, 2011b), which is slightly larger than the 20% and 21% for the GENEActiv upper arm and wrist for all activities included in our protocol.

The GT3X+-UA, GT3X+-W, GENEActiv-UA and GENEA-W monitors significantly over-predicted PAEE during rest by 0.31, 0.16, 0.32 and 0.54 kcal·min^{-1}, respectively. This might have implications with the accurate prediction of PAEE during free-living. Garcia-Masso *et al.*, (2013) observed a significant over-prediction of estimated $\dot{V}O_2$ using a MLM from a device worn at the wrist during a lying down activity. Both monitors at the wrist also significantly over-estimate PAEE for the folding clothes activity. Nevertheless over-estimation of PAEE for light-intensity activities (Atkin *et al.*, 2012) or the inability to accurately describe the association between activity counts and the metabolic cost of certain lifestyle related activities (Bassett *et al.*, 2000) is a common observation when using accelerometers in the able-bodied PA monitoring literature. Even considering these limitations accelerometers are still widely used during cross-sectional and epidemiological PA research in ambulatory populations, observing similar issues in predicting PAEE when worn at the wrist in wheelchair users should not discourage their use. Especially if their accuracy is better than methods currently used to quantify PA in this population. The relationships between raw acceleration at the upper arm and wrist (r = 0.87, r = 0.88) and criterion PAEE is better than the correlation between PARA-SCI scores and indirect calorimetry (r = 0.79) (Ginis *et al.*, 2005). The authors found that this relationship was reduced and non-significant for low intensity activities (r = 0.27) and consequently the PARA-SCI scores under-reported the amount of time spent doing activities of low intensity by 10%. This self-report measure was instrumental in informing the most recent PA guidelines for adults with a chronic SCI (Ginis *et al.*, 2011). The conversion of these scores using METS to predict EE would lead to a slight under-estimation. This is in contrast to our results and others (Garcia-Masso *et al.*, 2013), that accelerometers over-estimate PAEE for light intensity activities. It is of concern that error

with monitoring sedentary behaviours may be exacerbated in a population whereby sedentary time may be elevated. One limitation of this study is that only one ADL was incorporated into the protocol whereby PAEE could be misclassified by the devices. Considering that 6-8 hrs of the day is spent in occupational tasks future work should incorporate more of these work-day tasks into laboratory validation protocols.

Limitations of accelerometers in the able-bodied literature are that outputs do not always reflect PAEE during walking on a slope (Bouten *et al.*, 1997) or during load carriage (Willems *et al.*, 2009). To the best of our knowledge, there is only one previous study looking at the validity of an activity monitor (SWA) in quantifying EE during wheelchair propulsion over differing gradients (Davis *et al.*, 2010). It is clear that proprietary algorithms used by the SWA over-estimate metabolic rate (MAE range; 24 – 126%) (Hiremath & Ding, 2011a), but this overestimation and variability increased more when gradient was elevated, than when speed was increased (Davis *et al.*, 2010). This present study is the first to assess whether similar acceleration profiles with differing energy costs, such as changing gradient or load carriage, can be captured by new prediction models for tri-axial accelerometers in wheelchair users. There is a trend for all monitors to under-predict PAEE during propulsion on increasing gradients, and the GT3X+-W and GENEA-W significantly underestimated (-23 and -20%) PAEE during propulsion at 4km·hr^{-1} on a 3% gradient. Devices worn on the upper arm did not underestimate by the same magnitude as devices worn on the wrist during propulsion on differing gradients. It is possible that propulsion technique was modified, perhaps via an increase in flexion and extension of the shoulder to cope with the demands of uphill propulsion. Changes in propulsion patterns between conditions could be monitored using expensive motion analysis systems in future research studies.

Physical activity energy expenditure was not significantly different when an additional 8% of participant body mass was added to the chair during wheelchair propulsion at 4km·hr^{-1} (2.5 ± 0.7 vs. 2.4 ± 0.6 kcal·min^{-1}). Sagawa *et al.*, (2010) noticed no significant effect of a 5 kg additional mass on EE or HR. It is plausible that a load attached to the wheelchair has a minimal impact on EE during propulsion on the flat unlike load carriage during ambulation. This may be because an 8% load is spread evenly across the axial and

weight is supported in the vertical axis unlike walking. Importantly the MAE (table 4.4) is not significantly different between propulsion at 4km·hr^{-1} and when an additional 8% of body mass is added for all monitors. Furthermore, each device displays relatively negligible biases during propulsion with additional weight.

The strengths of the present study are that RMR was accounted for and a comprehensive evaluation of two commonly used accelerometers, using a robust treadmill protocol with a variety of velocities and gradients was conducted. Previous studies have not controlled for RMR, which varies substantially between individuals with SCI, depending on level and completeness of lesion (Buchholz & Pencharz, 2004). Previous validation work has often randomised the task order. With limited recovery time in between tasks it is therefore not always possible to exclude a carryover effect as a confounding variable, particularly when lower intensity activities follow higher intensity tasks, similar to Chapter 3. To avoid this, tasks were assigned in order of intensity as a method to prevent a carryover effect between trials. Fatigue seemingly had a minimal impact on our findings as we observed a strong linear relationship in physiological variables and accelerometer outputs across all tasks. These data would also suggest that assessing wheelchair propulsion using a controlled treadmill method is reflective of 'real world' propulsion. Despite using an independent group of participants and a portable metabolic analyser, PAEE during propulsion on the treadmill at 4km·hr^{-1} is identical to PAEE recorded during propulsion on an athletics track at 4km·hr^{-1} (2.4 ± 0.6 vs. 2.4 ± 0.9 kcal·min^{-1}) (Chapter 3). This is encouraging considering it has previously been recognized that treadmill walking/ running can affect gait mechanics and therefore may not reflect true metabolic costs of ambulation at a given speed over the ground (Parvataneni *et al.*, 2009). Another considerable strength is that a 'leave-one-out' cross validation analysis of our generated prediction equations was conducted, an approach strongly advocated for future research whereby recruitment of participants with specific injury characteristics might be problematic. Reporting raw acceleration data in SI units (g·min^{-1}) is a significant advantage as it allows easier comparison between devices and subsequently future research studies (Intille *et al.*, 2012). The developed linear regression model for the GENEActiv device could be utilised by other activity monitors that have the function or are capable of reporting raw acceleration values. However, the equivalency of raw outputs between monitors needs to be assessed in the future with regards to differences in

dynamic sensing capacities (i.e. GENEActiv ± 8 *g* compared to ± 6 *g* for the GT3X+) or type of microelectromechanical systems (MES) sensor used.

This study demonstrated, for the first time, that the measurement of raw acceleration signals using the GENEActiv offered an improvement in the prediction of PAEE in wheelchair users. Specific on-board by-pass filtering methods intrinsic to the GT3X+ when reporting accelerometer data as activity counts appear to impact on the devices measurement sensitivity, particularly during low frequency movements (e.g. folding clothes). In keeping with the rapid development of activity monitoring over the past six years in ambulatory populations we expect the acquisition of raw data to become more prevalent in the prediction of PAEE during free-living. However, even raw signals tended to under-estimate PAEE during propulsion on various gradients, whereby acceleration profiles are similar but ultimate energy costs are different. Therefore, we recommend that the validity of multi-sensor devices, which incorporate accelerometry and physiological signals, to predict PAEE in wheelchair users be rigorously assessed.

CHAPTER 5: PREDICTING PHYSICAL ACTIVITY ENERGY EXPENDITURE IN WHEELCHAIR USERS WITH A MULTI-SENSOR DEVICE

5.1. INTRODUCTION

Despite an elevated risk of metabolic disease in disabled groups, there is a paucity of research focussing on the impact of PA on their health, particularly in wheelchair users. There are an estimated 750,000 wheelchair users in the United Kingdom. Locomotion and movement patterns in wheelchair users are very different to ambulatory individuals and, as such, further studies are required to develop tools to quantify physical activity levels.

Previous research has assessed the validity of a number of objective methods to predict physical activity levels of wheelchair users. These include attaching a custom data logger onto the wheel (Tolerico *et al.*, 2007) or a tri-axial accelerometer (Coulter *et al.*, 2011) to the frame of the wheelchair to capture certain mobility characteristics such as average speed and distance travelled. Whilst unobtrusive, these devices offer limited information on the intensity of activities performed and offer somewhat modest associations with energy expenditure. Recently hand rim propulsion power (Conger *et al.*, 2014) was evaluated to address this limitation. However, any device on the wheelchair cannot distinguish between self or assisted propulsion and cannot quantify non-wheelchair activity. An alternative approach has been the use of body-borne movement sensors. Chapters 3 & 4 identified that the wrist is the most appropriate anatomical location to accurately predict PA in wheelchair users during a range of outdoor propulsion speeds and in a laboratory environment. Whilst this is encouraging, accelerometry alone doesn't capture the physiological strain associated with movement behaviours that produce similar acceleration profiles but have a different energy cost, such as changing gradient or load carriage (Lamonte & Ainsworth, 2001). This was observed in Chapter 4, as the preferred device (GENEActiv-W) significantly under predicted PAEE by - 20% during propulsion at 4km·hr^{-1} on a 3% gradient. With this in mind we wanted to see whether

incorporating physiological signals into the prediction of PAEE might improve the accuracy of objective monitoring tools.

Multi-sensor devices, which integrate accelerometry and physiological signals to predict PAEE, are commonly used in studies of able-bodied participants. Previous validation work in wheelchair users has focussed on the integration of dual-axis accelerometry and physiological measures (e.g. heat flux, galvanic skin response & temperature) to predict energy expenditure (EE) using the Sensewear device (Chen *et al.*, 2012). This device and the development of specific algorithms for wheelchair users has been described in chapter 2. Whilst the development of specific algorithms (Hiremath *et al.*, 2012) has led to substantial improvements in the accuracy of predicting EE in wheelchair users (16.8% error), thermoregulatory responses have been shown to be disrupted in persons with SCI (Petrofsky, 1992) which may limit the applicability of these physiological signals for this population. Ultimately, the calculation of EE by the Sensewear device is determined by proprietary algorithms which utilizes upwards of twenty possible output parameters. Researchers should have open access to these underlying equations. Currently it is not clear how each parameter contributes to the prediction of EE in this device.

Previous studies in able-bodied participants have supported the utility of combined heart rate (HR) and accelerometer devices to estimate EE (Brage *et al.*, 2005: Thompson *et al.*, 2006). The Actiheart (AHR) is a commercially available multi-sensor device which incorporates HR monitoring and accelerometry into a single unit. It is widely used to measure free-living PA in able-bodied individuals (Turner *et al.*, 2010; Betts *et al.*, 2014) and further research, in diverse populations, has been recommended (Atkin *et al.*, 2012). The validity of combined heart rate and movement sensor PAEE prediction in wheelchair users remains to be established. Its utility may also be heavily reliant on individual calibration, as a result of the high variability in cardiovascular responses to exercise in individuals with differing levels/completeness of SCI (Furlan & Fehlings, 2008). Therefore, the aim of this study was to assess the error of the AHR device in predicting PAEE in wheelchair users and to assess the efficacy of an individual HR calibration. It is hypothesised that applying an individual heart rate calibration will improve the prediction of PAEE compared to the proprietary algorithms in the AHR.

5.2. METHODS

5.2.1. Participants

The same seventeen male manual wheelchair users as in chapter 4 participated in this study. However due to two AHR malfunctions during testing only data from fifteen (n = 15) participants will be presented. All participants provided written, informed consent. Demographic characteristics of the participants are presented in Table 5.1.

5.2.2. Study Protocol

Resting metabolic rate and anthropometric variables were collected as described in Chapter 4. All data were collected at the Centre for DisAbility Sport and Health (DASH), following an overnight fast. Participants completed a wheelchair propulsion protocol on an adapted treadmill (HP Cosmos Saturn 250/100r, HaB International Ltd, UK) and a folding clothes task. This activity protocol is identical to that described in chapter 4.

5.2.3. Assessment of Energy Expenditure

Expired gases were analysed continuously during each activity using the same methods as described in chapter 4. Participants also wore a Polar T31 HR monitor (Polar Electro Inc., NY, USA), which transmitted HR to a wireless receiver module connected to the TrueOne® 2400 computerized metabolic system.

Participants wore an AHR (ActiheartTM, Cambridge Neurotechnology Ltd, Papworth, UK), which integrates accelerometer and HR signals. The AHR unit has been described in detail previously (Brage *et al.*, 2005). The main body of the device contains an omni-directional accelerometer with a sampling rate of 32 Hz and a dynamic range of ± 2.5 *g*. When exposed to time-varying acceleration the voltage signal generated by the piezo-electric element is converted into a binary signal by an eight-bit analogue to digital converter. The accelerometer in this device has a linear (R^2 = 0.999) response to

acceleration (Brage et al, 2005). The AHR frequency range is 1 Hz to 7 Hz with a memory capacity capable of storing 21 days of data when recording at 60 s epochs. The AHR consists of two clips which were attached to standard adhesive ECG electrodes (Telectrode T815, Bio-Protech Inc., Exeter, UK), which were then fitted to the participant according to manufacturer's instructions. HR (bpm) is generated from an ECG signal. The device is worn in the upper position (Figure 5.1) so that the Polar T31 HR monitor could be worn underneath to simultaneously measure HR. AHR's were initialised to long-term recording with 30 s epochs.

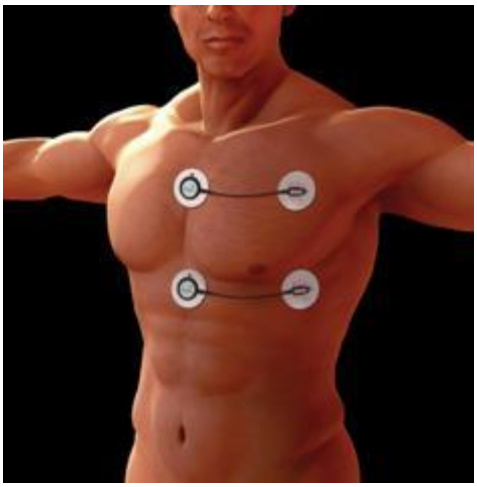

Figure 5.1: AHR wear locations

The branched equation model used by the AHR software (Actiheart version 4.0.23, Cambridge Neurotechnology Ltd, Papworth, UK) to predict PAEE using the group calibration (Brage *et al.*, 2007) is shown in the diagram below (Figure 5.2). The chosen 'activity value' (25 counts·min^{-1}) was the lowest value recorded during cycling, this prevents cycling from taking the low intensity route in the branched model.

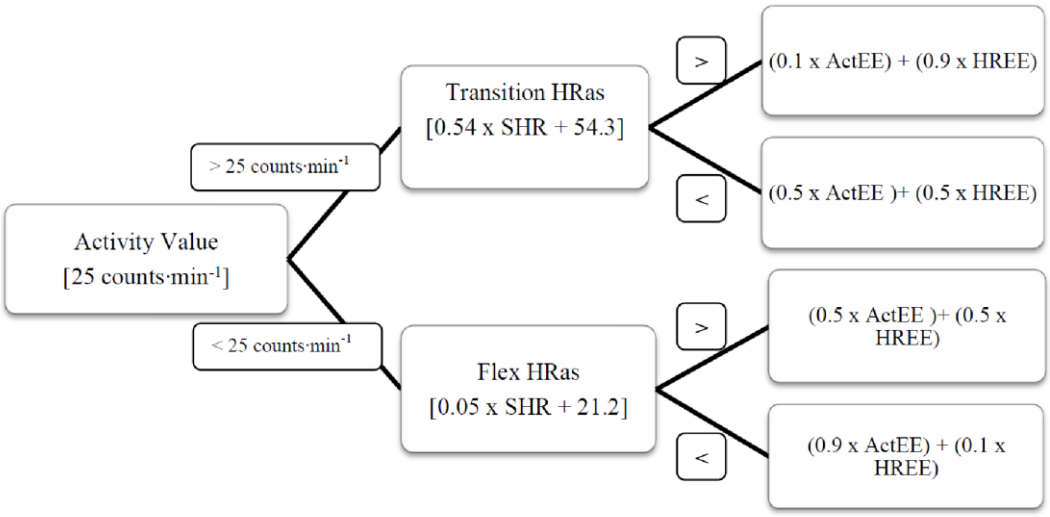

Figure 5.2: AHR branched equation model *(Taken with permission from Horner, 2012)*
HRas: Heart rate above sleep
Heart rate energy expenditure (HREE) is determined by: HREE = 5.5 ∗ HRas + (1.6 * HRas ∗ gender) – (7.8 ∗ SHR ∗ gender) + (338 ∗ gender) – (4.7 ∗ SHR + 207)

5.2.4. Resting Measures

Following a 10-min rest in a semi-recumbent position, resting HR and metabolic rate (RMR) were measured (Chapter 4; Compher *et al.*, 2006). Breath-by-breath data were averaged into four 5-min samples, with additional samples collected if values varied by >100 kcal·day^{-1}. The mean of these samples was accepted as RMR.

5.2.5. Incremental Arm Crank Ergometry Test

Participants underwent a 9-12 minute peak oxygen uptake ($\dot{V}O_2$ peak) test using an electrically braked arm crank ergometer (Lode Angio, Groningen, Netherlands). This was conducted at the end of the activity protocol, using a continuous, incremental test until volitional exhaustion. A cadence of 75 rpm was required throughout and a starting intensity of 35 W was typically chosen, although this was based on participants training

history. The resistance was increased by 14 W every three minutes. EE and HR were averaged over the final min of each stage. The same $\dot{V}O_2$ peak endpoint criteria were used as in Chapter 4.

5.2.6. Twenty-Four-Hour Record

Participants were asked to carry out their normal daily activities for 24 h while being monitored using AHR to determine sleeping HR (Brage *et al.*, 2005). This provided a 24 h 'snapshot' of habitual PA. Furthermore, permanent wheelchair users (n = 13) were asked to log their PA as accurately as possible to estimate PAEE using the adapted PA compendium (Conger & Bassett, 2011). Twenty-four-hour PAEE was estimated from self-reported PA and AHR. These data are only available for 8 participants.

5.2.7. Statistical Analyses

Assuming that dietary-induced thermogenesis was negligible (i.e. participants were fasted), RMR ($kcal \cdot min^{-1}$) was subtracted from total energy expenditure, to generate PAEE for each activity. Comparisons between the 'criterion' measurement of PAEE and AHR were made between the final 2-min of each activity.

Data from the AHR unit were downloaded and participant's descriptive characteristics (i.e. gender, age, mass and height) entered retrospectively. Common equations to predict RMR in the general population are inappropriate to use for individuals with SCI and have been shown to over-predict by 5-32% (Buchholz & Pencharz, 2004). Measured RMR was entered, as the Schofield equation over-predicted by 12% (range -6 to 27%). This difference can be explained by a 14 – 27% reduction in basal metabolic rate (BMR) in individuals with SCI (Buchholz & Pencharz, 2004). Sleeping HR, measured during the 24 hr record, and max HR measured during the $\dot{V}O_2$ peak test, were also entered into the AHR software.

The AHR software has a function whereby individual HR calibration data can be used in the calculation of PAEE instead of a group calibration. This is accessed by clicking on the 'view/edit' button in the Advanced Energy Expenditure screen. We selected the other HR calibration tab and entered criterion measured PAEE ($J \cdot min^{-1} \cdot kg^{-1}$) for a selection of corresponding HRs determined at rest and during the incremental arm ergometry test. As advised by the manufacturer, the Fill function was used which extrapolated any missing data in a linear manner between entered values. These individual calibration data were stored and later used to predict PAEE. This function allows us to retrospectively compare the validity of using generic group calibration (GC) and individual HR calibration (IC) models.

Predicted PAEE data were copied into a spreadsheet (MS Excel) and compared to corresponding criterion measures of PAEE. Pearson product moment correlation coefficients (*r*) and coefficients of determination (R^2) statistics were conducted to assess the association between criterion PAEE and predicted PAEE (GC and IC). Standard Error of the Estimate (SEE) was calculated for each correlation. Error statistics, including mean absolute error (MAE) and mean signed error (MSE) were calculated. As absolute error is likely to increase with exercise intensity (Staudenmayer *et al.*, 2012), percentage error of estimate was also calculated. R^2, *r* and SEE statistics were determined to assess the relationship between twenty-four-hour self-reported PAEE and predicted PAEE (GC and IC). Independent t-tests were performed to assess differences between predicted PAEE (GC and IC) and the PA log during the twenty-four-hour follow-up. Statistical significance was set at *a priori* of $\alpha < 0.05$.

5.3. RESULTS

5.3.1. Laboratory Validation

Accelerometer counts, HR and RPE all increased linearly with increasing exercise intensity (Table 5.2). Absolute HR on its own explained 57% of the overall variance in PAEE (r = 0.76, SEE = 1.07 kcal·min^{-1}). Acceleration along the longitudinal axis of the trunk explained 65% of the variance in the prediction of PAEE (r = 0.81, SEE = 0.96 kcal·min^{-1}). Three and two participants were unable to complete the 7km·hr^{-1} propulsion speed and 4km·hr^{-1} (3% gradient) tasks, respectively. Unusable HR traces were recorded for one participant in the folding clothes and 4km·hr^{-1} (3% gradient) trials, and for separate participants in the 3 and 5 km·hr^{-1} propulsion trials. These data points were therefore excluded from the analyses.

Table 5.1: Participant Characteristics

Variable	Mean ± SD	Range (lowest – highest)
Age (years)	36 ± 11	19 - 50
Body mass (kg)	72.7 ± 10.2	54.2 - 87.5
Height (m)	1.70 ± 0.13	1.40 - 1.88
Time since injury (years)	16 ± 15	2 - 50
Sleep HR ($b \cdot min^{-1}$)	56 ± 11	42 – 74
Rest HR ($b \cdot min^{-1}$)	65 ± 12	50 – 88
RMR ($kcal \cdot day^{-1}$)	1621 ± 248	1201 – 2152
$\dot{V}O_2$ peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	28.3 ± 6.9	16.7 – 41.1
Reason for WC use	SCI[1] (T1 – L4) (n = 8), Spina bifida (n = 3), Scoliosis (n = 1), Cerebral Palsy (n = 1), Amputation[2] (n = 1), AB[3] (n = 1)	

[1] All SCI volunteers indicated that they had complete lesions.

[2] Regular wheelchair user (>70% of locomotion)

[3] AB wheelchair basketball player (> two years)

AB: Able-bodied, SCI: Spinal Cord injury, WC: Wheelchair

Criterion PAEE was very strongly and near perfectly associated with GC (r = 0.76, P < 0.01) and IC (r = 0.95, P < 0.01), respectively. The GC explained 57% of variance in the prediction of PAEE with a SEE of 1.07 $kcal \cdot min^{-1}$, compared to the IC which explained 91% of variance in PAEE with a SEE of 0.49 $kcal \cdot min^{-1}$ (Figure 5.3).

The degree of agreement between estimated and criterion PAEE is displayed graphically through the use of Bland and Altman plots (Figure 5.4 a-b). The mean bias ± 95% Limits of Agreement (LoA) was 0.51 ± 3.75 $kcal \cdot min^{-1}$ and -0.22 ± 0.96 $kcal \cdot min^{-1}$ for the GC and IC, respectively. Error statistics between the criterion and estimated PAEE for each activity are shown in Table 3. Removal of these data for the able-bodied basketball player did not impact the nature of the regression relationships or error statistics in any meaningful way.

Table 5.2: Measured PAEE, Predicted GC and IC PAEE, heart rate, accelerometer counts, RPE and number of participants per trial for each activity (mean ± SD)

Activity	Measured PAEE (kcal·min^{-1})	Predicted PAEE (kcal·min^{-1})		Heart rate (b·min^{-1})	Acceleration (counts·min^{-1})	RPE	n
		GC	IC				
Resting	0.0 ± 0.0	0.1 ± 0.2	0.1 ± 0.1	65 ± 12	0 ± 0	-	15
Folding clothes	1.1 ± 0.2	0.8 ± 0.6	0.6 ± 0.2	85 ± 15	6 ± 5	8 ± 2	14
3km·hr^{-1}	1.9 ± 0.4	1.8 ± 1.0	1.7 ± 0.6	90 ± 13	70 ± 50	9 ± 2	14
4km·hr^{-1}	2.4 ± 0.6	2.7 ± 1.7	2.3 ± 0.7	97 ± 20	127 ± 100	10 ± 3	15
5km·hr^{-1}	3.2 ± 1.0	4.0 ± 2.9	3.0 ± 1.1	114 ± 23	160 ± 95	11 ± 3	14
6km·hr^{-1}	4.3 ± 1.7	5.5 ± 3.7	3.9 ± 1.6	130 ± 33	229 ± 116	13 ± 3	15
7km·hr^{-1}	4.7 ± 0.9	5.4 ± 2.7	4.1 ± 1.0	136 ± 26	282 ± 137	14 ± 3	12
4km·hr^{-1} (+ 8% of body mass)	2.6 ± 0.7	3.4 ± 2.3	2.6 ± 0.8	111 ± 20	112 ± 80	10 ± 3	15
4km·hr^{-1} (2% gradient)	3.2 ± 0.9	4.2 ± 2.8	3.2 ± 1.2	119 ± 24	156 ± 110	12 ± 3	15
4km·hr^{-1} (3% gradient)	4.0 ± 1.0	4.6 ± 2.3	3.5 ± 0.9	128 ± 22	162 ± 86	13 ± 4	12

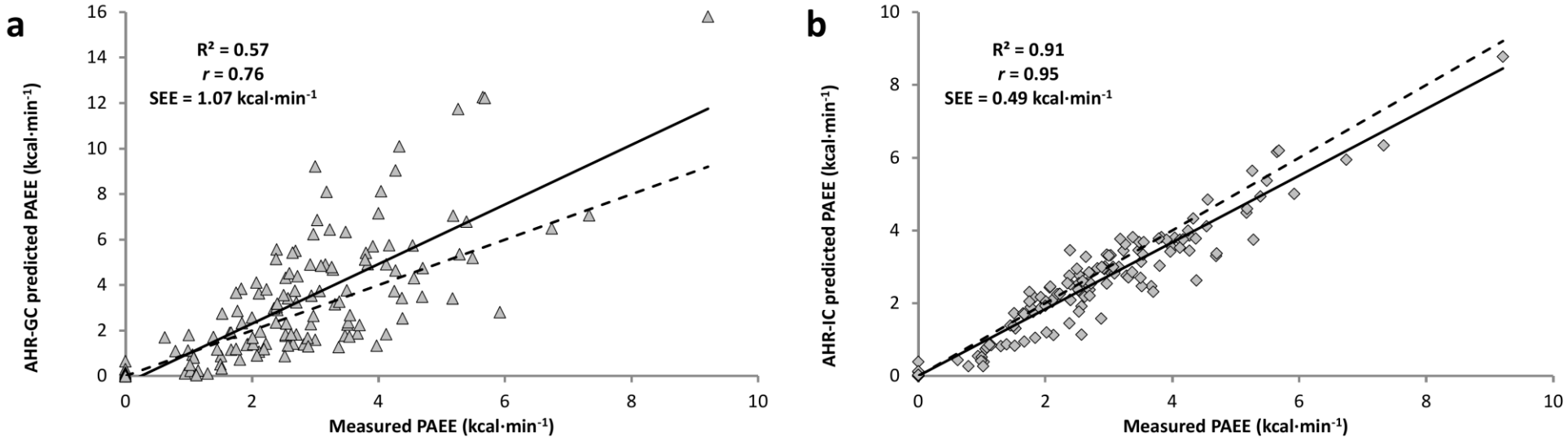

Figure 5.3: Scatterplots showing the relationship between criterion PAEE and predicted PAEE using GC (a) and IC (b). The *straight line* represents the best fit, and the *dashed line* indicates the line of identity

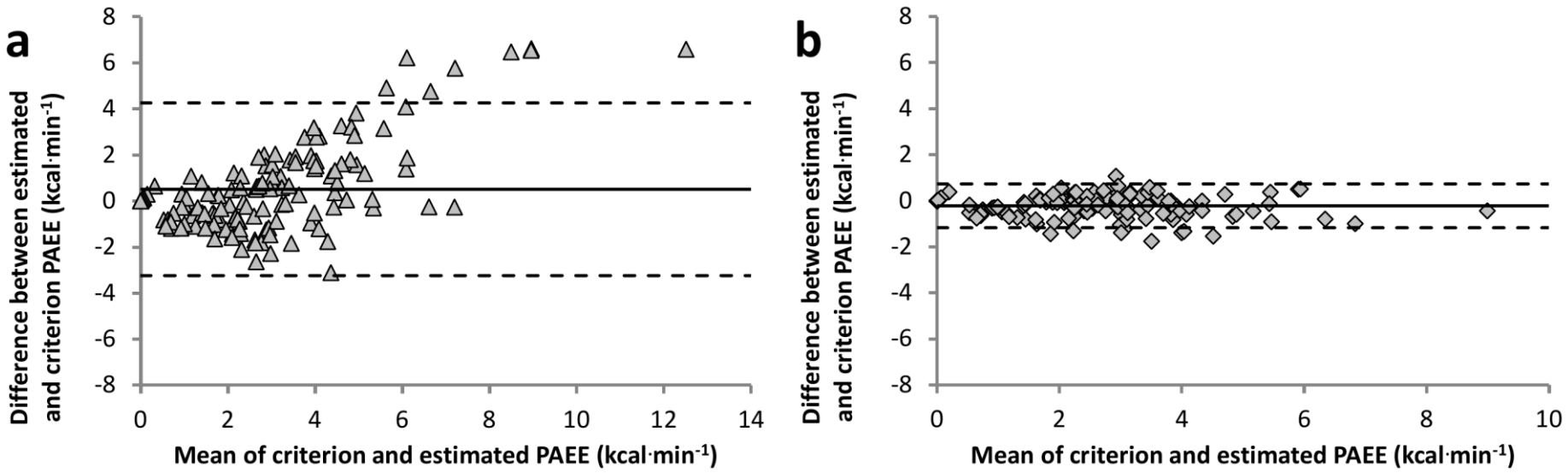

Figure 5.4: Bland and Altman plots for the criterion and estimated PAEE, using GC (a) and IC (b). *Bold line* represents the mean difference and *dashed lines* represent the upper and lower 95% LoA

Table 5.3: Mean Signed Error (MSE) and Mean Absolute Error (MAE) expressed as kcal·min^{-1} and a percentage of predicted PAEE for the GC and IC

Activity	MSE (kcal·min^{-1})		Mean percentage error (%)		MAE (kcal·min^{-1})		Mean absolute percentage error (%)	
	GC	IC	GC	IC	GC	IC	GC	IC
Resting	0.08 ± 0.18	0.05 ± 0.10	-	-	0.08 ± 0.18	0.05 ± 0.10	-	-
Folding clothes	-0.30 ± 0.75	-0.46 ± 0.17	-19.1 ± 78.9	-43.1 ± 16.2	0.68 ± 0.39	0.46 ± 0.17	66.3 ± 43.5	43.1 ± 16.2
3km·hr^{-1}	-0.08 ± 0.98	-0.16 ± 0.41	-4.3 ± 52.6	-8.5 ± 21.5	0.80 ± 0.52	0.30 ± 0.31	43.1 ± 28.0	16.2 ± 16.0
4km·hr^{-1}	0.34 ± 1.43	-0.10 ± 0.49	12.9 ± 53.8	- 3.8 ± 20.7	1.07 ± 0.97	0.32 ± 0.37	42.4 ± 33.9	13.4 ± 15.8
5km·hr^{-1}	0.83 ± 2.37	-0.14 ± 0.41	24.1 ± 65.6	-4.4 ± 12.7	1.83 ± 1.66	0.34 ± 0.25	56.5 ± 38.6	10.4 ± 8.1
6km·hr^{-1}	1.18 ± 2.65	-0.43 ± 0.45	26.8 ± 62.0	-9.5 ± 12.0	2.23 ± 1.79	0.50 ± 0.37	54.7 ± 37.5	12.0 ± 9.3
7km·hr^{-1}	0.77 ± 2.68	-0.55 ± 0.71	19.1 ± 59.3	-11.0 ± 15.3	2.15 ± 1.68	0.68 ± 0.57	48.6 ± 36.6	14.2 ± 12.0
4km·hr^{-1} (+ 8% of body mass)	0.80 ± 1.89	0.04 ± 0.52	28.4 ± 63.4	3.1 ± 21.6	1.50 ± 1.36	0.37 ± 0.36	56.8 ± 37.7	15.6 ± 14.7
4km·hr^{-1} (2% gradient)	0.93 ± 2.27	-0.08 ± 0.52	23.3 ± 60.1	-4.1 ± 16.3	1.62 ± 1.81	0.40 ± 0.32	47.5 ± 42.2	12.5 ± 10.8
4km·hr^{-1} (3% gradient)	0.58 ± 2.34	-0.50 ± 0.51	19.7 ± 72.6	11.9 ± 12.7	1.74 ± 1.60	0.56 ± 0.44	50.4 ± 54.1	13.6 ± 10.6
All Activities	**0.51 ± 1.90**	**-0.22 ± 0.49**	**14.6 ± 63.2**	**-10.1 ± 20.7**	**1.35 ± 1.44**	**0.39 ± 0.37**	**51.4 ± 38.9**	**16.8 ± 15.8**

5.3.2. Twenty-Four-Hour Record

The mean ± SD reference method-derived PAEE (self-reported PA log) was 662 ± 353 kcal·day^{-1}, but predicted to be 631 ± 428 kcal·day^{-1} by GC, and 588 ± 500 kcal·day^{-1} by IC. There were no significant differences in predicted PAEE between the reference standard and both AHR methods. PAEE, quantified by the reference method, was very strongly associated with IC (R^2 = 0.50, *P* = 0.03) but only moderately associated with GC (R^2 = 0.16, *P* = 0.24) (Figure 5.5). The SEE were 269 and 365 kcal·day^{-1} for the IC and GC, respectively.

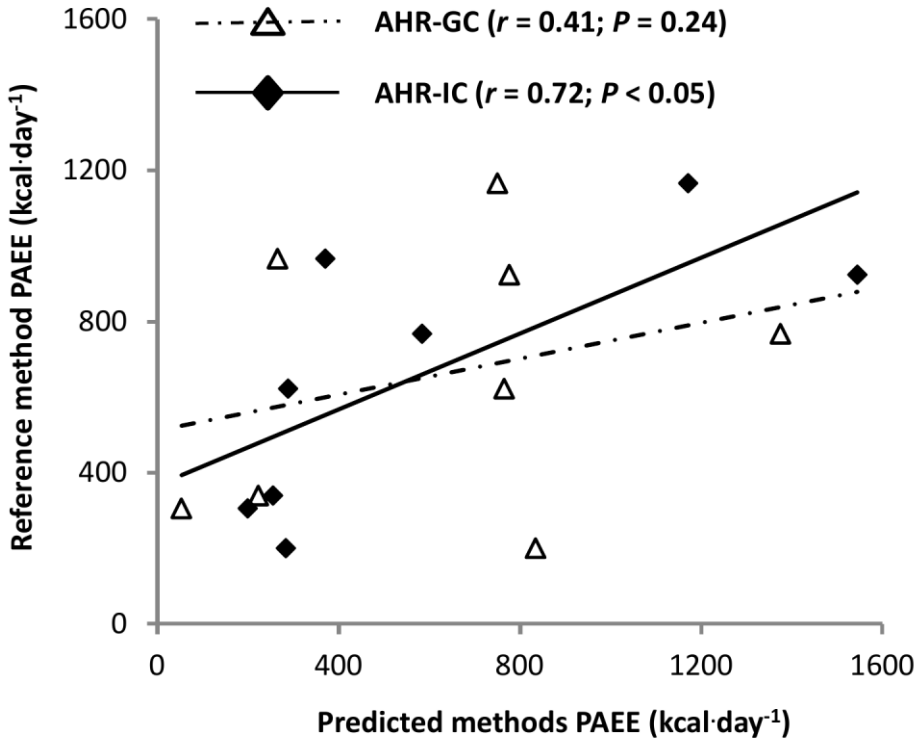

Figure 5.5: The relationship between predicted PAEE GC (white open triangle: *dash/ dot line*) and IC (black diamond: *solid line*) against the reference physical activity log method

5.4. DISCUSSION

This study aimed to assess the validity of using a multi-sensor (AHR) device to predict PAEE in a heterogeneous sample of wheelchair users. These results show that, accounting for inter-individual variance by conducting individual HR calibration, can improve the accuracy of predicting PAEE. IC better estimated PAEE than GC and explained an additional 34 percent of the variance in PAEE (91% vs 57%), measured across a range of activities conducted in a controlled laboratory environment. The findings seem intuitive given the large inter-individual variance in cardiovascular function and response to exercise in wheelchair users. These findings highlight the importance of using individual heart rate calibration when practitioners and researchers use multi-sensor devices, incorporating physiological signals, to predict PAEE in wheelchair users.

Initial research into the validity of using another multi-sensor activity monitor (Sensewear) in wheelchair users revealed sizeable EE estimation errors ranging from 24.4 to 125.8% during activities from resting and deskwork to wheelchair propulsion and arm crank ergometry (Hiremath & Ding, 2011a). This error was likely a result of the manufacturer's prediction model not being able to classify the types of upper body physical movements commonly performed by wheelchair users. More recent work (Hiremath *et al.*, 2012), using new prediction models to track these upper body movements, has reported reduced mean absolute estimation errors of 16.8%. This is identical to that reported for IC in this present study. Even tri-axial accelerometers worn on the wrist have been found to predict 86 and 74% of the variance in predicting PAEE and $\dot{V}O_2$, respectively, in wheelchair users across a range of propulsion speeds (Chapter 3) and in a laboratory environment (Garcia-Masso *et al.*, 2013). However, these previous studies did not include gradients or additional mass on the chair.

Chapter 4 found that raw acceleration outputs from a GENEActiv device worn on the wrist explained 77% of the variance in predicting PAEE. However, this device using developed regression equations, under-predicted PAEE by 10.6 and 20.3% during the 2 and 3% gradients, respectively. Mean absolute error was also 22.6% for the eight percent

of body mass task (Chapter 4). In the present study, IC under-predicted by 4.1% and over predicted by 11.9% during the 2 and 3% gradients, respectively. Furthermore, MAE was not noticeably elevated for the gradient and load carriage tasks compared to 4km·hr^{-1} trial. This supports the fact that, integrating individually calibrated HR and acceleration data, captures the differing energy cost of activities despite similar acceleration profiles.

Heart rate is advantageous as a physiological variable as it increases linearly and proportionately with exercise intensity and thus oxygen uptake (Chen *et al.*, 2012). Heart rate alone in this study explains 57% of the variance in the prediction of PAEE. Garcia-Masso *et al.*, (2014) found when extracting 7 features from HR signals that a complex artificial neural network model provided a better estimation of oxygen uptake (r= 0.88, MSE= 4.4ml·kg^{-1}·min^{-1}) than a multiple linear model (r= 0.78; MSE= 7.63 ml·kg^{-1}·min^{-1}), during simulated laboratory activities. Whilst new mathematical models may offer an improvement, extracting data to provide rich information is currently difficult for practitioners. Simply using raw HR data may not be useful to predict PAEE due to a large degree of inter-individual variance in the HR-PAEE relationship (Brage *et al.*, 2007). Some of the inter-individual variance can be accounted for by using HR above resting level and adjusting for gender (Brage *et al.*, 2004; Brage *et al.*, 2005). These variables are factored into the AHR proprietary algorithms (GC), which might help capture generic differences in cardiovascular function.

As HR at lower exercise intensities is affected by other factors, such as psychological or thermal stress, integration of acceleration values may offer a more reliable prediction of PAEE. This is an issue when monitoring a population who predominantly perform sedentary and light intensity activities in a free-living environment (Ginis *et al.*, 2010a). To counteract this issue with HR, during low intensity activities the branched model equation (Brage *et al.*, 2004), intrinsic to the AHR software, gives a relatively low weighting to HR in the prediction of PAEE. For higher intensity activities, where HR has been shown to be more accurate in predicting PAEE for individuals with SCI (Hayes *et al.*, 2005), the AHR utilises the branch which favours HR over acceleration in the prediction of PAEE (Figure 5.2). Even with these processing features our results suggest

that combining HR and acceleration along the longitudinal axis of the trunk explains no more of the variance in the prediction of PAEE than HR alone (57%), when using GC.

Whilst multi-sensor technologies have potential for increasing the accuracy of assessing PAEE in various populations, it could be that another processing step is necessary in a heterogeneous population of wheelchair users that display substantial HR variability as a result of differing disabilities and resulting cardiovascular function. Hayes *et al.*, (2005) found that HR alone only explained 8.5% of the variance in measured EE, but this improved to 55% when an individual calibration was performed. This individual calibration was similar to that performed in this current study whereby an individualised relationship between HR and $\dot{V}O_2$ was established and applied. Likewise these results indicate an improvement in the accuracy of AHR predicted PAEE when an individual HR calibration option was utilised.

The movement patterns of wheelchair users are primarily restricted to the upper limbs and such exercise appears to elicit a somewhat different $\dot{V}O_2$-HR relationship. Raymond *et al.*, (1997) showed that $\dot{V}O_2$ was 25 % higher (1.58 $L \cdot min^{-1}$ vs. 1.26 $L \cdot min^{-1}$), but HR was 13 % lower (132 $b \cdot min^{-1}$ vs. 149 $b \cdot min^{-1}$) during combined arm & electrical stimulation-induced leg cycling exercise compared to arm cranking exercise alone at the same power output in individuals with SCI. The lack of lower limb muscle innervation and absence of the skeletal muscle pump leads to a reduction in venous return and a compensatory increase in HR to maintain cardiac output. As such, the gradient of the $\dot{V}O_2$-HR relationship for upper body exercise may be shallower than for lower body exercise. The GC model derived from Brage *et al.*, (2007) and utilised here was designed to predict energy expenditure during ambulation. Therefore, a given HR could be misinterpreted as corresponding to a higher $\dot{V}O_2$ resulting in an elevated PAEE estimate. This attenuated HR response to upper body exercise could account for the 14.6% mean over-prediction across all activities for the GC.

Visual inspection of Figure 5.4a indicates a considerable degree of heteroscedasticity, and the sizeable 95% LoA (± 3.75 kcal·min^{-1}) shows a large degree of inter-individual variance for the GC, potentially linked to disability aetiology. For individuals with higher level lesions (≥ T6: n = 8) normal cardiovascular homeostasis can be disrupted (Bauman *et al.*, 1999). Autonomic nervous system disruption can result in a blunted CV response to exercise and, in some instances, an absence of sympathetic drive to increase HR above 130 b·min^{-1} (Jacobs & Nash, 2004). Our results reflect the variability in HR responses to exercise in this population, with peak HR responses ranging from 130 to 200 b·min^{-1}. Another factor known to have an impact on the HR-PAEE relationship is the variance in fitness (Keytel *et al.*, 2005). Our sample had a wide spread of aerobic capacities, with peak oxygen uptake ranging from 16.7 to 41.1 ml·kg^{-1}·min^{-1}. The range in aerobic capacity in wheelchair users is large and reflects the degree of functional impairment and autonomic nervous system disruption in certain conditions (Janssen *et al.*, 2002). Considering the type of exercise performed, the attenuated CV responses to exercise and large variation in fitness we advocate that an individual HR calibration is of upmost importance when assessing PAEE in wheelchair users.

The majority of PA validation research in this population has mostly been performed in a controlled-laboratory environment. In this study free-living 24 hr PAEE was compared to a self-reported PA log to confer concurrent validity. This reference method has been used previously in wheelchair users (Warms *et al.*, 2008). Our analysis was conducted using a relatively small subsample of participants, as PA logs from five of the full-time wheelchair users lacked detailed information to derive an accurate estimation of PAEE. This is perhaps unsurprising considering that the PA compendium for individuals with disabilities (Conger & Bassett, 2011) only describes the energy cost of 63 wheelchair activities. Consequently, this offers considerably less variety to code activities than the 821 specific activities included in the updated version of the compendium of physical activities for able-bodied individuals (Ainsworth *et al.*, 2011). In summary, this highlights a significant limitation with using self-report PA methods in this population. However, daily PAEE determined from the reference method and AHR were similar to that reported using doubly-labelled water in a small cohort of individuals with SCI 680 ± 389 kcal·day^{-1} (Tanhoffer *et al.*, 2012). Considering the difficulties with criterion PAEE monitoring

during free-living for individuals who use a wheelchair, other researchers have encouraged simply evaluating the agreement and disagreement between measures (Tudor-Locke & Myers, 2001). In this study, IC 24-hr free-living predicted PAEE was significantly associated with the reference method (r = 0.72) whereas GC was not (r = 0.41).

While only one activity of daily living was included, this allowed us identify the relatively large error estimate, even with the individual calibration (IC error 43.1%). This reflects the somewhat atypical movement patterns associated with such tasks. More activities of daily living and those of moderate-vigorous intensity should be included in future studies. There was a diverse range of disabilities within our participant sample, yet this is in keeping with previous research (Conger *et al.*, 2014) and in accordance with best practice recommendations for PA validation studies (Bassett *et al.*, 2012). Many previous studies have focussed solely on individuals with SCI (Hiremath *et al.*, 2012; Tanhoffer *et al.*, 2012) but, compared to the present study, these previous results are limited in their generalisability to other individuals who use wheelchairs.

In conclusion, this study demonstrated for the first time that PAEE can be accurately predicted using a multi-sensor device, which incorporates acceleration and individual HR calibration, in wheelchair users. The error associated with predicting PAEE in manual wheelchair users, is improved approximately threefold by using individual heart rate calibration. Considering the inter-individual variance in cardiovascular response to exercise is high among individuals who use wheelchairs we advocate the importance of using an individual HR calibration. Through the meticulous method development conducted in chapters 3, 4 & 5 we believe that we have validated tools capable of accurately predicting PAEE in wheelchair users during habitual free-living. As such we plan to utilise the GENEA-W (Chapter 4) and AHR with individual calibration (Chapter 5) to monitor behavioural changes during a RCT to assess the link between PA and metabolic health in individuals with SCI (Chapter 6).

CHAPTER 6: THE IMPACT OF A HOME-BASED EXERCISE INTERVENTION ON MARKERS OF METABOLIC AND CARDIOVASCULAR HEALTH IN INDIVIDUALS WITH CHRONIC PARAPLEGIA

6.1. INTRODUCTION

Those with SCI and paralysis (~35,000 individuals in the UK) are at increased risk of chronic disease. In comparison to age and sex matched able-bodied counterparts, adults with SCI are four-times more likely to develop type-2 diabetes (Bauman & Spungen, 1994) and three times more likely to have circulating high-density lipoprotein (HDL) concentrations < 1.94 $mmol \cdot L^{-1}$ (Lavis *et al.*, 2007). Such metabolic abnormalities are also associated with endothelial dysfunction that, when combined, predisposes individuals to the development of atherosclerosis and associated cardiovascular events (Beckman *et al.*, 2002). Consequently, CVD is the leading cause of mortality in individuals with SCI, also occurring earlier in the lifespan than able-bodied controls (Garshick *et al.*, 2005).

SCI creates a complex pathology whereby level and completeness of injury, plus other lifestyle factors, can lead to increased sedentary behaviours and alterations in body composition. Simplistically, overweight and obesity are caused by an energy imbalance, be it through increased energy intake and/or reduced physical activity levels. It was previously thought that adipose tissue was just a store for energy in the form of TAG, which are a combination of fatty acids and glycerol. However, adipose tissue is more complex, secreting and responding to various hormones that are involved in the regulation of appetite, energy expenditure, insulin sensitivity, inflammation, immunity, endocrine and reproductive systems as well as bone metabolism (Fantuzzi, 2005). The hormones produced by the adipose tissue are termed 'adipokines'. These impact on metabolic control, via adipocyte insulin resistance, and consequently increase concentrations of blood lipids (Kahn *et al.*, 2006). Increased visceral and subcutaneous adipose tissue, common in individuals with SCI (Edwards *et al.*, 2008), has been associated with a whole array of chronic disease indicators, including hyperlipidaemia, hypertension, insulin

resistance, increased pro-inflammatory mediators and prothrombotic agents (Grundy, 2004; Hutley & Prins, 2005; Ritchie & Connell, 2007).

The contribution of regular PA to achieve weight balance, metabolic control and cardiovascular fitness is well documented and broadly accepted in the able-bodied population (Kesaniemi *et al.*, 2001; Haskell *et al.*, 2007). In an able-bodied experimental model, short-term (i.e. one week) overfeeding and reduced PA resulted in impaired metabolic function (Walhin *et al.*, 2013). However, these changes were mostly counteracted by vigorous-intensity exercise, even in the face of an additional energy surplus and subsequent weight gain. Therefore, it is possible that exercise has independent effects on health besides its role in contributing to energy balance and body composition.

Involvement in sports and recreation is often restricted by loss of voluntary motor control, as well as autonomic dysfunction and early onset of muscle fatigue (Nash, 2005). There are also numerous psychosocial and environmental barriers to exercise for individuals with SCI such as reduced self-esteem, lack of accessible facilities, unaffordable equipment, fear of injury and parental or medical over protection (Kehn & Kroll, 2009). Therefore a convenient and accessible form of exercise is necessary to maximise exercise compliance in certain disabled populations. A recent 16-week randomised controlled trial (RCT) (Bakkum *et al.*, 2015), advocated that researchers should consider how to make exercise interventions more feasible to individuals with SCI in order to avoid large drop-out rates. Home-based arm ergometer exercise has previously been utilised in polio patients (Murray *et al.*, 2012) and would overcome transportation barriers and the lack of accessible exercise equipment.

The current literature on PA research for individuals with SCI has recently been systematically classified (Nery *et al.*, 2013). Most studies between 2000 and 2012 have been categorised as either: Phase 1 (linking PA and health outcomes); Phase 2 (validating or developing PA monitors) or; Phase 3 (identifying factors influencing behaviour or examining theories of behaviour change). This correctly implies that this field is still in

the early stages of development and research should focus on Phase 4 (evaluating interventions) and Phase 5 (disseminating health promotion policies and translating research into practice). Based on the inconsistent findings across studies, concluded via a systematic review requested by the Consortium for Spinal Cord Medicine (Carlson *et al.*, 2009), it would appear that current evidence is insufficient to determine whether exercise improves carbohydrate and lipid metabolism disorders among adults with SCI. These inconsistencies may well be caused by considerable heterogeneity in study participants, the type of exercise programme and/or the outcome measures adopted. Researchers have been encouraged to employ more rigorous methodological designs to reduce bias and confounding variables, and include a variety of outcome measures to reflect the potential benefits of exercise on health and function in this cohort (Silverman *et al.*, 2012).

Thus, in accordance with the above recommendations, whereby confounding variables are controlled, we proposed a rigorous trial design (randomised controlled trial) and associated methodology focussing on a well-defined study population (individuals with chronic paraplegia). We hypothesised that moderate-intensity upper body exercise would improve biomarkers of cardiovascular and metabolic health. Secondary hypotheses related to upper body exercise improving body composition, cardiorespiratory fitness and perceptions of wellbeing. Poor physical function can compromise independence and quality of life in individuals with SCI and, as such, an emphasis will also be placed on quantifying these parameters. In order to overcome some of the methodological problems in previous studies, we have adopted a contrived study design where exercise equipment is given to the participant, thus removing a psychosocial barrier to performing PA. However, we will also quantify compliance with the intervention periodically, monitoring PA using validated monitors (Chapters 4 & 5).

6.2. METHODS

6.2.1. Trial Design

A pre-post randomised parallel group design was used for this study (registration number: ISRCTN57096451), with participants assigned to a 6-week exercise intervention (INT)

or control period (CON). There is limited and conflicting data on the effect of various exercise interventions on carbohydrate metabolism and insulin sensitivity in individuals with SCI. Using a similar arm crank exercise protocol (Time; 18 to 32 min, Frequency; 2 x wk, Intensity; 65 – 75% heart rate reserve (HRR), Duration; 16 wks) to that in the present study, Bakkum *et al*., (2015) reported an improvement in insulin sensitivity (assessed via HOMA-IR) of -0.5 ± 0.2. Based upon these data (Cohens *d* = - 2.5) it was estimated that 6 participants are required to detect a statistically significant change in insulin sensitivity in the exercise intervention group. The power was 0.95 and the alpha was set at 0.05. Participants performed 32 individual training sessions compared to the 24 proposed in this current study. With this in mind, plus a 20% withdrawal rate associated with longitudinal testing in the INT group for this population, twenty (INT; 12, CON; 8) participants with chronic paraplegia were recruited to participate in this study.

The first nine participants were randomly allocated by a third party to a 6-week exercise intervention (INT) or control period (CON). Within a highly heterogeneous population (individuals with SCI), we decided to use minimisation (Altman & Bland, 2005) to ensure balance between the two groups for several baseline characteristics (age, body mass, FM, level of injury, physical activity level). Subsequent participants (n = 11) that enrolled on the trial were therefore allocated to either the INT or CON group in order to balance the groups in the above variables of interest. The INT group completed 6 weeks of arm crank ergometry in a home-based environment, following an individualised exercise prescription. The CON group were asked to maintain their normal habitual lifestyle for a 6-week period.

The duration and the dose of the intervention were selected on the balance of available literature regarding exercise in this population. Various exercise intervention protocols have been employed in studies of participants with SCI, including arm crank ergometry (ACE; de Groot *et al.*, 2003), functional electrical stimulation (FES; Jeon *et al.*, 2002) or wheelchair propulsion (Bougenot *et al.*, 2003). Previous interventions have been 5 to 57 weeks in duration, incorporating 2 to 3 exercise sessions per week, lasting 30 to 60

minutes per session. Therefore a 6-week ACE intervention was designed, comprising 4 x 30- 45 min sessions per week, in order to provide a considerable exercise stimulus. It is evident that moderate ACE at an intensity between 60 – 80% of max heart rate (HR) or 60 – 65% $\dot{V}O_{2peak}$, seems sufficient to improve aerobic capacity (Hicks *et al.*, 2011). However, little is known regarding the impact of this intensity of exercise on biomarkers of metabolic and cardiovascular health in individuals with SCI.

The primary outcome measures were changes in insulin sensitivity and glycaemic control, reflected by fasting values and incremental Area Under the Curve (iAUC), measured at baseline and follow-up. Other blood markers relating to metabolic control and inflammation were secondary outcome measures, along with fitness and body composition.

6.2.2. Recruitment

It was previously stated that RCT participant recruitment, especially in the absence of direct access to a clinical population, requires considerably more resources and time than initially anticipated in order to achieve adequate enrolment (Nary *et al.*, 2011). In a systematic review, Ross *et al.*, (1999) described patient barriers to recruitment for RCTs. These included: (a) additional demands of the trial increasing participant burden and (b) patient preferences for or against a particular treatment. Barriers to research participation are perhaps even more exaggerated for people with disabilities due to complex health problems (Kosma *et al.*, 2004), lack of transportation (Yilmaz, 2006), cognitive impairments and financial stress (Bell *et al.*, 2008). With this in mind, we set up arm crank ergometers in participants' own homes, thereby minimising any potential accessibility/transport barriers to participants becoming more active. Transportation needs is a major participation barrier for individuals with disabilities, and so travel expenses to the University for laboratory testing were reimbursed. Whilst participants may have had a strong preference to receive the intervention and not be in the control group, we tried to overcome this by offering a waiting-list control. Participants in the control group were offered the opportunity to participate in the intervention once they had completed the control period.

We expected recruiting individuals with SCI to be more complex than recruiting non-disabled populations and carefully considered the recruitment challenges proposed by Nary *et al.*, (2011). Without direct access to clinical populations it was essential that we nurtured relationships with key gatekeepers. The University's press release for this RCT was endorsed by the English Federation for Disability Sport and various recruitment material was promoted by nationwide charities such as Spinal Injuries Association (SIA), ASPIRE, Back-up Trust and Wheelpower. Posters and flyers were displayed in the waiting areas of a SCI rehabilitation centre (The London Spinal Cord Injury Centre (LSCIC), Stanmore). Initial recruitment strategies had focussed on working with NHS SCI specialists across the South of England. One of the lessons learned for Nary *et al.*, (2011) was *'don't assume health care agencies will value research activities and welcome and facilitate study recruitment'*. Unfortunately, for reasons unknown, with the exception of LSCIC, other SCI rehabilitation centres were reluctant to allow study information to be disseminated to their patients, which made study recruitment even more difficult. Other media outlets (television- BBC Points West and radio- BBC Radio Bristol and Wiltshire), as well as internet forums and social networking sites were used to facilitate ongoing recruitment. Our group was also actively involved with public engagement activities to create a visible public profile for the Centre for DisAbility Sport and Health. Previous participants (Chapter 3 & 4) who agreed to be contacted and met the inclusion criteria of the trial were notified directly about the study via email. Unfortunately, a detailed log of how interested individuals learned about the study was not maintained. Anecdotally most of the exposure was generated through television and an advertisement in FORWARD magazine (SIA bi-monthly publication).

Over the 11 months of recruitment, seventy-four persons with SCI expressed an interest in participating in this study. Thirty-six percent (n = 27) were deemed ineligible during an initial telephone consultation and the reasons described in Figure 6.1. Fliers and posters were produced, providing a phone number and email address for interested individuals to contact the PI. Upon initial contact (be it email or telephone), the study was briefly described and those interested in enrolling were asked to read a detailed Participant Information Sheet and complete a health screen questionnaire. Interested individuals were

given 48 hours before they were screened via a telephone conversation to ascertain eligibility. There was a focus on establishing a good rapport at this initial contact and also as individuals progressed through the enrolment process. Reaching potential participants is a crucial first step, although retaining eligible participants is equally important. Of the 47 eligible participants, 21 (45%) attended baseline assessments and 26 ultimately opted not to participate, 22 (85%) of whom could not be contacted or did not provide a reason why. This is considerably better than the 11.2% of participants who received an invitation letter and eventually participated in a 16-week hybrid and hand-cycle RCT (Bakkum *et al.*, 2015).

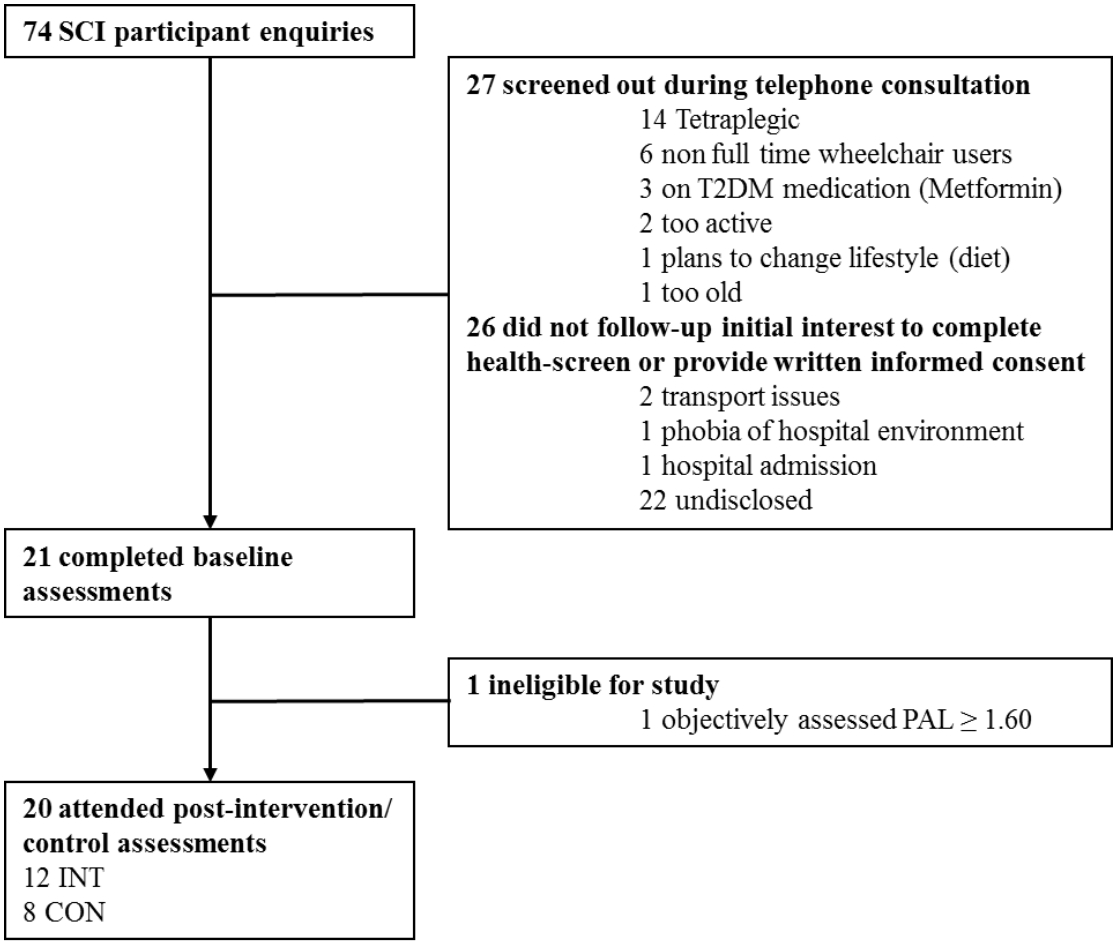

Figure 6.1: Flow of participants through the study

6.2.3. Participants

Twenty one inactive individuals with a chronic (>1 year), spinal cord lesion between T3 to L3 attended baseline assessments. Participants were recruited based on the following inclusion criteria: aged 18 – 65 years; classified as inactive (physical activity level (PAL) < 1.60); weight stable (± 3 kg) for at least 6 months and no conscious plans to change diet or exercise behaviours. Participants completed a health-screen questionnaire (Appendix) to determine eligibility and also provided written and verbal consent consistent with the requirements of the South West (Exeter) National Research Ethics Service Committee, who approved this study (REC reference number 14/SW/0106). Volunteers with neurological incomplete injuries were considered eligible if they were wheelchair users for >75% of their waking day. Individuals with active medical issues including pressure sores, urinary tract infections, heart disorders, cardiovascular contra-indications for testing (Goosey-Tolfrey, 2007) or musculoskeletal complaints of the upper extremities were excluded. One participant was excluded for having a PAL ≥ 1.6; thus, twenty participants (INT, n = 12: CON, n = 8) completed the full experimental procedures and are included in this data analysis (Table 6.1).

Habitual PA was estimated over a representative 7-day period at baseline using the AHR-IC (Chapter 5) and the GENEActiv-W using developed and cross-validated algorithms (Chapter 4). Participants wore these monitors continuously (24 hrs a day) and were instructed only to remove them when showering or bathing.

Table 6.1: Participant Characteristics

Variable	INT (n = 12) (9M/3F) (10A/2C†)		CON (n = 8) (6M/2F) (7A/1C†)		*P* value
	Mean ± SD	Range	Mean ± SD	Range	
Age (y)	46 ± 6	32 - 58	48 ± 10	36 - 61	0.68
Height (m)	1.73 ± 8.40	1.60 – 1.85	1.73 ± 7.48	1.61 – 1.81	0.98
Body Mass (kg)	76.9 ± 13.7	54.4 – 99.6	76.8 ± 11.3	59.6 – 92.4	0.98
Fat Mass (kg)	28.2 ± 10.4	14.4 – 56.8	26.0 ± 6.8	17.0 – 36.7	0.57
Waist circumference (cm)	91.4 ± 6.3	76.6 – 98.8	93.3 ± 6.8	80.1 – 101.2	0.53
TSI (y)	15 ± 11	3 - 32	20 ± 10	4 - 39	0.35
Lesion level*	16 ± 4	11 - 21	16 ± 4	12 - 22	0.98
RMR (kcal·day^{-1})	1475 ± 199	1096 - 1753	1474 ± 232	1152 - 1899	0.81
$\dot{V}O_2$ peak (l·min^{-1})	1.41 ± 0.51	0.84 – 2.35	1.47 ± 0.59	0.88 – 2.21	0.89
$\dot{V}O_2$ peak (ml·kg^{-1}·min^{-1})	18.0 ± 5.0	12.6 – 29.4	18.8 ± 6.21	11.6 – 27.3	0.76
Maximal workload (W)	77 ± 29	42 - 126	75 ± 39	35 - 147	0.90
PAL	1.37 ± 0.11	1.20 – 1.51	1.38 ± 0.12	1.23 – 1.59	0.87
Sedentary (min·day^{-1})[a]	1220 ± 125	1039 - 1413	1226 ± 105	1117 - 1366	0.90
Light (min·day^{-1})[a]	205 ± 116	28 - 390	191 ± 95	52 - 303	0.77
Moderate (min·day^{-1})[a]	15 ± 15	0 - 45	21 ± 25	0 - 78	0.57
Vigorous (min·day^{-1})[a]	0 ± 0	0 - 0	1 ± 3	0 - 8	0.29

† The American Spinal Injury Association (ASIA) impairment scale.

A = complete, C = incomplete

* Lesion level was converted to a continuous variable for each vertebrae (C1 = 1; C8 = 8, T1 = 10; T12 = 20, L1 = 21; L5 = 25)

[a] Sedentary = < 1.5 METs; Light = < 3 METs; Moderate = ≥ 3 METs; Vigorous = ≥ 6 METs

6.2.4. Design Summary

The first nine participants were randomly allocated using a block randomisation plan (fixed block size of 9; allocation ratio of 2:1; no stratification) selected by a third party to either the experimental group (exercise intervention) or control group.

1) 4 x 45 minutes per week moderate-intensity (60-65% $\dot{V}O_2$ peak) arm crank exercise (INT) n = 12. This equated to an additional 799 Kcal·week^{-1} energy expended above rest through increased PA.
2) Control group, maintenance of normal lifestyle (CON) n = 8

The experimental design is summarised below (Figure 6.2). Participants in the INT group completed a 6-week individually prescribed and progressive arm crank ergometry exercise programme, whereas participants in the CON group were asked to maintain their existing lifestyle.

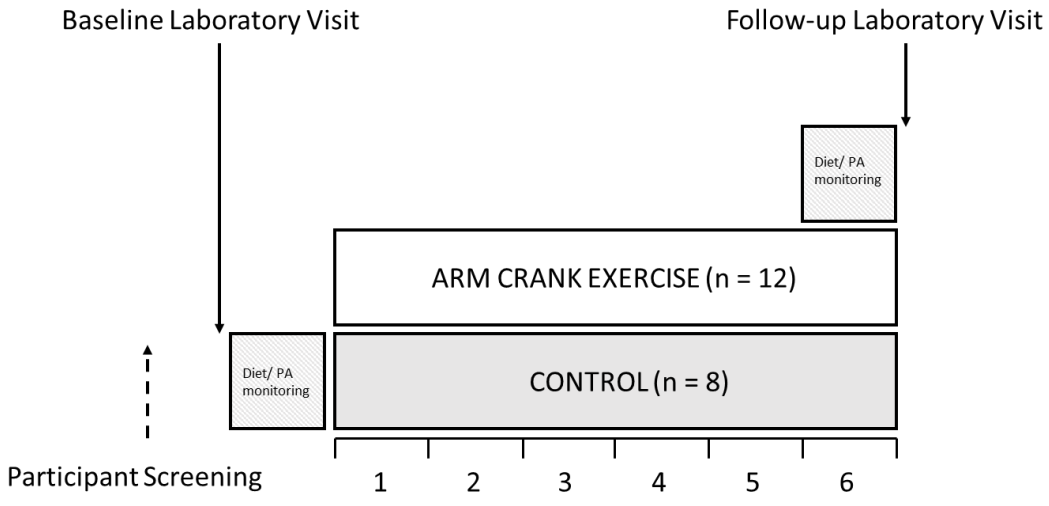

Figure 6.2: Schematic of study design

All participants underwent pre- and post- intervention testing for fasting lipid profile, markers of inflammation, insulin sensitivity, body composition and peak aerobic capacity. Insulin sensitivity was assessed during an oral glucose tolerance test (OGTT) and peak aerobic capacity was assessed during an incremental arm crank ergometer test to volitional fatigue. Baseline testing was performed approximately two weeks before training/control period commenced. Importantly, this allowed exactly 8 weeks between baseline and follow-up testing which ensured that female participants were at the same stage of their menstrual cycle. Pulido & Salazar, (1999) found considerable variation in insulin sensitivity during different phases of the menstrual cycle. Therefore, testing for the two eumenorrheic women in this study was conducted during the follicular phase of the menstrual cycle (3 – 10d after onset of menses). Of the other three female participants two were postmenopausal, and one had been amenorrheic since sustaining her SCI. Participants abstained from strenuous exercise, caffeine (tea/coffee) and alcohol intake the day before each trial. The final exercise bout prescribed in the INT group was > 36 hrs before follow-up testing in order to reduce acute effects from the previous bout of exercise. Participants were also asked to drink one pint of water on the morning of testing to ensure adequate hydration.

6.2.5. Main Trial Days

The same experimental procedures were completed on both baseline and follow-up trial days. On arrival at the centre for DisAbility Sport and Health laboratory at 08.30 ± 1 h, following an overnight fast (≥10 h), participants voided and had body mass measured in light clothing using platform wheelchair scales (Detecto ® BRW1000, Missouri, USA) as described in Chapter 3. Participants transferred onto the Dual-energy X-ray absorptiometry (DEXA) scanning table (Discovery, Hologic, Bedford, UK). Supine length was measured in centimetres to the nearest tenth, along the left hand side of the body using a non-elastic tape measure (Lufkin, US). Body composition was estimated using a whole-body DEXA scan. After descriptive characteristics were entered into the QDR for Windows software (Hologic, Bedford, UK), participants were positioned centrally on the scanning table with feet spaced evenly either side of the mid-point of the body, with arms placed mid-prone with an equal gap to the trunk on both sides. For

participants who experienced leg spasms, knees were flexed at a 45º angle supported by a pillow. An individual trained in ionising radiation (medical exposure) regulations performed the scan, whilst participants were instructed to remain as still as possible. Scans were analysed for total and regional (trunk, legs, arms) FM, LM, bone mineral content and fat percentage, following the guidelines described in the QDR for Windows manual (Hologic, Bedford, UK). All scans were conducted following a daily QC scan of a Spine Phantom as per the manufacturer's instructions.

RMR was estimated by indirect calorimetry from expired air samples collected into 200 L Douglas Bags (Hans Rudolph, MO, USA) via falconia tubing (Baxter, Woodhouse and Taylor Ltd, Macclesfield, UK) with concurrent measurement of inspired air composition; a reliance of standard atmospheric concentrations was recently discouraged (Betts & Thompson, 2012). The process of indirect calorimetry has been described in detail in Chapter 3. In this instance, expired concentrations of O_2 and CO_2 were measured, in a known volume of the sample using paramagnetic and infrared analysers, respectively (MiniMP 5200, Servomex Ltd., Sussex, UK). Samples for RMR were collected in accordance with best practice guidelines (Compher *et al.*, 2006). Participants also wore a Polar T31 heart rate monitor (Polar Electro Inc., Lake Success, NY, USA) during RMR measurement; resting heart rate values were averaged over the 20 minute collection period.

6.2.5.1. Oral Glucose Tolerance Test (OGTT)

A cannula (BD Venflon Pro, BD, Helsingborg, Sweden) was inserted into an antecubital vein and, a 25 ml fasting sample drawn. Participants then consumed 113ml of Polycal (Polycal, Nutricia Advanced Medical Nutrition, Trowbridge, UK) and 87 ml of water, equivalent to 75g of anhydrous glucose. Further 5 ml blood samples were drawn at 15 min intervals for the next 2 hours. The intravenous cannula was kept patent through periodic flushing with 0.9% NaCl (B.Braun, UK) infusion, with the first 5 ml of each blood draw discarded. Serum was obtained by dispensing whole blood from the syringe

into a serum separation tube, which was left to stand at room temperature for 15 min before centrifugation. Plasma was obtained by dispensing whole blood into tubes coated with ethylenediaminetetraacetic acid (EDTA) and immediately centrifuged. Samples were centrifuged (Heraeus Biofuge Primo R, Kendro Laboratory Products Plc., UK) at 5000 rpm for 10 min at 4ºC, with serum/plasma subsequently dispensed into 0.5 ml aliquots and immediately cooled on dry ice and then stored at -80ºC. Blood pressure (mmHg) was also measured during the final 15 minutes of the OGTT using an automated blood pressure monitor (Boso Medicus Prestige, Bosch + Sohn, Germany) as described in Chapter 4.

6.2.5.2. Submaximal and Peak Oxygen Uptake Exercise Testing

Approximately forty-five minutes after a standardised snack (556.8 kcal, 74.2g Carbohydrate, 26.7g Fat, 7.2 g Protein) participants performed an incremental submaximal arm crank ergometry test using a portable desktop ergometer (Monark compact rehab 871E, Dalarna, Sweden). This test lasted three 3-min stages, separated by a one min rest period during which the resistance was increased. Participants were instructed to maintain a cadence of 75 rpm throughout. A variety of power outputs was chosen that were sufficient to cover the relative exercise intensities (60 – 65% of $\dot{V}O_2$ peak) employed during training sessions in the INT group. During the final minute of each stage $\dot{V}O_2$ (measured using the online gas analysis system described in Chapter 4) and HR were averaged. This was to determine the relationships between $\dot{V}O_2$, exercise intensity (work rate) and HR in order to calculate the correct power output to obtain 60% and 65% of $\dot{V}O_2$ peak. Submaximal exercise testing was conducted on the same portable desktop ergometer that participants were assigned in their own home.

Approximately 15 min following the submaximal exercise test, participants completed a $\dot{V}O_2$ peak test on an electrically braked arm crank ergometer (Lode Angio, Groningen, Netherlands). This test has been described in Chapter 4. The power output to start the test was dictated by the data recorded during the submaximal test, with an initial power

eliciting approximately 65 – 75% of age-estimated maximum HR. This test usually lasted between 9 – 12 min, until the point of volitional exhaustion. A number of criteria were applied to determine whether this endpoint was reflective of a valid $\dot{V}O_2$ peak value. These were; (1) a peak RER value ≥ 1.1, (2) a peak heart rate ≥ 95 % of age-predicted maximum (200 $b \cdot min^{-1}$ minus chronological age) and an increase in $\dot{V}O_2 \leq 2$ $ml \cdot kg^{-1} \cdot min^{-1}$ in response to an increase workload (Goosey-Tolfrey, 2007). Each participant met at least two of these criteria. The EE and HR data from the final minute of each stage of both exercise tests was used to inform the individual calibration of the Actiheart as described in Chapter 5. Following approximately a 15 minute rest, work rate and HR necessary to elicit 60% of $\dot{V}O_2$ peak, determined through linear regressions, were checked using a 5 minute arm crank test on the portable desktop ergometer. Oxygen uptake was measured during the final 2 min of the test and compared to the value calculated to be representative of 60% of $\dot{V}O_2$ peak. If these values differed by more than 5% (n = 3), initial work rate for the first exercise session of the INT was adjusted accordingly.

6.2.6. Measures of Health and Wellbeing

Various questionnaires were administered during baseline and follow-up testing. Quality of Life and health status were measured using the SF-36 (Ware & Sherbourne, 1992) and EQ-5D-5L (Herdman *et al.*, 2011), with certain questions adapted for wheelchair propulsion instead of ambulation. The use of the SF-36 in individuals with SCI has previously been summarised in a review article (Ku, 2007). Compared with four other instruments used to measure health-related quality of life in persons with SCI, Leduc & Lepage, (2002) reported better validity of the SF-36 with regard to quantifying the health status of participants. Original responses were transformed into recorded values (taking into account items which were negatively scored) and specific questions were averaged to return a value for general health using the RAND 36-Item Health Survey 1.0 scoring method. This value will range from 0 to 100, with 100 representing the best health possible. The EQ-5D-5L was developed by the EuroQol group and is applicable to a wide range of health conditions, including individuals with SCI (Whitehurst *et al.*, 2014). It consists of two pages; the EQ-5D-5L descriptive system (page 2), which comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression)

and the EQ visual analogue scale (EQ VAS: page 3). Participants are asked to rate each dimension of the EQ-5D-5L, no problems (value code: 1), slight problems (2), moderate problems (3), severe problems (4), and extreme problems (5). Values for each dimension and the EQ VAS were compared pre- post.

Shoulder pain was assessed using the Wheelchair User's Shoulder Pain Index (WUSPI: Curtis *et al.*, 1995). This consists of 15 questions, whereby participants indicate their response on a visual analogue scale ranging from no pain to worst pain ever experienced. The performance corrected WUSPI score (PC-WUSPI) was used; it accommodates participants who do not perform certain functions (i.e. item 13: *driving?*). This involves multiplying the average response for all items by the number of questions attempted, with higher values indicating a greater degree of perceived shoulder pain. The fatigue severity scale (FSS) was administered to measure the severity of fatigue and its effects on certain behaviours. The FSS was initially developed to be used in multiple sclerosis patients (Krupp *et al.*, 1989), but has also been shown to have acceptable test-retest reliability and validity in 48 community living individuals with SCI (Anton *et al.*, 2008). The 9-item questionnaire is scored on a 7 point scale (1= strongly disagree; 7= strongly agree). As such the minimum total score = 9 and maximum score possible = 63. The higher the score the greater the fatigue severity. Self-efficacy was assessed using the SCI Exercise Self-Efficacy Scale (ESES; Kroll *et al.*, 2007), which was developed specifically to cover issues associated with this unique population. The ESES consists of 10 items and requires participants to respond on a 4-point Likert scale (1- not at all true; 4- always true). A total score (range from 10 – 40) is derived from summing together scores from the individual items, with a higher score indicating greater perceived self-efficacy

6.2.7. Assessment of Physical Activity Energy Expenditure

The number of days required to assess habitual PA using wearable devices has been discussed at length (Matthews *et al.*, 2002). The consensus was that monitoring for 3 – 4 days is required to achieve 80% reliability in activity counts. In our work we decided to use an inclusion criteria of ≥ 4 days (providing one of these days was a weekend day).

This also ensures that we capture more PA behavioural information than the PARA-SCI (3-day recall telephone interview) which has been widely used to quantify free-living PAEE in wheelchair users (Martin Ginis *et al.*, 2007: Buchholz *et al.*, 2009). A valid day will require at least 80% of data for that 24-hr period. SVM data from the GENEA (y axis) was plotted against the corresponding 24-hr timestamp (x axis) and visually inspected. Non-wear time was defined by an interval of at least 60 consecutive minutes whereby SVM values remained constant. This was cross referenced with lux and temperature data from the GENEA device to confirm non-wear time. Non-wear time SVM data was then excluded from the daily average ($g \cdot \text{min}^{-1}$).

6.2.8. Assessment of Dietary Intake

Participants were asked to keep a detailed record of their food and fluid intake for a "typical" 7 days after their baseline visit, and again during the week leading up to their follow-up testing. Previous work has demonstrated variation between weekday and weekend energy intake (Whybrow *et al.*, 2008), therefore 7 days is a suitable period to allow accurate representation of habitual energy intake. Each participant received a set of weighing scales (PL11B Digital Scale, Smart Weigh, NY, US) to accurately weigh and record foodstuffs, which negates any potential errors in estimation of food weight (Gittelsohn *et al.*, 1994). Martin *et al.*, (2002), has shown that weighed food records are a more valid measure of energy intake than dietary recall methods. Diets were subsequently analysed using Nutritics software (Nutritics Ltd., Dublin, Ireland), to estimate energy intake.

It has been well established that food records are liable to error, principally underreporting (Livingstone & Black, 2003; Poslusna *et al.*, 2009). Cut off limits have previously been proposed to improve the feasibility of food records and identify underreporting (Black, 2000b; Goldberg *et al.*, 1991), although these limits are realistically only applicable when individuals are maintaining energy balance. As weight stability might change over the course of the 6 weeks through exercise creating an energy deficit, we decided not to utilise previously proposed cut offs. Whilst this might introduce some error as a result of

unidentified underreporting, it has been suggested cut offs have limited application on an individual basis when identifying changes pre-post (Black, 2000a).

6.2.9. Home-Based Exercise Intervention

The exercise intervention consisted of moderate intensity (60 – 65% $\dot{V}O_2$ peak) home-based exercise 4 times/wk on the same portable desktop ergometer used during submaximal testing. The intervention progressed in duration by 5 minutes during each session in the first week, from 30 to 45 min. The intensity was increased from ≈ 60% $\dot{V}O_2$ peak for the first 3 weeks to ≈ 65% $\dot{V}O_2$ peak for the second 3-week period. Participants were expected to cycle at a cadence of 75 rpm. The first training session was supervised by a member of the research team who ensured that the arm crank ergometer was set up appropriately and that the correct duration and intensity of exercise was adhered to. Subsequent home-based exercise sessions were performed under the supervision of a carer or spouse as agreed on the informed consent document. To attain the desired intensity in each session, participants wore a Polar T31 heart rate monitor and were instructed to adjust the resistance in order to achieve the target HR. Each exercise session was monitored (GENEActiv-W) to ascertain compliance, and was checked against an activity diary where participants recorded the date, time, duration, difficulty and total revolutions. Sampling at 30 Hz the GENEA is capable of recording PA for up to three weeks. At the midway point a newly initialised and charged GENEA device was posted to the participant. Adherence to the intervention was maintained with regular weekly telephone calls and emails. No dietary constraints were imposed, and participants in both groups were free to consume food and fluid *ad libitum*.

6.2.10. Analytical Methods

Differential leukocyte counts were obtained from 2 ml of whole blood collected at baseline using an automated haematology system (SF-300, Sysmex Ltd., Milton Keynes, UK). Analysis of serum samples for high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides (TAG), non-esterified fatty acids (NEFA), C-Reactive Protein (CRP) and plasma glucose was determined using an automated analyser (Randox RX

Daytona, Co. Antrim, UK), in accordance with manufacturer's instructions using commercially available immunoassays (Randox Laboratories, Co. Antrim, UK).

Commercially available enzyme-linked immunosorbent assays (ELISA) were used according to manufacturer's instructions to measure serum adiponectin, leptin (Quantikine, R&D Systems Inc., Abingdon, UK), interleukin 6 (IL-6; Quantikine HS, R&D systems Inc., Abingdon, UK) and insulin (Mercodia AB, Uppsala, Sweden). All ELISA blood samples were performed in duplicate in a batch analyse after the conclusion of the study, and samples from each participant were included on the same plate. Absorption was determined using a microplate reader (SPECTROstar Nano, BMG LabTech, Ortenberg, Germany) at the wavelengths specified by the kit manufacturer. Intra and inter-assay coefficients of variation (CV) and sensitivity provided by the manufacturer for each ELISA/automated immunoassay are shown below (Table 6.2).

Table 6.2: Reported sensitivity, intra and inter-assay precision for all analytical methods used

Parameter	Sensitivity	Intra-assay precision (CV)	Inter-assay precision (CV)[a]
Automated			
CRP	0.3 $mg \cdot l^{-1}$	1.9 %	4.0 %
Glucose	0.060 $mg \cdot l^{-1}$	2.9 %	4.4 %
HDL	0.189 $mmol \cdot l^{-1}$	2.5 %	2.8 %
NEFA	0.04 $mmol \cdot l^{-1}$	4.8 %	4.4 %
TAG	0.134 $mmol \cdot l^{-1}$	2.5 %	2.4 %
Total cholesterol	0.865 $mmol \cdot l^{-1}$	3.8 %	1.4 %
Manual ELISAs			
Adiponectin	0.25 $ng \cdot ml^{-1}$	4.2 %	6.8 %
hs IL-6	0.04 $pg \cdot ml^{-1}$	7.4 %	7.8 %
Insulin	1 $mU \cdot l^{-1}$	1.9 %	3.1 %
Leptin	7.8 $pg \cdot ml^{-1}$	3.9 %	4.4 %

[a] Where only one ELISA plate was analysed (Adiponectin, hs IL-6 and leptin) values from the manufacturers data sheet were quoted for inter-assay CV. Insulin inter-assay CV was calculated from the standards from ten plates.

Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (Friedewald. W.T *et al.*, 1972);

$$LDL = Total\ Cholesterol - HDL - (\frac{Triglycerides}{2.2})$$

Incremental area under the curve (iAUC) was calculated for the plasma glucose and serum insulin responses during the OGTT using the trapezoid rule (Wolever, 2004). Homeostasis model assessment for insulin resistance (HOMA-IR; Turner *et al.*, 1979) was calculated as:

$$HOMA\text{-}IR = \frac{Fasting\ glucose\ (mmol{\cdot}l^{-1}) \times fasting\ insulin\ (mU{\cdot}l^{-1})}{22.5}$$

Homeostasis model assessment for β-cell function (HOMA-β; Matthews *et al.*, 1985) was calculated as;

$$HOMA\text{-}\beta = \frac{Fasting\ insulin\ (mU{\cdot}l^{-1}) \times 20}{Fasting\ glucose\ (mmol{\cdot}l^{-1}) - 3.5}$$

The Insulin Sensitivity Index ($ISI_{Matsuda}$: Matsuda & DeFronzo, 1999), which has been shown to strongly correlate with the gold standard hyperinsulinemic-euglycemic clamp, was calculated as;

$$ISI_{Matsuda} = \frac{10{,}000}{\sqrt{\begin{matrix}\left[Fasting\ glucose\left(mg{\cdot}dl^{-1}\right) \times fasting\ insulin\left(\mu U{\cdot}ml^{-1}\right)\right] \times \\ [mean\ OGTT\ glucose\ value\left(mg{\cdot}dl^{-1}\right) \times mean\ OGTT\ insulin\ value\ (\mu U{\cdot}ml^{-1})]\end{matrix}}}$$

6.2.11. Statistical Analysis

In order to simplify data analysis and facilitate the interpretation of a complex data set (Hopkins *et al.*, 2009; Matthews *et al.*, 1990), serial measurements of glucose and insulin responses to the OGTT at baseline and follow-up were converted into simple summary statistics (i.e. within-subject fasting and peak concentrations, time to peak, iAUC and estimates of insulin sensitivity and resistance; Wolever & Jenkins, 1986). Responses within and between trials were analysed by two-way (group [INT, CON] x day [baseline, follow-up]) and three-way (group [INT, CON] x day [baseline, follow-up x time] x OGTT time point [0, 15, 30, 45, 60, 75, 90, 105, 120]) mixed-model analysis of variance (ANOVA). ANOVA were performed irrespective of any minor deviations from a normal distribution (Maxwell, 2004), but with Greenhouse-Geisser corrections applied to intra-individual contrasts where $\varepsilon < 0.75$ and the Huynh-Feldt corrections applied for less severe asphericity (Atkinson, 2002). Where significant interactions were observed, multiple t-tests were applied to determine the location of variance both between treatments at each time point and between time points within each treatment relative to baseline. Both methods were subjected to a Holm-Bonferroni stepwise adjustment (Atkinson, 2002). Data are presented in text as means and standard deviations (SDs), whereas figures display means with variance bars representing normalised confidence intervals (CIs). The CIs have been corrected to remove inter-individual variation (Masson & Loftus, 2003). Pearson product-moment correlation coefficients were used to determine correlations between variables. For CRP and IL-6, the mean and SD of the change (Δ) were calculated using all data points. When the Δ was over 3 SD away from the mean these data were excluded, as this would most likely have been due to an acute inflammatory response or undiagnosed urinary tract infection, common in this population. Statistical significance was set at *a priori* of $\alpha < 0.05$. All analyses were performed using IBM® SPSS® Statistics 20 for Windows (IBM, Armonk, NY, USA). Standardised effect sizes (Cohens *d*) were also calculated for all variables, but only reported in the results for all significant effects and those approaching significance ($P \leq 0.10$). Based upon the magnitude of correlation between trials, thresholds of > 0.2 (small), > 0.5 (moderate) and > 0.8 (large) have been suggested (Cohen, 1988). This provides an interpretation of the size of the effects in our outcome measures when using a parallel-group's study design.

6.3. RESULTS

In the INT group, eleven out of twelve participants completed all 24 training sessions, i.e., 100% compliance. One participant missed two non-consecutive sessions over the course of the 6 weeks (92% compliance). All participants have been retained in the final analysis.

The mean subjective ratings of difficulty for the INT group over all exercise sessions over the 6 weeks ranged from 6 – 8 (1: easy, 10: hard). The mean exercise duration for the group over the 6 weeks was 44 ± 1 min and power output was 45 ± 19 W. Measured heart rate was 144 ± 12 b·min^{-1}. On average, nine participants achieved the heart rate prescribed at baseline to elicit 60 – 65% of $\dot{V}O_2$ peak (difference from target 9 ± 6 b·min^{-1}). Three participants were unable to achieve the heart rate prescribed at baseline (difference from target – 9 ± 4 b·min^{-1}).

No significant baseline differences were present for personal and injury characteristics between the two groups (Table 6.1; all p values > 0.35). Baseline Homeostasis Model Assessment of β cell function (HOMA-β) was significantly (P = 0.047) higher in the INT group compared to the CON group (Table 6.6). No significant baseline differences were present for any of the other outcome measures (all p values > 0.11). Metabolic syndrome (defined in Section 2.4.4) was observed in 8 of the 20 participants (INT = 4; CON = 4) and 5 of the 20 participants (INT = 2; CON = 3) at baseline and follow-up, respectively.

6.3.1. Physical Activity Outcomes

Physical activity characteristics pre and post-intervention/control are summarised in Table 6.3. Significant day × group interaction effects were noted for PAEE measured by the AHR-IC (P = 0.049) and GENEActiv (P = 0.001). There was also a main effect of day across both groups for PAEE measured by the GENEActiv (P = 0.001). PAEE significantly (P < 0.05) increased at follow-up in the INT group from 349 ± 186 to 431 ±

205 kcal·day^{-1} (*d* = 0.46) (Figure 6.3) and 892 ± 69 to 993 ± 60 kcal·day^{-1} (*d* = 1.08); measured by the AHR-IC and GENEActiv, respectively. Consequently, there was a significant day × group interaction effect (P = 0.036; *d* = 0.52) for PAL (TEE/RMR), which significantly (P = 0.021) increased from 1.37 ± 0.12 to 1.43 ± 0.13 in the INT group, yet remained unchanged in the CON group 1.38 ± 0.12 to 1.38 ± 0.13. There was a main effect of day (P= 0.001) across both groups for max HR; this was primarily explained by an 18 (9 to 28) b·min^{-1} increase in the INT group, and a considerable effect size when comparing between groups (*d* = 1.92). There was a significant day × group interaction (P = 0.015; *d* = 0.54) for time spent performing moderate-intensity activities. Minutes spent performing moderate-intensity activity significantly (P = 0.015) increased in the INT group from 16 ± 16 to 25 ± 15 min·day^{-1}, yet remained the same for the CON group; 21 ± 27 to 18 ± 23. Time spent performing vigorous-intensity activities also significantly (P = 0.045) increased by 5 (0 to 10) min·day^{-1} in the INT group, with a large effect size observed between groups (*d* = 2.20). Physical activity monitoring devices were worn for 6 ± 1 days, with a daily wear time percentage of 97 ± 4% across both groups at each time point.

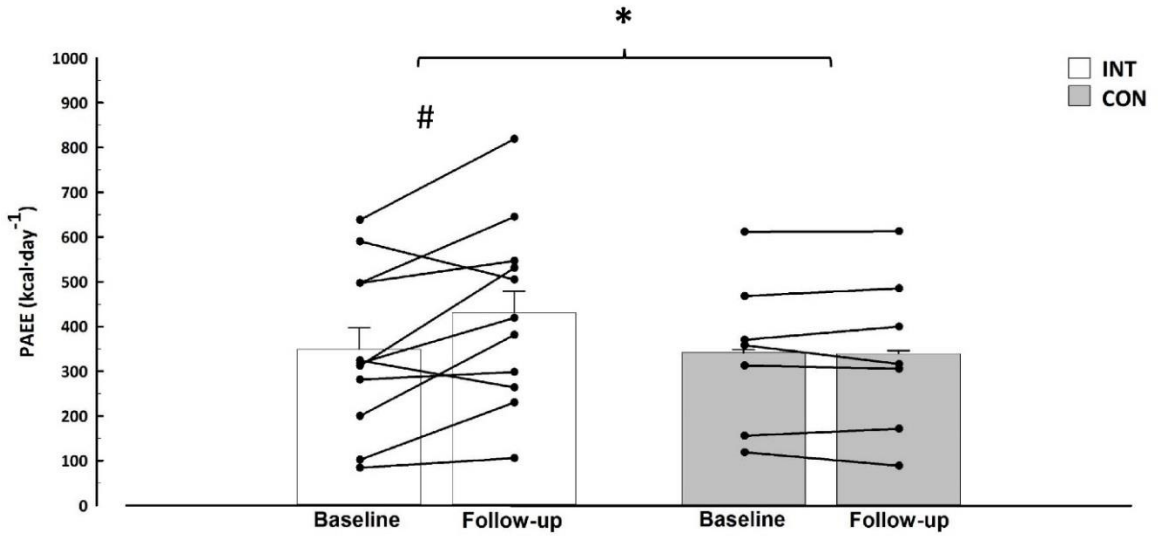

Figure 6.3: PAEE at baseline and follow-up measured by the AHR-IC for the INT (n = 11) and CON (n = 7) group. Values are means ± CI. * denotes a day × group interaction (P = 0.049). # denotes values different pre-post within INT group (P = 0.023)

Table 6.3: Physical activity outcomes at baseline and follow-up for both groups measured by GENEActiv and AHR-IC. Mean ± SD. Mean change scores (Δ) shown with 95% confidence intervals. One AHR device malfunction and < 4 days wear time at follow-up for the INT (n = 11) and CON group (n = 7), respectively. Three GENEActiv devices were not worn continuously in the INT group at baseline, as such (n = 9). † denotes a main effect of day (i.e. Baseline vs. Follow-up for both groups; $P < 0.05$). ***** denotes a day × group interaction ($P < 0.05$). # denotes values are different pre-post within INT group ($P < 0.05$)

	INT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
GENEActiv						
PAEE (kcal·day^{-1})	892 ± 69	993 ± 60	101 (61 to 142) ***†#**	948 ± 90	956 ± 134	8 (-37 to 53) ***†**
SVM (g·min^{-1})	70.9 ± 14.9	92.6 ± 13.0	21.7 (12.9 to 30.4) ***†#**	83.1 ± 19.3	84.6 ± 29.1	1.5 (-8.4 to 11.4) ***†**
AHR-IC outputs						
Sedentary (min·day^{-1})	1223 ± 130	1192 ± 120	-31 (-77 to 16)	1219 ± 115	1199 ± 129	-21 (-53 to 12)
Light (min·day^{-1})	201 ± 120	218 ± 106	17 (-26 to 61)	198 ± 100	224 ± 116	26 (-11 to 63)
Moderate (min·day^{-1})	16 ± 16	25 ± 15	9 (2 to 15) ***#**	21 ± 27	18 ± 23	-3 (-9 to 3) *****
Vigorous (min·day^{-1})	0 ± 0	5 ± 7	5 (0 to 10) **#**	1 ± 3	2 ± 4	1 (-1 to 2)
PAL	1.37 ± 0.12	1.43 ± 0.13	0.06 (0.01 to 0.10) ***#**	1.38 ± 0.12	1.38 ± 0.13	-0.01 (-0.03 to 0.02) *****
Max HR (b·min^{-1})	105 ± 6	123 ± 15	18 (9 to 28) ***†#**	112 ± 15	108 ± 12	-4 (-10 to 2) ***†**

6.3.2. Diet Composition

Caloric intake and diet composition at baseline and follow-up are summarised in Table 6.4. No significant changes were observed between groups or over time for total energy intake or macronutrient composition (P > 0.225).

6.3.3. Body Composition and Physiological Measures

Body composition and physiological characteristics pre and post intervention/control are summarised in Table 6.5. There was a trend for total body mass to be reduced at follow-up across both groups (day effect; P = 0.088), with a change of - 0.9 (-2.1 to 0.3) kg and -0.7 (-2.2 to 1.0) kg, in the INT and CON group, respectively. LM measured in the legs was significantly reduced at follow-up in both groups; there was a main effect of day (P = 0.025). There were trends for day × group interaction effects for LM in the arms (P = 0.063) and FM in the trunk (P = 0.063). However, effect sizes between groups were smaller than the cut off considered trivial (d < 0.2), d = 0.11 and -0.11 for LM in the arms and FM in the trunk, respectively. Blood pressure: both systolic and diastolic remained unchanged in both groups.

Table 6.4: Total energy intake and diet composition at baseline and follow-up for both groups. Mean ± SD. Mean change scores (Δ) shown with 95% confidence intervals

	INT			**CON**		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
Energy intake (kcal·day^{-1})	1695 ± 500	1666 ± 498	-28 (-258 to 201)	1658 ± 299	1508 ± 213	-151 (-509 to 208)
Protein intake (kcal·day^{-1})	299 ± 76	297 ± 103	-1 (-55 to 52)	334 ± 75	283 ± 123	-50 (-138 to 38)
Carbohydrate intake (kcal·day^{-1})	730 ± 248	727 ± 286	- 3 (-112 to 106)	737 ± 197	650 ± 76	-87 (-242 to 68)
Fat intake (kcal·day^{-1})	629 ± 227	602 ± 210	-27 (-163 to 109)	572 ± 109	541 ± 126	-30 (-183 to 122)
Alcohol intake (kcal·day^{-1})	39 ± 48	32 ± 37	-7 (-36 to 22)	14 ± 26	32 ± 49	18 (-14 to 50)

Table 6.5: Body composition and physiological characteristics measured at baseline and follow-up for the INT and CON groups. Mean ± SD. Mean change scores (Δ) shown with 95% confidence intervals. † denotes a main effect of day (i.e. Baseline *vs.* Follow-up for both groups; P = 0.025)

	INT			CON		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
Body Mass (kg)	76.9 ± 13.7	76.0 ± 14.3	- 0.9 (-2.1 to 0.3)	76.8 ± 11.3	76.1 ± 10.6	- 0.7 (-2.2 to 1.0)
Fat Mass (kg; DEXA)						
Total	28.2 ± 10.4	27.6 ± 10.4	- 0.6 (-1.5 to 0.2)	26.0 ± 6.8	26.0 ± 7.0	0.0 (-0.5 to 0.5)
Arms	1.4 ± 0.5	1.4 ± 0.5	0.0 (-0.1 to 0.1)	1.4 ± 0.5	1.3 ± 0.5	- 0.1 (-0.2 to 0.1)
Legs	4.9 ± 2.5	4.7 ± 2.5	- 0.2 (-0.3 to 0.0)	4.3 ± 1.5	4.3 ± 1.6	0.0 (-0.2 to 0.1)
Trunk	14.9 ± 5.1	14.4 ± 5.0	- 0.5 (-0.9 to 0.0)	13.8 ± 3.8	13.9 ± 3.9	0.1 (-0.2 to 0.4)
Lean Mass (kg; DEXA)						
Total	47.8 ± 7.9	47.5 ± 7.6	- 0.3 (-0.9 to 0.4)	49.8 ± 11.3	49.1 ± 11.3	- 0.7 (-1.8 to 0.4)
Arms	3.6 ± 0.8	3.7 ± 0.9	0.1 (-0.0 to 1.7)	3.8 ± 1.4	3.8 ± 1.4	0.0 (-0.2 to 0.1)
Legs	5.8 ± 1.3	5.6 ± 1.2	- 0.2 (-0.3 to 0.0)†	6.1 ± 1.6	5.9 ± 1.6	- 0.2 (-0.4 to 0.1)†
Trunk	25.1 ± 4.1	24.9 ± 3.8	- 0.2 (-0.6 to 0.3)	25.9 ± 5.6	25.6 ± 5.4	- 0.3 (-0.9 to 0.4)
Systolic BP (mmHg)	130 ± 22	125 ± 20	-5 (-11 to 2)	128 ± 15	126 ± 12	-3 (-7 to 2)
Diastolic BP (mmHg)	79 ± 14	76 ± 11	-3 (-9 to 3)	81 ± 13	77 ± 10	-4 (-9 to 2)

6.3.4. Resting Metabolic Rate & Respiratory Exchange Ratio

There was a trend for a day × group interaction (P = 0.08) in RMR and a trivial effect size between groups (*d* = 0.37). Whilst non-significant, there was an increase of 3% (1450 ± 199 to 1499 ± 186 kcal·day^{-1}) and a decrease of 2% (1483 ± 224 to 1453 ± 170 kcal·day^{-1}) in resting metabolic rate for the INT and CON group, respectively. There was a significant day × group interaction (P = 0.03) as shown in Figure 6.4 for fasting RER, with values decreasing by 1% (0.81 ± 0.04 to 0.80 ± 0.03) and increasing by 3% (0.82 ± 0.04 to 0.85 ± 0.05) for the INT and CON group, respectively. This was considered a large effect (*d* = -1.04).

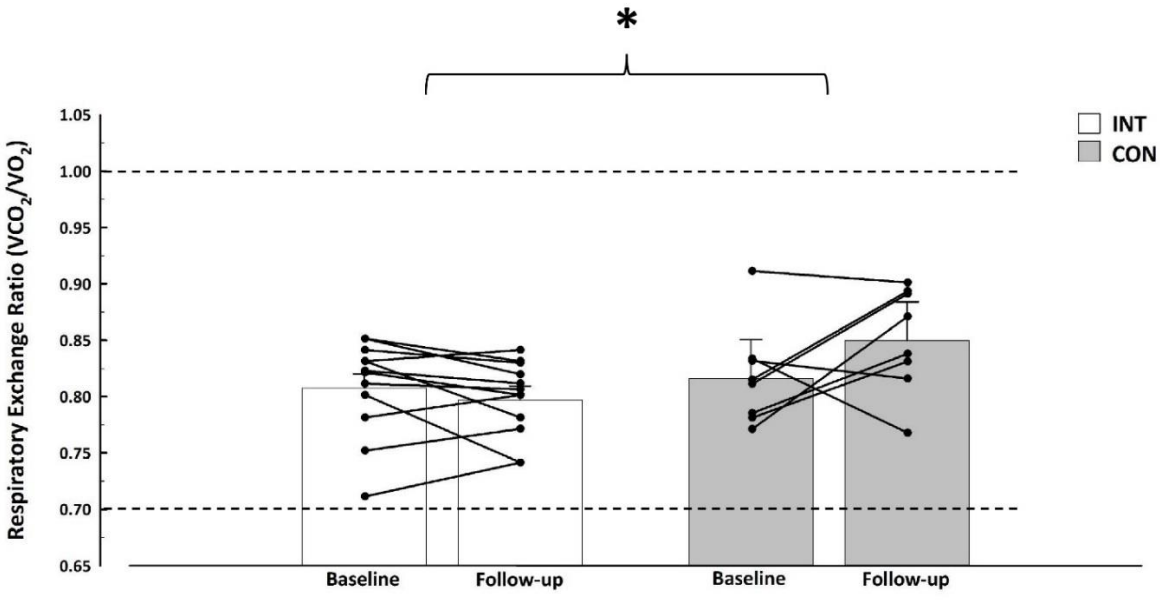

Figure 6.4: Respiratory Exchange Ratio at baseline and follow-up for the INT group and CON group. Values are means ± CI. * denotes a day × group interaction (P = 0.03). Dotted lines represent the expected RER range based on carbohydrate (1.00) and lipid oxidation (0.70) only

6.3.5. Functional Capacity

There was a main effect of day ($P = 0.001$) and a day × group interaction ($P < 0.001$) for peak oxygen uptake ($\dot{V}O_2$ peak), as shown by Figure 6.5. $\dot{V}O_2$ peak) significantly ($P < 0.001$) increased at follow-up in the INT group from 18.0 ± 5.0 to 21.2 ± 5.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (19%), whereas it remained unchanged in the CON group from 18.8 ± 6.2 to 18.3 ± 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (-3%). These responses were supported by maximal workload data. Again, there was a main effect of day ($P < 0.001$) and a day × group interaction ($P < 0.001$) (Figure 6.6). Maximal workload increased significantly at follow-up in the INT group from 77 ± 29 to 95 ± 32 W (25%) and remained similar in the CON group 75 ± 39 to 73 ± 36 W (-2%). There were moderate effect sizes between groups of $d = 0.66$ and 0.58 for $\dot{V}O_2$ peak and maximal workload, respectively.

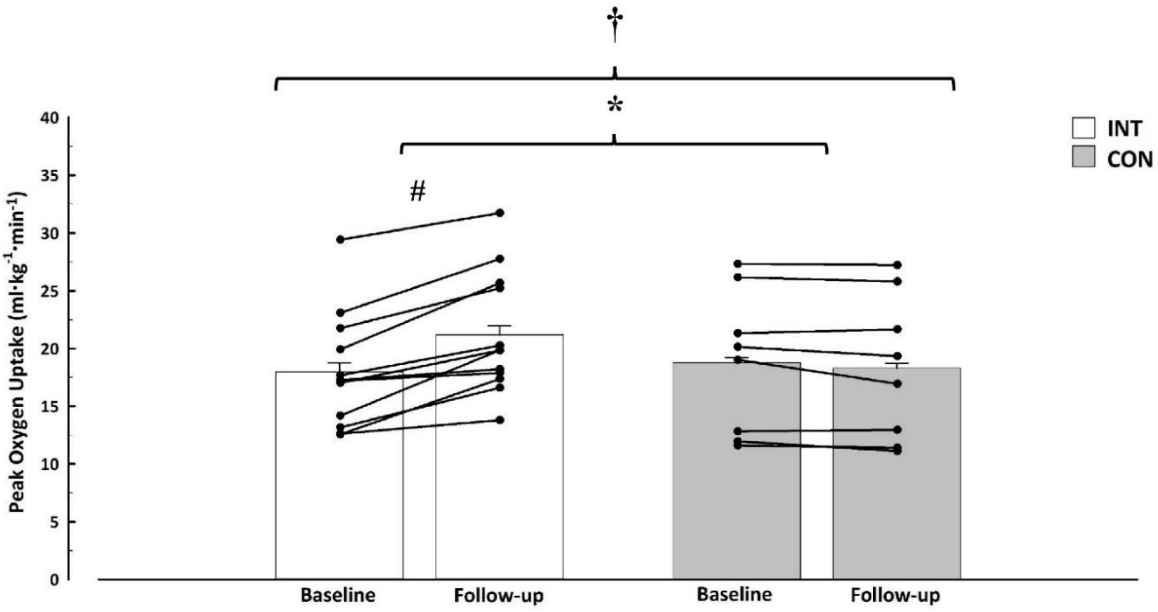

Figure 6.5: Peak oxygen uptake at baseline and follow-up for the INT group and the CON group. Values are means ± CI. † denotes a main effect of day (i.e. Baseline vs. Follow-up for both groups; P = 0.001). * denotes a day × group interaction (P < 0.001). # denotes values are different pre-post within INT group (P < 0.001)

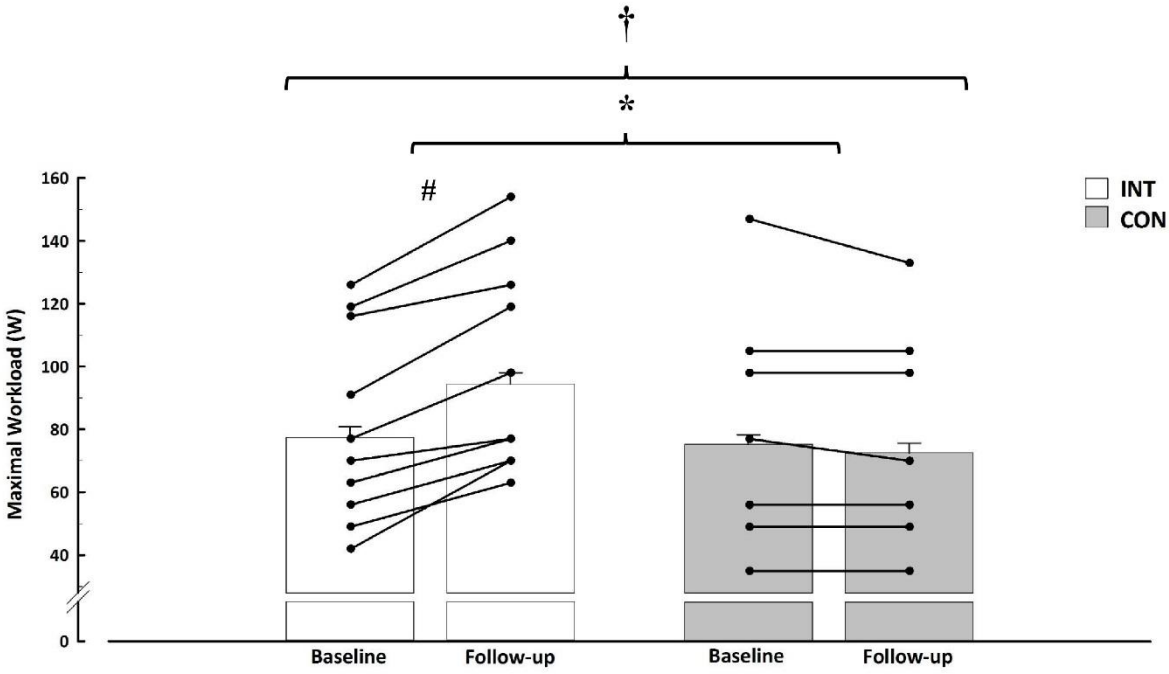

Figure 6.6: Maximal workload at baseline and follow-up for the INT group and the CON group. Values are mean ± CI. † denotes a main effect of day (i.e. Baseline vs. Follow-up for both groups; P < 0.001). * denotes a day × group interaction (P < 0.001). # denotes values are different pre-post within INT group (P < 0.001)

6.3.6. Insulin and Glucose Responses to OGTT

Serum Insulin

The serum insulinaemic response (iAUC) during the OGTT was unchanged in both groups (Figure 6.8). There was a significant day × group interaction (P = 0.047) as shown by Figure 6.9 for serum fasting insulin and a moderate effect size (*d* = -0.54) between groups. Serum fasting insulin was significantly (P = 0.04) reduced (-14%) at follow-up in the INT group from 52.3 ± 28.3 to 41.7 ± 19.3 pmol·l^{-1}, but remained unchanged in the CON group, 35.7 ± 15.7 to 38.3 ± 17.8 pmol·l^{-1}. There was no change pre-post in serum insulin peak concentration over the course of the OGTT. Furthermore, the individual peak serum insulin time was unaffected in both groups.

Plasma Glucose

Plasma glucose responses at each 15 minute time point during the 2 hr OGTT were unaffected in both groups shown by Figure 6.10. The plasma glycaemic response (iAUC) was unchanged (INT; 294 ± 281 to 316 ± 269 mmol·120 min·l^{-1}, CON; 293 ± 252 to 268 ± 228 mmol·120 min·l^{-1}). There was no change pre-post in plasma glucose fasting and peak concentrations. Moreover, the individual peak plasma glucose time was unaffected in both groups.

Indices of Insulin Sensitivity/Resistance

There was a tendency for a difference in the change in insulin resistance (predicted by the Homeostasis Model of Assessment of Insulin Resistance; HOMA-IR) pre- post between the two groups (P = 0.079; day × group interaction). There was also a trend for a day × group interaction effect (P = 0.052) for Homeostasis Model Assessment of β cell function (HOMA-β). HOMA-β significantly decreased at follow-up in the INT group, from 89 ± 48 to 65 ± 26% (P = 0.024). There was a trivial effect size for HOMA-IR; *d* = -0.49, yet a moderate effect size for HOMA-β (*d* = -0.58). Insulin sensitivity, predicted using the $ISI_{Matsuda}$, remained unchanged in both groups (Table 6.6).

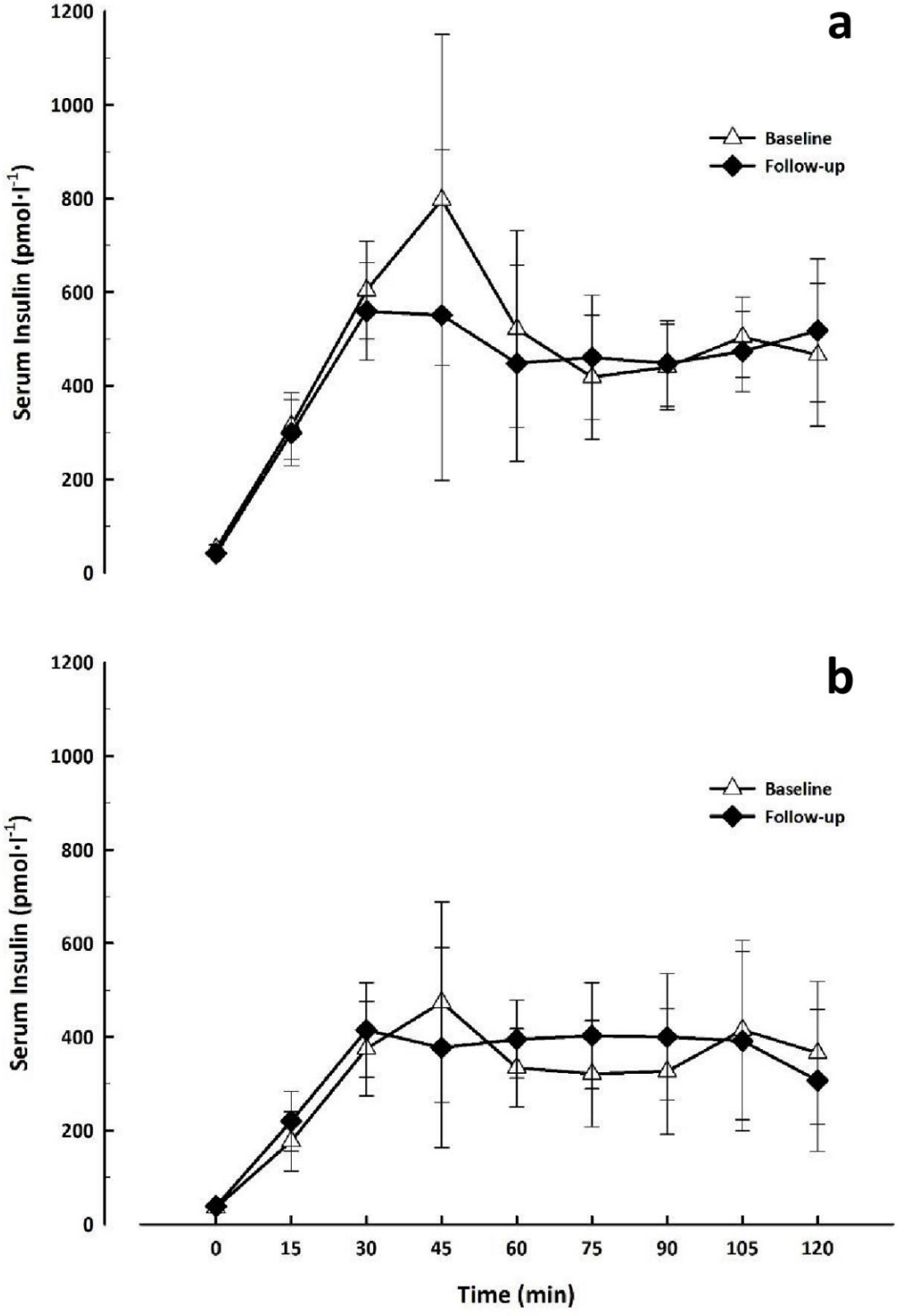

Figure 6.7: Serum insulin concentrations in response to the OGTT at baseline and follow-up (Panel a: INT group, n =11; Panel b: CON group, n = 8). Values are means ± CI

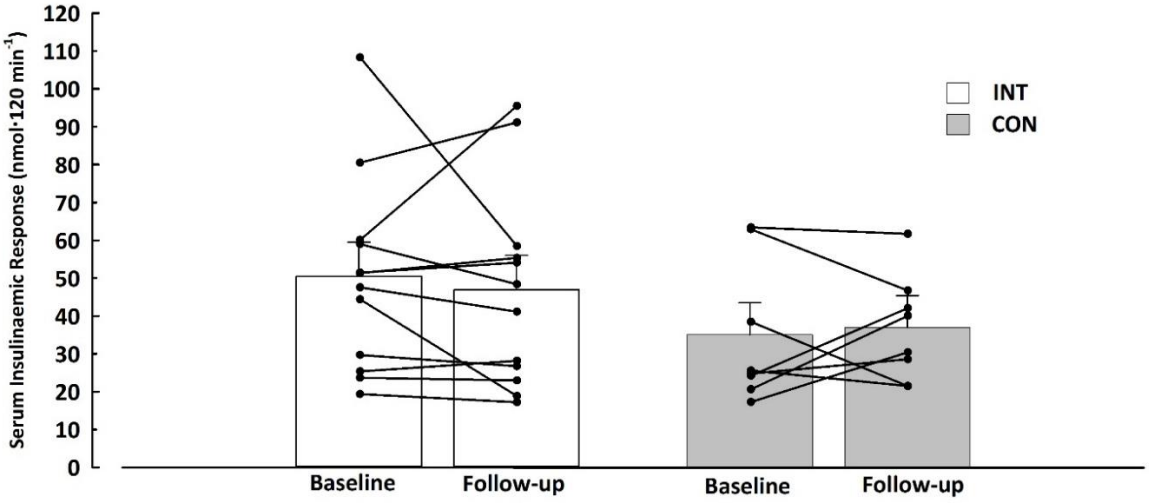

Figure 6.8: Serum insulinaemic responses during 2 hr OGTT at baseline and follow-up for the INT and CON group. *Please note; iAUC was calculated for one participant in the INT group using finger prick capillary samples, taken pre-post at the following time points 0, 30, 60, 90 and 120, due to problems with cannulation*

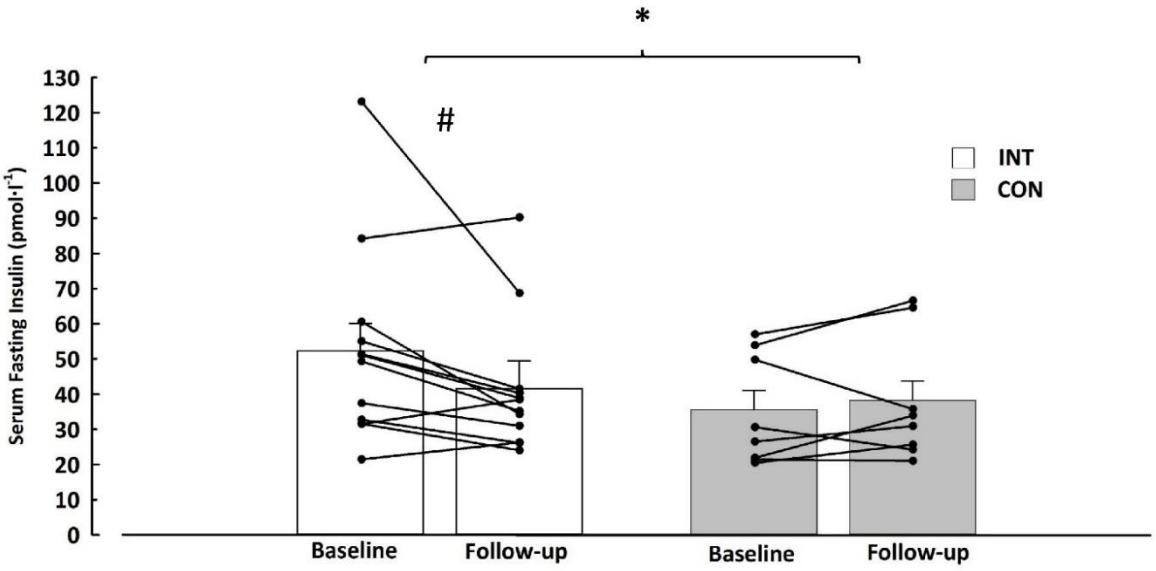

Figure 6.9: Serum fasting insulin concentrations at baseline and follow-up for the INT group and CON group. Values are means ± CI. * denotes a day × group interaction (P = 0.047). # denotes values are different pre-post with INT group (P = 0.040)

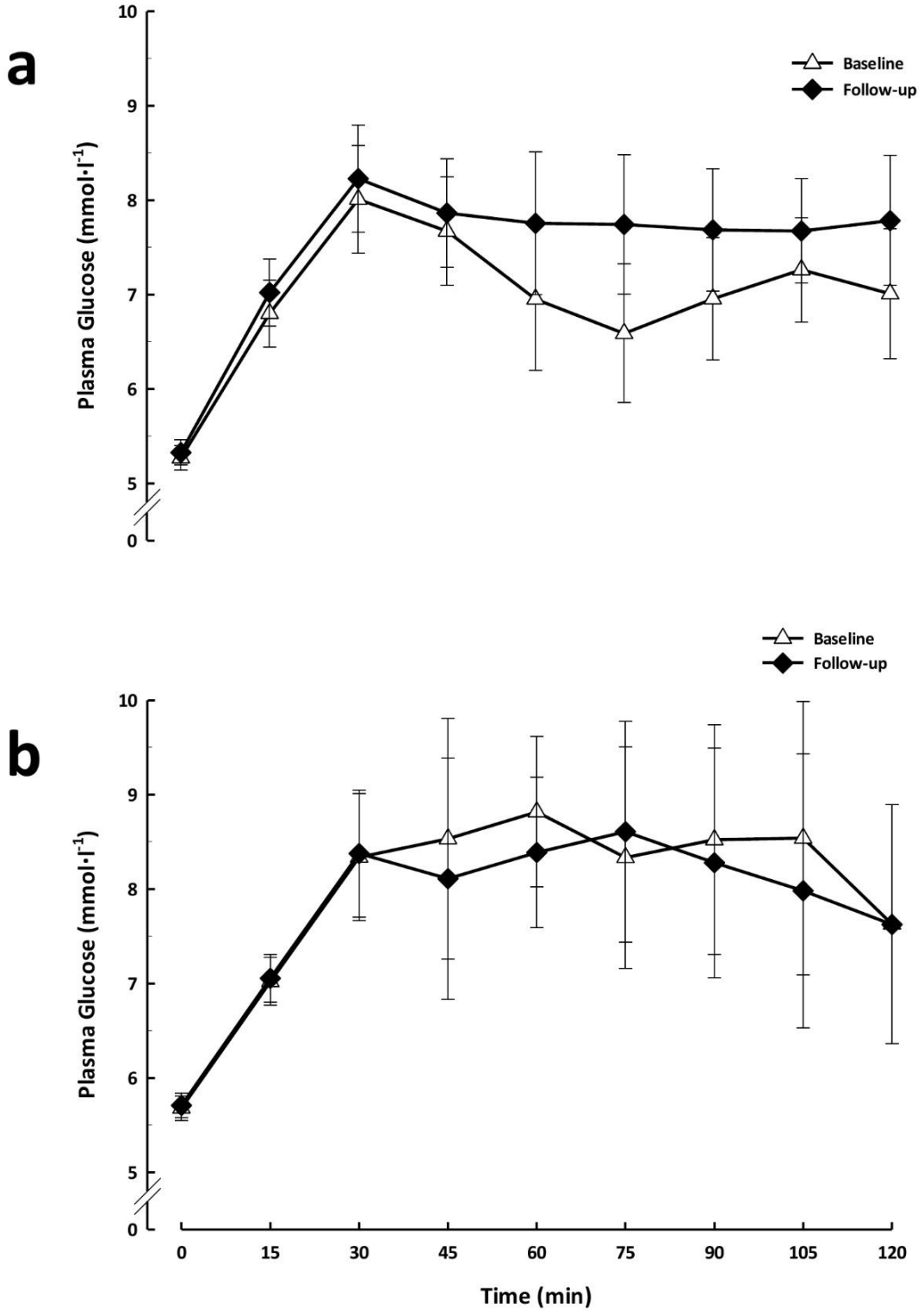

Figure 6.10: Plasma glucose concentrations in response to the OGTT at baseline and follow-up (Panel a: INT group, n =11; Panel b: CON group, n = 8). Values are means ± CI

Table 6.6: HOMA-IR, HOMA-β and $ISI_{Matsuda}$ values at baseline and follow-up. Mean ± SD. Mean change scores (Δ) shown with 95% confidence intervals. # denotes values are different pre-post within INT group (P = 0.024). Please note: *Matsuda Index was calculated for one participant in the INT group using finger prick capillary samples, taken pre-post at the following time points 0, 30, 60, 90 and 120, due to problems with cannulation*

	INT			**CON**		
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**
HOMA-IR	1.84 ± 1.10	1.46 ± 0.78	-0.37 (-0.81 to 0.06)	1.30 ± 0.62	1.42 ± 0.74	0.12 (-0.16 to 0.39)
HOMA-β (%)	89 ± 48	65 ± 26	-24 (-45 to -4) #	54 ± 24	56 ± 22	2 (-13 to 16)
$ISI_{Matsuda}$	5.0 ± 2.6	5.6 ± 2.4	0.6 (-0.2 to 1.4)	6.9 ± 3.3	6.1 ± 2.4	-0.7 (-2.8 to 1.3)

6.3.7. Fasted Blood Measurements

Adipokines

Serum adiponectin concentrations significantly decreased at follow-up in both groups; there was a main effect of day (P = 0.014) as shown by Figure 6.11. This was primarily explained by a significant reduction in the INT group (8.31 ± 3.94 to 7.14 ± 4.32 ug·ml^{-1}, P = 0.017). Although non-significant, leptin was reduced (-12%) at follow-up in the INT group from 18,177 ± 20,619 to 14,035 ± 13,994 pg·ml^{-1} and remained unchanged in the CON group 13,895 ± 14,764 to 13,986 ± 15,828 pg·ml^{-1}.

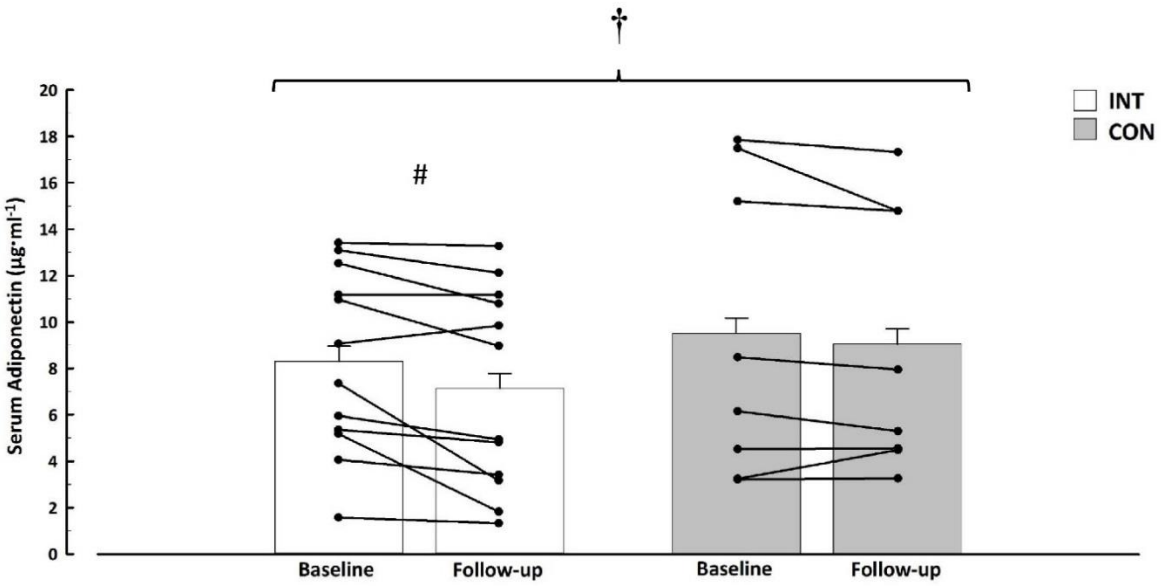

Figure 6.11*:* Serum adiponectin concentrations at baseline and follow-up for the INT and CON groups. Values are means ± CI. † denotes a main effect of day (i.e. Baseline vs. Follow-up for both groups; P = 0.014). # denotes values are different pre-post within INT group (P = 0.017)

Lipid Profiles

Serum cholesterol, HDL-C and LDL-C were unaffected in both groups (Table 6.7). There was a trend for a day × group interaction effect (P = 0.060) for serum TAG concentrations. There were trivial (*d* = 0.40) and large (*d* = -1.02) effect sizes for serum NEFA and TAG, respectively when comparing between groups.

Inflammation

Three participants (INT; n = 1, CON; n = 2) were removed from the inflammatory marker analysis as Δ >3 S.D, potentially due to the presence of underlying urinary tract infection or acute infection. The group mean difference from pre to post intervention for IL-6 approached significance (P = 0.104; day × group interaction), with a reduction in the INT group (0.85 ± 0.64 to 0.62 ± 0.31 $pg \cdot ml^{-1}$) and increase in the CON group (1.07 ± 0.88 to 1.34 ± 1.11 $pg \cdot ml^{-1}$). There was a moderate effect size (*d* = -0.67). Furthermore, when looking at the participants in the INT group with serum IL-6 concentrations ≥ 0.8 $pg \cdot ml^{-1}$ (n = 5) there is a 40% decrease at follow-up. The differences in these individuals compared to the CON group was considered a large effect size (*d* = -0.97). The group means are unchanged for CRP (INT; 3.94 ± 4.11 to 3.07 ± 4.44 $mg \cdot l^{-1}$, CON; 5.33 ± 4.67 to 5.39 ± 5.74 $mg \cdot l^{-1}$).

Table 6.7: Lipid profiles measured at baseline and follow-up for the INT and CON groups. *Mean ± SD. Mean change scores (Δ) shown with 95% confidence intervals*

	INT			CON			Interaction (day × group) P value	Cohen *d*
	Baseline	**Follow-up**	**Δ (95% CI)**	**Baseline**	**Follow-up**	**Δ (95% CI)**		
TC (mmol·l^{-1})	5.09 ± 1.14	4.95 ± 1.39	- 0.14 (-0.59 to 0.32)	5.14 ± 0.89	5.18 ± 1.13	0.04 (-0.46 to 0.54)	0.57	-0.17
HDL-C (mmol·l^{-1})	1.12 ± 0.29	1.14 ± 0.32	0.02 (-0.08 to 0.12)	1.03 ± 0.19	1.03 ± 0.27	0.00 (-0.09 to 0.09)	0.79	0.07
LDL-C (mmol·l^{-1})	3.39 ± 0.95	3.26 ± 1.12	-0.13 (- 0.50 to 0.24)	3.52 ± 0.77	3.35 ± 0.76	-0.17 (-0.55 to 0.21)	0.86	0.05
TAG (mmol·l^{-1})	1.27 ± 0.50	1.22 ± 0.58	-0.05 (-0.25 to 0.14)	1.29 ± 0.52	1.76 ± 1.10	0.47 (-0.23 to 1.18)	0.06	-1.02
NEFA (mmol·l^{-1})	0.56 ± 0.29	0.91 ± 0.55	0.35 (-0.10 to 0.80)	0.74 ± 0.58	0.69 ± 0.62	-0.06 (-0.87 to 0.75)	0.29	0.40

6.3.8. Health and Wellbeing Outcomes

Of the subjective constructs investigated, ratings of fatigue symptoms, general health and self-efficacy all displayed a significant day × group interaction ($P < 0.05$) (Figure 6.12). Total scores on the fatigue severity scale (FSS) significantly decreased at follow-up in the INT group from 35 ± 11 to 27 ± 10 ($P < 0.01$), yet remained unchanged in the CON group (33 ± 8 to 35 ± 11). Participants' perceptions of their general health significantly increased at follow-up in the INT group from 51 ± 21 to 65 ± 15 ($P < 0.05$) according to items on the SF-36. There was no change between time points in the CON group (54 ± 13 to 52 ± 18). Self-efficacy significantly increased at follow-up in the INT group from 31 ± 5 to 36 ± 2 ($P < 0.01$) but remained the same in the CON group (33 ± 5.0 to 29 ± 8.5). There were no significant differences in symptoms of shoulder pain between or within the two groups (INT; 10 ± 11 to 13 ± 15, CON; 19 ± 21 to 14 ± 15).

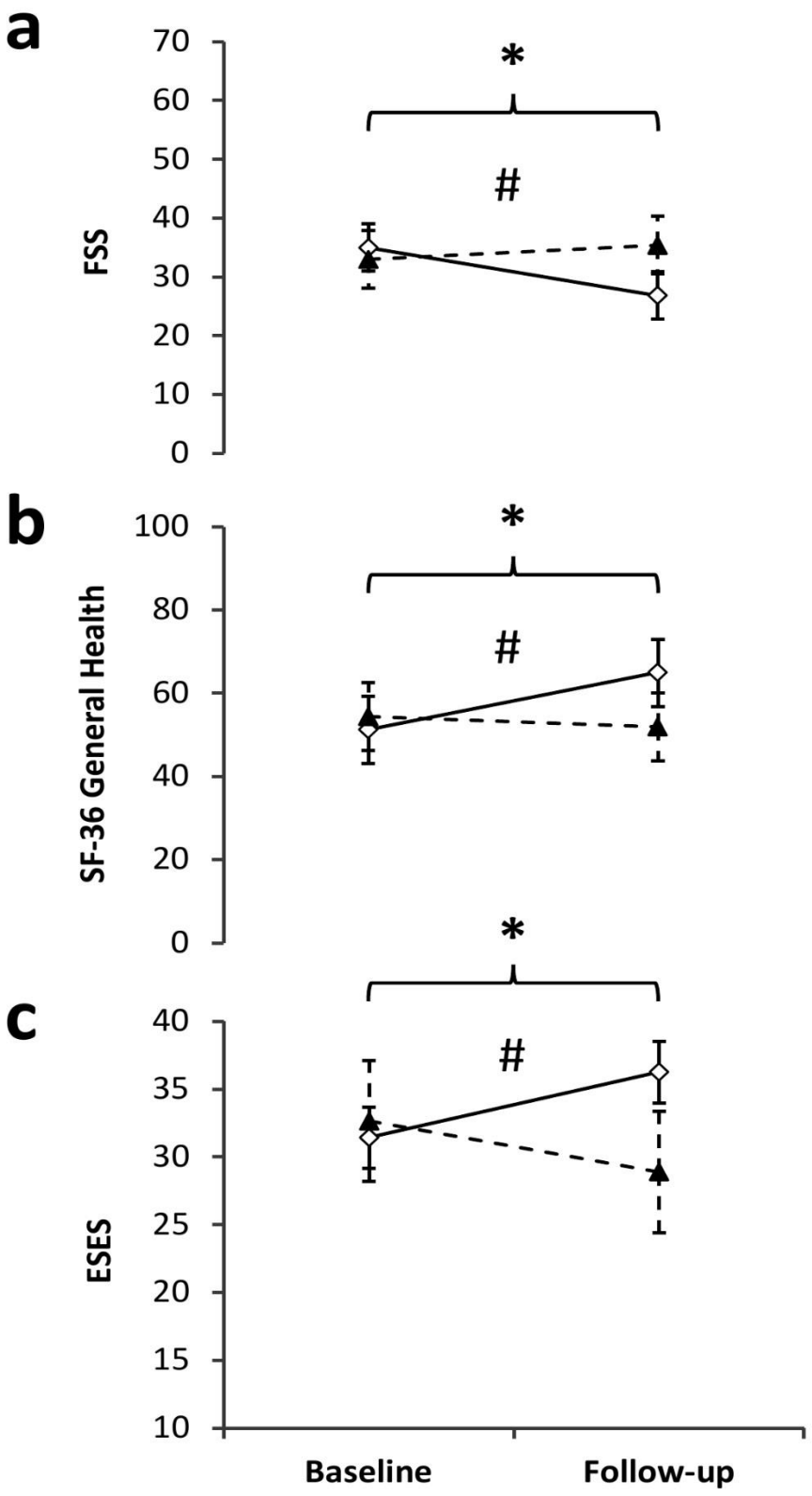

Figure 6.12: Fatigue Severity Scale (FSS) (**a**), SF-36 General Health (**b**) and Exercise Self-Efficacy Scale (ESES) (**c**) scores at baseline and follow-up for the INT (Solid black line and open diamond) and CON (Dashed line and black triangle) group. Values are means ± CI. * denotes a significant day × group interaction ($P < 0.05$). # denotes values are different pre-post within INT group ($P < 0.05$)

6.4. DISCUSSION

This current study assessed the impact of a moderate-intensity (60 – 65% $\dot{V}O_2$ peak) 6-week exercise intervention on markers of metabolic and cardiovascular health, functional capacity, body composition and wellbeing in individuals with chronic paraplegia. With regard to our primary hypothesis, these results demonstrate that 6 weeks of arm crank exercise improved fasting measures of insulin sensitivity (HOMA-β and HOMA-IR) and serum insulin concentrations. Functional capacity, quantified by peak oxygen uptake and workload, increased in the INT group yet remained unchanged in the CON group. There was a tendency for improved body composition; evident by increased LM in the arms and reduced FM in the trunk in the INT group. With respect to systemic inflammation, there was a moderate effect size (d = -0.67) for reduced IL-6 in the INT group. There were no significant differences in the responses pre-post between groups for lipid profiles, despite a trend for reduced and elevated serum TAG in the INT and CON groups, respectively. Importantly as exercise sessions were not supervised in the laboratory, PA behaviour was significantly different between groups, confirming a high level of compliance in the INT group. Furthermore, we noticed positive changes for health and wellbeing outcomes, with significant differences in symptoms of fatigue, perceptions of general health and self-efficacy in the INT compared to the CON group. With respect to the CON group, no significant changes were observed in any of the tested parameters.

6.4.1. Metabolic and Cardiovascular Health

Insulin Resistance/ Sensitivity

These results demonstrate that fasting plasma glucose levels are maintained with reduced circulating insulin concentrations with 6 weeks of moderate-intensity arm crank exercise. Also, estimation of β-cell function by HOMA-β suggests that there is a reduced pancreatic β-cell secretion of insulin in the INT group. However, assessing insulin secretion directly from systemic concentrations of insulin is a challenge, due to its complex interplay with insulin resistance and hepatic insulin clearance (Cobelli *et al.*, 2007). Manns *et al.*, (2005) suggested that PA was moderately associated with HOMA-IR (r = -0.429) and fasting insulin (r = -0.397), although these relationships were not-significant. Other cross-sectional research found no associations between LTPA and HOMA-IR or fasting insulin

(Buchholz *et al.*, 2009), or between time spent performing PA (min/week) and fasting insulin (Jones *et al.*, 2004). In a recent 16-week hand cycle training study, Bakkum *et al.*, (2015) observed similar improvements (mean Δ ± standard error) in HOMA-IR (- 0.5 ± 0.2 vs - 0.4 ± 0.2) and fasting insulin (-14.3 ± 4.0 vs. – 10.7 ± 5.0 pmol·L^{-1}) in comparison to the INT group in this present study. Whilst we only observed a trend for a day × group interaction effect between the two groups (P = 0.079) in HOMA-IR, that we can demonstrate a similar magnitude of change to previous research despite a considerably shorter protocol duration (6 weeks vs 16 weeks), is encouraging.

There is a distinct lack of research looking at the effect of upper body exercise on the response to a standardised glucose load in individuals with SCI. These studies have primarily been limited to FES of the lower extremities, with some finding positive effects on insulin sensitivity (Mohr *et al.*, 2001; Jeon *et al.*, 2002), whereas another study did not (Ryan *et al.*, 2013). Although our differences were not statistically-significant, insulin sensitivity ($ISI_{Matsuda}$) assessed over 2- hours during the OGTT, improved in the INT group (16%) and remained the same in the CON group (-3%) (*d = 0.*44). No changes were observed for plasma glycaemic or serum insulinaemic responses. Eight weeks of high-intensity (70 – 80% HRR) and low-intensity (40 – 50% HRR) arm crank training showed a *reduction* (-33%) and a non-significant improvement (56%), respectively, in insulin sensitivity assessed using the HOMA-CIGMA test (de Groot *et al.*, 2003). Different responses with high and low-intensity exercise in the de Groot and colleagues (2003) study may be explained by the groups not being matched (differences in age and sex at baseline); and the small sample size (n = 3 in each group). In contrast to this present study, participants had acute instead of chronic SCI and a different technique was used to assess insulin sensitivity.

Potentially, the reason why we did not see significant differences in plasma glycaemic or serum insulinaemic responses, might be due to the fact that between-test reliability of the response to an OGTT can be poor (CV; 8 – 15%) for repeated tests (Libman *et al.*, 2008; Jimenez-Navarro *et al.*, 2010). We observed considerable variability in insulin sensitivity assessed during the OGTT in the CON group pre-post (CV; 35%, 26% and 21% for glucose iAUC, insulin iAUC and $ISI_{Matsuda}$, respectively). This variability may have impacted on our ability to detect significant differences between the two groups. It has

been suggested that HOMA-IR (fasting) compared to the $ISI_{Matsuda}$ (postprandial), represents a different balance of sensitivity (hepatic vs. peripheral) (Matsuda & DeFronzo, 1999; Radziuk, 2014). The trend for a reduction in HOMA-IR and reduced fasting serum insulin in this current study, when viewed in light with the lack of change in $ISI_{Matsuda}$, suggests 6 weeks of moderate-intensity arm crank exercise improved hepatic (but not peripheral) insulin sensitivity.

Metabolic Regulation

A significant interaction effect was observed for fasting RER, with a large effect size (*d* = -1.04) between groups for reduced and increased values pre-post in the INT and CON group, respectively. Lower RER represents a greater reliance on fat oxidation in the fasted state. However, limitations have been proposed with using fasting RER to make assumptions regarding substrate oxidation; it can be sensitive to differences in energy balance and diet macronutrient composition in the days preceding the measurement (McNeill *et al.*, 1988; Schutz, 1993). Yet these changes in RER are supported by the trend ($P = 0.118$) for increased serum NEFA concentrations (Δ 0.35 ± 0.71 $mmol \cdot L^{-1}$) in the INT group. Taken together these data could suggest increased mobilisation and preferential oxidation of fatty acids. Increased reliance on fat oxidation in the fasted state has been associated with improved insulin sensitivity (Goodpaster *et al.*, 2003; Kelley, 2005), metabolic flexibility (Galgani *et al.*, 2008) and increase fat loss with exercise (Barwell *et al.*, 2009). Nevertheless, whole body RER and serum NEFA concentrations do not provide a direct measure of skeletal muscle metabolism.

Cross-sectional evidence has suggested TAG concentrations are reduced in active compared to inactive individuals with SCI (Nooijen *et al.*, 2012; Matos-Souza *et al.*, 2013), whereas other studies have found no association (Manns *et al.*, 2005; Hetz *et al.*, 2009a; Buchholz *et al.*, 2009; Flank *et al.*, 2014). Arm crank exercise at 70 – 80% HRR for 8 weeks - a similar intensity and duration to this present study, has shown a trend for ($P \leq 0.10$; Hooker & Wells, 1989) and significant (de Groot *et al.*, 2003) decreases in serum TAG. However, other research has revealed no change in TAG in response to 12 and 16 weeks of exercise training (El-Sayed & Younesian, 2005; Bakkum *et al.*, 2015). Whilst we also noticed no significant differences pre-post in the INT group with regards

to serum TAG, there was a trend for an interaction effect (P = 0.060) and a large effect size (*d* = -1.02) when compared to changes in the CON group. This could point to the maintenance of TAG turnover. Improvements in mitochondrial fatty acid oxidation and altered lipid content in skeletal muscle has been observed with exercise training (Holloszy & Coyle, 1984; Martin, 1996; Bruce *et al.*, 2006). Increased mobilisation of serum NEFA and differences in responses between groups in serum TAG concentrations could suggest the maintenance/increase tissue TAG turnover, which has been implicated with improvements in insulin resistance (Moro *et al.*, 2008; Stinkens *et al.*, 2015).

Blood Lipids

Dyslipidaemia was common in our participants, 50% had total cholesterol values ≥ 5 mmol·L^{-1} and 65% had elevated LDL-C (≥ 3 mmol·L^{-1}) and depressed HDL-C (≤ 1.03 mmol·L^{-1} for males and ≤ 1.29 mmol·L^{-1} for females). Despite this no significant differences were observed for total cholesterol, HDL-C or LDL-C. In support of our findings, a systematic review by Carlson and colleagues (2009) concluded there was insufficient evidence to suggest that exercise alone improves dyslipidaemia in people with SCI. In able-bodied individuals, greater improvements in lipid profiles have been observed following high-intensity exercise (O'Donovan *et al.*, 2005) or with higher amounts of weekly exercise (Kraus *et al.*, 2002). The variation in exercise intensities and time/duration of interventions reported previously in persons with SCI (Table 2.7), makes it difficult to tease out the effect of upper body exercise on lipid profiles. Even a short intervention (2 weeks) consisting of a high fibre, low fat diet plus 45 – 60 minutes of daily exercise (70 – 85% $\dot{V}O_2$ max) has shown significant (20 – 30%) reductions in total cholesterol and LDL-C in able-bodied participants (Izadpanah *et al.*, 2011). Therefore, it remains to be seen whether the combination of exercise and dietary restrictions are the most effective way of improving lipid profiles in persons with SCI.

Markers of Inflammation

Measured concentrations of CRP for our participants (mean ± SD; 4.43 ± 4.22 $mg \cdot L^{-1}$) were consistent with that typical of untrained chronic SCI (Wang *et al.*, 2007), with 40% of the participants showing an increased risk of CVD (CRP > 3 $mg \cdot L^{-1}$). However, IL-6 concentrations were somewhat lower than those commonly reported in persons with chronic SCI (Manns *et al.*, 2005; Bakkum *et al.*, 2015). A recent systematic review Neefkes-Zonneveld *et al.*, (2015), evaluated the effect of long-term PA on markers of systemic inflammation in persons with SCI. Following the assessment of titles and abstracts of 1825 papers, only 11 were included in the review after the authors read the full text. Of these papers 5 were cross sectional with subjective measurement of PAEE and there were no RCT's. The authors noted that these included studies had a high risk of bias and 'very low' levels of evidence; this reflects the dearth of quality research looking at the impact of exercise on markers of inflammation in persons with SCI. There were no significant differences in serum CRP measured in the present study. Adipose tissue is a source of inflammatory cytokines (Fain, 2010; Thompson *et al.*, 2012), which trigger the acute phase response, whereby proteins, such as CRP, are released from the liver (Moshage, 1997). Weight loss is therefore associated with a decline in CRP (Selvin *et al.*, 2007). Considering we observed only modest reductions in FM, with a trend at the trunk, it is perhaps not surprising there are no changes in serum CRP.

The interaction effect for IL-6 was approaching significance ($P = 0.104$), with a tendency for reduced and increased concentrations in the INT and CON group, respectively. There was a moderate effect size ($d = -0.67$), which became large ($d = -0.97$) after comparing the participants with serum IL-6 concentrations ≥ 0.8 $pg \cdot ml^{-1}$ ($n = 5$) in the INT group to the CON group. This finding is supported by the significant ($P < 0.05$) negative association ($R_s = -0.61$) between baseline IL-6 concentrations and Δ in IL-6 over the course of the 6 weeks in the INT group. Therefore, the largest reductions in IL-6 were observed in those with higher serum concentrations at baseline. Rosety-Rodriguez *et al.*, (2014) found a significant reduction in IL-6 concentrations with 12 weeks of ACE twice a week. However, their participants had substantially elevated serum IL-6 concentrations compared to our study cohort. They also observed a significant decrease in waist circumference (Δ 3.7 cm), which was used as a surrogate measure of central obesity.

These factors may explain the greater magnitude of change in serum IL-6 compared to this present study.

Adipokines

There was a day effect for adiponectin, with significantly (P = 0.014) reduced serum concentrations at follow-up across both groups. This was mainly driven by a significant (P = 0.017) decrease in the INT group (Δ mean ± SD, -1.17 ± 1.44 $ng \cdot ml^{-1}$). This is in contrast to findings by Rosety-Rodriguez *et al.*, (2014) who observed a non-significant increase in the exercise compared to control group. Adiponectin is said to be both 'insulin sensitising', inhibiting hepatic glucose production and increasing substrate metabolism (Yamauchi *et al.*, 2002; Kadowaki *et al.*, 2006), and is anti-inflammatory (Ouchi & Walsh, 2007). However, as levels have decreased with exercise this seems counter-intuitive. A systematic review, looking at the utility of exercise as a potential modifier of adiponectin levels in able-bodied persons, found the evidence from RCTs to be inconclusive (Simpson & Singh, 2008). Other factors are known to modulate insulin sensitivity besides adiponectin. As we have seen favourable changes in fasting indices of insulin resistance and there is conflicting evidence in able-bodied cohorts, more evidence is necessary to understand the role of exercise *per se* on adiponectin and the interplay with insulin sensitivity.

Unlike Rosety-Rodriguez *et al.*, (2014) there were no significant effects of moderate-intensity ACE exercise on serum leptin concentrations. These findings are of interest considering leptin and insulin compete for the same signalling molecules (Baranova, 2008). Consequently decreased leptin has been shown to improve insulin efficiency (Benomar *et al.*, 2005). As it is secreted from adipose tissue, circulating serum leptin concentrations directly correlate with FM (Maffei *et al.*, 1995; Das, 2001). Across our sample of individuals with chronic paraplegia, serum leptin concentration are significantly associated with whole-body FM measured via DEXA at baseline (r = 0.909, P < 0.001).

Functional Capacity

Based on physical capacity norms for men with paraplegia (Janssen *et al.*, 2002), only 20% of our cohort had average $\dot{V}O_2$ peak values at baseline (22.71 – 29.20 ml·kg^{-1}·min^{-1}), the rest were either considered fair (45%; 16.51 – 22.70 ml·kg^{-1}·min^{-1}) or poor (35%; < 16.50 ml·kg^{-1}·min^{-1}). No significant changes in $\dot{V}O_2$ peak or maximal workload were observed for the CON group. $\dot{V}O_2$ peak and maximal workload were significantly elevated in the INT group, by 19 and 25% respectively. This is similar to the group means of 18 and 23% found when summarising the effects of 4 – 32 weeks of upper body exercise on person with chronic paraplegia (Section 2.10.2.1). We noticed that PAL was positively associated with cardiorespiratory fitness at baseline (r = 0.651, P = 0.002), a finding which has also been observed previously (Muraki *et al.*, 2000; de Groot *et al.*, 2010; Nooijen *et al.*, 2012). No relationship was observed between changes in PAL and changes in cardiorespiratory fitness over the course of the 6 weeks in the INT group. Nevertheless, we strongly believe cardiorespiratory fitness is an outcome of habitual PA.

6.4.2. Body Composition

Both groups reduced body mass over the 6 weeks, -0.92 ±1.86 kg and -0.61 ± 1.87 kg for the INT and CON group, respectively. In overweight/obese individuals with chronic SCI, Chen *et al.*, (2006), showed significant weight loss (-3.5 ± 3.1 kg) with a 12-week weight management program (covering nutrition, exercise and behaviour modification). Previous exercise intervention studies have found no considerable changes in body mass (Midha *et al.*, 1999; Duran *et al.*, 2001). This is perhaps not surprising without controlling energy intake to create a significant energy deficit. It is also possible that changes in body mass with exercise alone are diminished as a result of compensatory behaviours, such as increased energy intake (King *et al.*, 2008; Melanson *et al.*, 2013; Blundell *et al.*, 2015). Although not our primary outcome measure, this study is the first to assess the impact of exercise on body composition in individuals with SCI whilst monitoring energy intake. There were no significant changes (P > 0.225) in total energy intake or macronutrient composition between groups. However, looking solely at body mass does not provide an indication of changes in body composition.

There was a day effect for decreased LM in the legs, with mean change values of -0.2 kg for both groups. Yet there was a tendency for day × group interaction effects for increased

LM in the arms (P = 0.051) and reduced FM in the trunk (P = 0.063) after 6 weeks of moderate-intensity exercise. However, the very modest increase in LM in the arms (0.1 kg) is only half of what was lost in the legs. There is potentially a loss of sensitivity with DEXA measurements when looking at smaller body compartments. A 3-day high carbohydrate diet, leading to increased glycogen storage alongside water in skeletal muscle, resulted in increased total and appendicular LM measured by DEXA (Rouillier *et al.*, 2015). Whilst it is possible that diet can influence DEXA measurements, there were no significant differences in carbohydrate intake between groups pre-post, and both groups lost the same amount of LM in the legs. This is disconcerting, as it would appear even participants with chronic paraplegia (TSI; 16.9 ± 10.3 years) continue to show LM atrophy in paralysed muscles over 6 weeks. Considering the importance of the quantity and quality of muscle mass with regards to insulin sensitivity (Section 2.4.3), training adaptations in response to upper body exercise may always be in the face of negative changes in paralysed muscle. Few studies have analysed changes in body composition following upper body exercise in different body compartments using DEXA. Although not significant, Bakkum *et al.*, (2015) observed an identical reduction in FM at the trunk (-0.5 kg) compared to this present study. The tendency for reduced FM in the trunk is of importance when you consider the adverse metabolic profile associated with increased central obesity in individuals with SCI (Gorgey *et al.*, 2011).

6.4.3. Energy Expenditure

Mean RMR across both groups was very similar to that reported in a sample of participants with chronic (TSI; 11.4 ± 9.5 years) paraplegia (1464 ± 199 vs 1472 ± 228 $kcal \cdot day^{-1}$) (Buchholz *et al.*, 2003a). To our knowledge no studies have previously looked at the effect of moderate-intensity exercise on RMR in this population. As RMR represents the largest component of TEE, any increase in response to exercise are potentially of great importance, particularly in persons with SCI who have a reduced RMR as a result of LM atrophy. We observed a trend (P = 0.08) for an increase (3%) in RMR in the INT group and decrease (-2%) in the CON group. Considering both groups lost total LM, the increase in the INT group maybe a response to biological adaptations to exercise training (Speakman & Selman, 2003).

PAL and PAEE measured at baseline by the AHR were lower than values reported previously for individuals with SCI using the Flex-HR method (1.37 ± 0.11 vs. 1.46 ± 0.25; Buchholz *et al.*, 2003b) or DLW (347 ± 166 vs. 679 ± 280 kcal·day^{-1}; Tanhoffer *et al.*, 2012), respectively. Whilst these differences could be attributed to bias inherent to the measurement technique, and variance in study populations (our cohort were older and had a greater TSI), it suggests our participants were by definition more inactive. In the INT group, where complete sets of pre-post AHR-IC and GENEActiv data are available (n = 8), the measured increase in PAEE over the 7-day monitoring period was 65 ± 104 and 102 ± 56 kcal·day^{-1} for the AHR and GENEActiv, respectively. This is compared to the estimated average daily increase in PAEE of 109 ± 41 kcal·day^{-1} as a result of the intervention, predicted during the test of the work rate to elicit 60% $\dot{V}O_2$ peak in the laboratory at baseline. As previous work suggested, there was more random error when predicting PAEE with the GENEActiv device, compared to the AHR-IC (Chapters 4 & 5); the AHR-IC was used as the most appropriate measure of PAEE in this study. As demonstrated by the large SD, there was noticeable variation in responses in the INT group measured by the AHR-IC, range -85 to 219 kcal·day^{-1}, with two participants showing a decrease in PAEE. It is conceivable that the prescribed ACE (60 – 65% $\dot{V}O_2$ peak) replaced non-prescribed (existing) PA of a similar intensity (wheelchair propulsion), explaining some of the variation in measured PAEE responses. This concept has been referred to as 'substitution' (Thompson *et al.*, 2014), and may explain the erosion of increased PAEE observed in certain participants. However, during the follow-up monitoring period participants in the INT group reduced time spent performing sedentary behaviours (-31 min·day^{-1}). In contrast, over a 7-day period the 4 x 45 minute training sessions would reduce sedentary time by 26 min·day^{-1}. Whilst there is a degree of inter-individual variability, this observation suggests substitution of physical activity behaviours had a minimal impact on the overall INT group's response, as there was a greater mean change than predicted. The ability to accurately quantify such concepts is a clear advantage of using validated wearable devices to measures free-living PAEE in this study.

Both PA monitoring devices were well tolerated, being worn for 6 ± 1 days, with a daily wear time percentage of 97 ± 4% across both groups at each time point. This is a longer duration than that used previously, to objectively quantify free-living PAEE in individuals

with SCI (2 days; Nooijen *et al.*, 2012) and the most accurate self-report method (PARA-SCI, 3 day PA recall questionnaire; Ginis *et al.*, 2005). The GENEActiv was primarily used to monitor compliance, utilising its 3 week battery life with a sampling frequency of 30 Hz. Compliance was excellent, with 92% of the cohort completing all 24 training sessions. Previous research in this population has reported high (46%) drop-out rates (Bakkum *et al.*, 2015), bringing into question the feasibility of long term exercise interventions in persons with SCI. Consequently, these results suggest that exercise in the home, may make exercise interventions more attractive for this population, overcoming transportation barriers alluded to previously (Section 6.2.2).

6.4.4. Health and Wellbeing Outcomes

Positive changes were observed for various psychological outcomes in this present study, with significant day × group interaction effects for ratings of fatigue, general health and exercise self-efficacy. In comparison to controls the INT group showed decreased symptoms of fatigue and increased perceptions of general health and self-efficacy. Quality of life and self-efficacy have previously been shown to increase in persons with SCI in conjunction with increased PA (Manns & Chad, 1999; Zemper *et al.*, 2003; Warms *et al.*, 2004). Furthermore, Tawashy *et al.*, (2009) suggested that greater levels of PA are associated with less secondary complications (pain, fatigue and depression) in individuals with SCI. These positive changes might have implications for the maintenance of behaviour change, and support the efficacy of the intervention from a psychological perspective. No significant differences in shoulder pain were observed with exercise, which is in conjunction with Dyson-Hudson *et al.*, (2007) who found using the WUSPI that 12 weeks of arm crank training does not increase shoulder pain in persons with SCI. This is of importance as concerns have previously been raised about the suitability of ACE as a training mode, as it may contribute to shoulder overuse and trigger the onset of pain and injury (Jacobs *et al.*, 2001; Nash *et al.*, 2002).

6.4.5. Inter-individual Variability

Recommendations for presenting continuous data in studies with a small sample sizes were recently published (Weissgerber *et al.*, 2015). The authors encouraged a more complete presentation of data. As such our figures have displayed individual responses as well as summary statistics, allowing for a more transparent and meaningful interpretation of results. This also allowed us to identify individuals in the INT group who responded differently to hypothesised in a number of metabolic control and inflammation outcome measures. It has been suggested that ~ 7% of participants experience adverse adaptations in two or more risk factors for CVD and T2DM in response to regular exercise (Bouchard *et al.*, 2012). The majority of participants in the INT group showed evidence of some 'improvement' post training in fasting outcomes of metabolic control (92%, 75% and 75% of participants for fasting insulin, HOMA-β and HOMA-IR, respectively) and inflammation (82% and 73% of participants for IL-6 and CRP, respectively). An alternative approach to the 'non-responders' hypothesis is to take a closer look at exercise compliance. Interestingly, the two participants who showed a decline in PAEE pre-post (-85 and -60 kcal·min^{-1}) in the INT group displayed increased insulin resistance (HOMA-β; 3% and 14%. HOMA-IR; 9% and 20%) and decreased insulin sensitivity ($ISI_{Matsuda}$;-27% and -15%). Questions could be raised about the compliance of one of these participants; they were -13 b·min^{-1} from the prescribed exercise heart rate and lacked progression in workload to maintain heart rate across the 6 weeks (Weeks 1 – 3: 155 b·min^{-1} and 39 W; Weeks 3 – 6: 151 b·min^{-1} and 38 W). This participant also increased FM (0.66 kg), and markers of inflammation (IL-6; 108% and, CRP; 130%). Another participant who did not attain the prescribed heart rate and only completed 22 exercise sessions out of 24, also displayed adverse adaptations to exercise (↑ FM; 0.34 kg, ↑ IL-6: 27% and, ↑ CRP: 51%).

6.4.6. Strengths and Limitations

Strengths of the current study include the well-defined (chronic Paraplegia) and relatively homogenous sample, compared with previous studies conducted in this population (mixture of acute/chronic and tetraplegic/paraplegic). Most studies have been conducted using only male participants. Therefore, very few findings to date can be generalised to females. The prevalence of females with SCI is 19.3% reported on the USA national

database, 25% of our cohort were females. Thus a similar ratio of males to females is represented in our sample. Unlike this present study, previous research which has sampled eumenorrheic females have not mentioned controlling for the phase of menstrual cycle, which has been shown to have profound effects on insulin sensitivity and fat oxidation (Pulido & Salazar, 1999; Lundsgaard & Kiens, 2014). Although we have included both complete and incomplete injuries, Bauman *et al.*, (1999) found no significant difference in the incidence of disorders of carbohydrate metabolism between the two neurological subgroups of patients with paraplegia (complete: 24% and incomplete: 31%). There was also an extra inclusion criteria for participants with neurological incomplete injuries; they needed to be regular wheelchair users (self-reported as > 75% of a waking day).

By allocating the last 11 participants to various treatment groups using the minimisation approach advocated by Altman & Bland, (2005), the two groups were well matched for various injury characteristic (Table 6.1). Consequently, there were no significant differences ($P > 0.29$) between groups with regards to injury or participant characteristics. Unfortunately, there was a significant difference between groups at baseline with regards to one of the outcome measures, HOMA-β ($P = 0.047$). Considering the huge variation with SCI injury characteristics, even within a well-defined group, and that differences were observed in only one of the many outcome measures included in this study, using the minimisation approach to match groups for confounding variables could be considered a strength. To our knowledge, only one previous study (Rosety-Rodriguez *et al.*, 2014) also used a 'true' control group to compare the impact of upper body exercise. Almost all of the exercise studies in individuals with SCI have been conducted in a laboratory setting or rehabilitation centre. By facilitating training in the home, we have observed elevated levels of compliance with no drop outs; perhaps a direct result of minimising additional time demands and/or removing transportation issues.

The use of validated devices to measure compliance and PA is another significant strength, as it allows us to tease out novel concepts from able-bodied research, such as 'substitution' which may diminish the impact of an exercise intervention. Moreover, using a validated PA monitoring device, specific for this population, allowed us to screen for inactive participants at baseline. Besides Bakuum *et al.*, (2015) this is only the second study that we are aware of to employ inclusion criteria based on PA. Consequently, our

cohort had low PAL (1.37 ± 0.11) and cardiorespiratory fitness (18.47 ± 5.28 $ml \cdot kg^{-1} \cdot min^{-1}$), with 40% of participants displaying metabolic syndrome or an increased risk of CVD based on serum CRP concentrations. This is similar to the prevalence of metabolic syndrome reported in a cross-sectional study on persons with SCI (Nelson *et al.*, 2007). This approach meant our cohort was a fairly representative sample of the wider population of individuals with chronic paraplegia. Moreover, previous research has mostly relied on fasting indices of insulin resistance. Yet this current study also utilised a dynamic test (OGTT) to assess changes in insulin sensitivity, which to our knowledge, has not previously been used in upper body exercise interventions in this population before.

In the context of other upper body training studies conducted in persons with SCI (Table 2.7) our sample size (n = 20) is one of the largest reported. However, in some of the secondary outcome measures, where trends and moderate effect sizes have been observed, our ability to detect significant effects is probably limited by the small sample size. Furthermore, the duration of the intervention was relatively short, and no follow-up was included to determine whether positive effects on PA behaviour, psychological outcomes and health induced by exercise were maintained. Although we included a 'true' control group there was considerable variation in their response in a number of outcome measures. While follow-up measurements suggest no change in PA behaviour, the fact that there was a reduction in body mass might indicate changes in dietary habits. Although non-significant, the weighted food records showed the CON group to consume fewer calories at follow-up compared to the INT group (-151 vs -28 $kcal \cdot day^{-1}$). The limitations with self-reported energy intake have been widely acknowledged (Livingstone & Black, 2003; Poslusna *et al.*, 2009), but a recent publication suggests they are inaccurate and unacceptable for use in scientific research (Dhurandhar *et al.*, 2014). Considering this, and that the change in body mass in the CON group is primarily explained by a loss of LM in the trunk and legs, this change in body mass is most likely a result of muscle fibre atrophy of paralysed muscles over the 6-week period.

6.4.7. Conclusion

A 6-week moderate-intensity home-based ACE intervention improved insulin resistance in males and females with chronic paraplegia. Our findings would also suggest that fasting fatty acid oxidation was increased, with a reduction in serum TAG concentrations. Peak oxygen uptake and workload were also improved with 6 weeks of exercise at 60 – 65% $\dot{V}O_2$ peak. Objectively measuring baseline PA behaviour, taking a holistic approach addressing numerous outcome measures in one study, including various health and wellbeing constructs and using a rigorous research design (RCT with true control group), this study is in accordance with recent recommendations (Carlson *et al.*, 2009; Silverman *et al.*, 2012). Positive changes in health and wellbeing constructs, coupled with excellent compliance, suggests home-based ACE has the potential to be used as a long-term behavioural strategy to improve clinical outcomes in persons with SCI.

CHAPTER 7: GENERAL DISCUSSION

7.1. OVERVIEW

The first three experimental chapters of this thesis were designed to assess the accuracy of various commercially available tri-axial accelerometers and a multi-sensor device in the prediction of PAEE in wheelchair users. Specifically, **Chapter 3** analysed the mechanical reliability of the GT3X+ device, using a robust multi-axis shaker table protocol, comprised of various acceleration conditions to replicate a range of physiological movements. This study also sought to identify the most appropriate anatomical location to wear the GT3X+ device, in order to minimise measurement error in the prediction of PAEE in wheelchair users. Human validity was determined using an activity protocol which consisted of outdoor wheelchair propulsion velocities and simulated deskwork. A device comparison study was conducted in **Chapter 4**, where outputs from the GT3X+ were compared to raw acceleration signals from the GENEActiv. Both devices were worn on the upper arm and wrist. The performance of these devices was assessed across a wide range of wheelchair propulsion velocities, and differing gradients, along with an activity which could be misclassified as wheelchair propulsion in a controlled laboratory setting. Physical activity energy expenditure prediction models were developed using corresponding criterion data and outputs from each device from each task, using linear regression analysis. Error statistics were then determined using a leave-one-out cross validation analysis.

Chapter 5 aimed to determine the validity of using a multi-sensor device, which incorporated heart rate and acceleration signals (Actiheart), to predict PAEE in wheelchair users, using the same laboratory protocol as **Chapter 4**. Considering the inter-individual variance in cardiovascular responses to exercise is high among this population, the benefit of conducting an individual heart rate calibration from data collected during a maximal ACE test to exhaustion was also explored. Furthermore, concurrent validity was assessed over a twenty-four hour free-living period by comparing the Actiheart to a self-reported PA log. **Chapter 6** aimed to assess the impact of a six week home-based moderate-intensity ACE exercise intervention on insulin resistance in persons with chronic paraplegia. Secondary outcome measures included changes in functional

capacity, body composition, markers of inflammation, serum adipokine concentrations and various health and wellbeing outcomes. A RCT using minimisation to control for confounding variables was adopted as the study design, recruiting inactive male and female participants at baseline (PAL $\leq$ 1.60). Changes in outcome measures were compared to a lifestyle maintenance control group.

A summary of the results of all four experimental chapters is outlined below:

Physical Activity Monitor Method Development

Chapter 3: Influence of anatomical placement and mechanical reliability of the GT3X+ accelerometer in the prediction of physical activity energy expenditure in manual wheelchair users

- The commercially available GT3X+ device demonstrated excellent intra- (range; 0.2 to 4.7%) and inter-unit (0.9 to 5.2%) reliability across all axes during mechanical testing.
- Of the three anatomical locations considered, a wrist mounted GT3X+ provide the most accurate prediction of PAEE in manual wheelchair users during outdoor propulsion.
- The GT3X+ showed poor validity (R_s = 0.25, P < 0.01) when compared to criterion acceleration during mechanical testing, an artefact of tight frequency-dependent bandwidth filters influencing physical activity count outputs.

Chapter 4: Device comparison and development/validation of specific algorithms for the prediction of physical activity energy expenditure in manual wheelchair users

- Raw acceleration signals from the GENEActiv device, worn on either the upper arm or wrist, provided the most valid prediction of PAEE in wheelchair users during a laboratory protocol.
- Error statistics, calculated using a leave-one-out cross-validation analysis, varied between the GENEActiv and GT3X+ as a result of inherent differences in internal components, on-board filtering processes and outputs of each device.
- There were considerable errors (+ 122%) in the prediction of PAEE using the GT3X+ during the folding clothes task, suggesting poor measurement sensitivity for light intensity activities.
- Raw acceleration signals tended to under-estimate PAEE during propulsion on various gradients, suggesting that physiological outputs might be necessary to predict PAEE during tasks with similar acceleration profiles but different energy costs.

Chapter 5: Predicting physical activity energy expenditure in wheelchair users with a multi-sensor device

- PAEE can be accurately and precisely estimated using a combined accelerometer and heart rate monitor device (Actiheart).
- Mean absolute errors across a laboratory activity protocol were substantially reduced with individual heart rate calibration, derived during a maximal ACE exercise test, compared to the manufacturer's proprietary algorithms (mean absolute percentage error; 16.8 ± 15.8% vs. 51.4 ± 38.9%).
- Seemingly, the inclusion of HR with acceleration can better capture the physiological strain associated with propulsion up a gradient or load carriage.

- Twenty-four hour free-living predicted PAEE by the Actiheart with individual heart rate calibration was significantly associated with the reference method (self-reported PA log) ($r = 0.72$), whereas the Actiheart with manufacturer's proprietary algorithms were not ($r = 0.41$).

RCT: Home-based Exercise Intervention

Chapter 6: The impact of a home-based exercise intervention on markers of metabolic and cardiovascular health in individuals with chronic paraplegia

- We found improvements in fasting serum insulin and estimations of β-cell function, a trend for improved insulin resistance (HOMA-IR) in the INT group, but not for insulin sensitivity assessed using plasma glucose and serum insulin responses ($ISI_{Matsuda}$) during an OGTT. These data perhaps reflect an improvement in hepatic but not peripheral (skeletal muscle) insulin sensitivity.
- Our findings would suggest fasting fatty acid oxidation was increased/maintained, with a reduction in serum TAG concentrations, in response to 6 weeks of moderate-intensity upper body exercise. In the face of stable whole-body adiposity, these data suggest an increased TAG turnover.
- Peak oxygen uptake and workload were significantly increased by 19 and 25%, respectively.
- Whilst there was a tendency for reduced FM in the trunk and increased LM in the arms in the INT group, these differences were minimal, - 0.5 kg and 0.1 kg, respectively.
- No differences were observed between groups with regards to lipid profiles or serum adipokine concentrations.
- There was a tendency for reduced IL-6 concentrations, which was more pronounced for participants with higher serum IL-6 levels at baseline, reflected by a moderate effect size between groups (d = -0.67). No changes in CRP concentrations were found.

- Positive changes were observed compared to the CON group for ratings of fatigue, general health and exercise self-efficacy. In conjunction with the excellent compliance, home-based exercise may have the potential to be used as a long-term strategy to improve clinical outcomes in persons with SCI.

7.2. GENERAL DISCUSSION POINTS

7.2.1. The Accurate Measurement of Physical Activity in Wheelchair Users

There is strong evidence from large scale epidemiological studies in the able-bodied population that increased levels of PA, assessed using objective measurement devices, are associated with reduced metabolic risk (Healy *et al.*, 2008; O'Donovan *et al.*, 2013; Loprinzi & Ramulu, 2013; Barreira *et al.*, 2014; Philipsen *et al.*, 2015). However, the quality of comparative evidence in individuals with SCI is reduced, partly due to smaller sample sizes, but also the lack of accurate and validated objective measurement tools to quantify upper body PA commonly performed by this population. Persons with SCI experience an increased incidence of chronic diseases, CVD (Garshick *et al.*, 2005) and T2DM (LaVela *et al.*, 2006; Cragg *et al.*, 2013), plus a heightened frequency of specific component risk factors for CVD (Duckworth *et al.*, 1980; Bauman *et al.*, 1992; Gater, 2007; Bauman & Spungen, 2008) compared to able-bodied counterparts. Therefore, it is of upmost importance to develop methods capable of accurately and reliably quantifying PA in this population, in order to better understand the role that physical inactivity may play in the development of chronic diseases. Improved assessment of habitual PA would permit; appropriate cross-sectional comparisons, allow researchers to comment on the efficacy of behaviour change interventions and potentially inform PA guidelines (Brage *et al.*, 2005).

In agreement with research published whilst this PhD was being written (Garcia-Masso *et al.*, 2014), it is clear that the wrist is the most appropriate anatomical location to wear tri-axial accelerometers in order to predict PAEE in wheelchair users. The GT3X+ worn on the wrist in **Chapter 3** explained the highest amount of variance and displayed the lowest random error when predicting criterion PAEE during outdoor wheelchair propulsion. With movement restricted to the upper limbs in manual wheelchair users, the

most distal anatomical location seemingly offers improved sensitivity to the detection of PAEE during wheelchair propulsion. Previous human testing in able-bodied participants observed a 'plateau/ inverted- U phenomenon' for physical activity count outputs from the GT3X during more vigorous-intensity exercise at higher running speeds (John *et al.*, 2012). Human testing in **Chapter 3** did not reveal this effect during wheelchair propulsion up to speeds of 8 $km \cdot hr^{-1}$. However, counter-intuitive findings of decreased physical activity counts were observed during mechanical testing, when acceleration was held constant but frequency increased. This is a consequence of the on board bandwidth filtering process (0.25 – 2.5 Hz), used by the GT3X+ to discard what it believes to be physiologically unrelated vibrations or noise. Although in reality the majority of humans movements tend to fall between 0.3 and 3.5 Hz (Sun & Hill, 1993), and maximum angular velocities of the forearm during the drive phase in elite wheelchair racers has a frequency component of 3.6 Hz (Wang *et al.*, 2008). As a result, **Chapter 4** was carried out to determine whether these filters had any impact on the prediction of PAEE in comparison to another commercially available tri-axial accelerometer (GENEActiv).

The main output from the GENEActiv is raw acceleration signals, reported as signal vector magnitude (SVM) in *g*-seconds ($g \cdot s^{-1}$). Using SI units has been widely encouraged by subject matter experts in the accelerometry field (Freedson *et al.*, 2012) as it improves accuracy, utility and facilitates easier comparison between devices (Heil *et al.*, 2012; Intille *et al.*, 2012). Results from **Chapter 4** indicate that derived regression equations, using raw acceleration signals from the GENEActiv, better predicted criterion PAEE than physical activity counts from the GT3X+ worn either on the upper arm or wrist. A light-intensity activity of daily living (folding clothes) was chosen whereby activity monitors worn on the upper extremity might over-predict PAEE. The leave-one-out cross validation analysis revealed a sizeable overestimation of PAEE (+122%) using the algorithm developed for the GT3X+ worn on the wrist. This is most likely a result of the GT3X+ having half power frequencies of 0.5 and 2.5Hz. This does not mean that movements within these limits are measured full scale while those outside are not registered at all, but that a scaling filter is applied. Consequently, movements with certain frequency components that are measured full scale, such as folding clothes, would register greater physical activity counts and lead to the over-estimation of PAEE during light intensity activities in free-living. Whilst the raw acceleration signals from the GENEActiv

more accurately predicted criterion PAEE than the GT3X+ device across the laboratory protocol, they tended to under-predict PAEE during propulsion on various gradients. Consequently, the use of a multi-sensor device (Actiheart) was assessed (**Chapter 5**), to see if the addition of a physiological variable was able to distinguish between activities, whereby acceleration profiles were similar but energy costs are different.

To our knowledge, this is the first time the Actiheart device, which incorporates dual-axis accelerometry and heart rate into a single unit worn on the chest, has been assessed in persons with SCI. Findings demonstrated that using proprietary algorithms intrinsic to the device had sizeable PAEE absolute estimation errors (51.4%), which were substantially improved with the use of an individual heart rate calibration (16.8%). Through the use of activity specific algorithms, researchers in the Department of Rehabilitation Science and Technology at the University of Pittsburgh have detailed similar improvements in absolute EE estimation error from 66.1% (Hiremath & Ding, 2011a) to 16.8% (Hiremath *et al.*, 2012) for the multi-sensor SenseWear device in persons with SCI. These findings provide encouragement for the use of multi-sensor devices in this population. The Actiheart, with individual calibration, may be used in future research to give clinicians and researcher a better indication of the volume and intensity of PA necessary to achieve optimal health in wheelchair users. However, associated EE measurement error is still comparatively low compared to that reported for the SenseWear in the able-bodied individuals (Berntsen *et al.*, 2010). Despite improvements in estimation error throughout the method development process in this thesis, it is advisable, when more studies have been published in the area, that the academic community produce a consensus statement addressing the clinical limits of PA assessment in this population.

7.2.2. The Impact of Physical Activity on the Health of Persons with Spinal Cord Injury

Our findings in **Chapter 6** suggest that six weeks of moderate-intensity ACE, four times per week for 45 minutes, improves fasting insulin sensitivity and aerobic fitness in inactive persons with chronic paraplegia. However, no significant improvements were seen with regards to other CVD risk factors. The frequency and duration of exercise sessions in this intervention were considerably greater than the SCI specific PA guidelines

of at least 20 minutes moderate to vigorous-intensity aerobic activity two times per week as proposed by Ginis and colleagues (2011). Furthermore, the 180 minutes of moderate-intensity exercise was also greater than the PA guidelines of 150 minutes suggested by the American College of Sports Medicine required to improve metabolic health (Haskell *et al.*, 2007). Consequently, in agreement with Cowan & Nash, (2010), there are certainly no indications that the minimum dose of PA for persons with SCI are less than the minimum dosing for able-bodied individuals. Especially when you consider voluntary exercise is restricted to the arms, making it difficult to achieve the same whole-body oxygen uptake and energy expenditure associated with exercising the larger muscle groups in the legs. Whilst trends for improved body composition in various body segments were observed, non-significant differences in whole-body FM may explain why no reduction in inflammatory markers were found. Church *et al.*, (2010), demonstrated in 162 sedentary men and women with elevated CRP ($\geq$ 2.0 $mg \cdot L^{-1}$) that exercise training without weight loss is not associated with a reduction in CRP.

There was also a day effect across the groups for reduced LM (-0.2 kg) in the legs over the 6 weeks. Whilst a trivial amount over such a short period, extrapolated over the year this equates to 1.7 kg. Interestingly this was in persons with chronic paraplegia (TSI 17 ± 10 years). Potentially, the inactivity of paralysed skeletal muscle in the legs leads to a reduced muscle protein synthesis (MPS), accounting for much of the induced muscle atrophy (Glover *et al.*, 2008). Two study designs have been proposed in the future directions (Section 7.4) of this thesis which addresses the reduction in whole-body FM and maintenance/increase in LM in the legs. Overall, **Chapter 6** demonstrated that improvements in hepatic insulin sensitivity can be accomplished without favourable changes in body composition.

7.3. CONSIDERATIONS

Specific considerations for each study are discussed in each representative experimental chapter.

7.3.1. Limitations of Method Development Studies (Chapter 3, 4 and 5)

Perhaps the principal limitation of the method development experimental chapters, and other validation research in this population, was the small sample size used. Furthermore, each sample consisted of various aetiologies responsible for wheelchair use. This approach has been taken before (Conger *et al.*, 2014) and provides a robust model for the assessment of PAEE in the broader wheelchair user population. Yun & Ulrich, (2002) suggested that obtaining a representative sample of the entire population of interest is necessary, rather than using only a subgroup of that population. The inclusion of a diverse range of participants is also in accordance with best practice recommendations for PA validation studies (Bassett *et al.*, 2012), and we showed no differences in prediction error when various aetiologies responsible for wheelchair use were analysed separately (**Chapter 4**). The requirements for large and representative samples present unique challenges, focusing around cost or time involvement, and this is even more problematic when considering the difficulties associated with recruiting from various disabled populations (Yilmaz, 2006). Yet it remains to be seen whether certain algorithms developed specifically for individuals with paraplegia, tetraplegia, or other disabling conditions that require the use of a wheelchair, will offer improvements in the prediction of PAEE. In order to achieve this we strongly encourage research groups to work in unison rather than isolation to foster progress in the development of objective monitoring tools to be used in this population.

The ability to capture raw acceleration data now permits more sophisticated methods of predicting PAEE and allows researchers to detect the types of activity a person is performing (Bonomi *et al.*, 2009a). This might be highly relevant to populations that perform atypical movement patterns, such as wheelchair users. It is possible that predicting PAEE from linear regression equations, as in **Chapter 4**, may be too simple

an approach to examine complex movements or behaviours (Strath *et al.*, 2012). Whilst linear regression models performed well enough to quantify PAEE across various wheelchair propulsion speeds, it cannot be concluded whether this is the case for other activities. A diverse range of activities of daily living were not included in our validation protocols. Furthermore, the one light-intensity activity of daily living (folding clothes) which we incorporated into **Chapter 4**, resulted in considerable over-estimated PAEE values of 122% and 29% for the GT3X+ and GENEActiv both worn on the wrist, respectively. Heil *et al.*, (2012) advised that the shortest possible epoch (1 second) should be selected for activity monitor data collection, to ensure that as much information as possible regarding the original PA related biosignal is retained. This then permits the use of new data analysis methodologies, including hidden Markov models (Pober *et al.*, 2006), artificial neural networks (Staudenmayer *et al.*, 2009; Trost *et al.*, 2012) and classification trees (Bonomi *et al.*, 2009b), which use the rich information to classify certain activities and derive a more accurate estimate of PAEE (Bassett *et al.*, 2012). Future research should take a closer look at these techniques across diverse activity protocols, which include light-intensity ADLs and vigorous-intensity wheelchair propulsion.

7.3.2. Limitations of Randomised Controlled Trial, Home-based Exercise Intervention Study (Chapter 6)

Whilst we objectively confirmed that the CON group did not make any conscious changes to their PA behaviour, we cannot conclude that diet remained the same due to limitations and poor validity associated with self-reported energy intake (Livingstone & Black, 2003; Poslusna *et al.*, 2009). Moreover, this technique would have lacked the sensitivity to quantify the degree of compensation (potential for increased energy intake, Melanson *et al.*, 2013) as a result of additional energy expenditure in the INT group. Whilst objective measures of energy intake are not as advanced or accurate as those used currently to predict free-living energy expenditure, emerging alternatives such as digital photography and, chewing and swallowing monitors are beginning to emerge (Martin *et al.*, 2009; Sazonov *et al.*, 2010; Martin *et al.*, 2012). Although in the early stages of development, and future work is required to develop these tools, they may offer promising alternatives for the accurate measurement of energy intake. Furthermore, these techniques could be used with self-report visual analogue scales to provide free-living subjective ratings of

appetite and satiety. Using overlapping techniques would hopefully minimise limitations inherent to each method of assessment, allowing a more complete understanding of real-life eating behaviours and responses to exercise in the SCI population.

We implemented a rigorous standardisation procedure for the 24 hours preceding each laboratory visit (participants abstained from strenuous exercise, caffeine and alcohol intake) and participants confirmed on arrival at the University that they had fasted overnight (≥ 10 hours). Yet we did not consider controlling for nutritional intake, which may explain some of the variation in responses observed in the lifestyle maintenance CON group. In future research, in order to better isolate the effects of exercise training, it would be beneficial (but potentially costly and impractical with participants staying in overnight accommodation) to standardise meals over the day/s prior to testing.

Carbohydrate ingestion prior to an acute bout of exercise has been shown to suppress the subsequent activation of skeletal muscle AMPK (Guerra *et al.*, 2010), whereas carbohydrate restriction post exercise can elevate the increase in GLUT mRNA levels during recovery (Holloszy, 2005). Training in the fasted state compared to the fed is more effective in increasing skeletal muscle oxidative capacity and enhances intramyocellular lipid breakdown (Van Proeyen *et al.*, 2011), along with improving whole-body glucose tolerance and insulin sensitivity (Van Proeyen *et al.*, 2010). In light of these findings, it is worth pointing out that we did not control the timing or macronutrient composition of food in the hours preceding or following each ACE exercise session. Moreover, to facilitate autonomy and ensure compliance with the busy lifestyle of our participants, we did not control for sessions to be completed at a set time of day or control recovery periods between sessions. Recent evidence would suggest changes in performance outcomes with respect to circadian rhythms (Hill, 2014), and diurnal fluctuations in circulating hormone concentrations may influence skeletal muscle training adaptations (Teo *et al.*, 2011). Therefore, it is entirely plausible to speculate that differences between feeding strategies and time of day when exercise sessions were completed, might be responsible for the variability in responses of the outcome measures in the INT group.

OGTTs were performed following an overnight fast, potentially liver glycogen levels could be depleted. The liver gets first refusal of any glucose absorbed from the gut. Therfore the liver, not adaptations in skeletal muscle in response to the INT, will play a major role in the systemic concentrations of glucose and insulin measured in response to an oral glucose load on the fasted state. Thus, it is possible changes in peripheral (skeletal muscle) insulin sensitivity may have been underestimated using this approach. This is elequantly supported by findings from a year long FES training study (Mohr *et al.*, 2001), which found impovements in whole-body insulin sensitivity using the euglycemic, hyperinsulinemic clamp technique but showed no improvement in glucose tolerance nor the insulin response to an OGTT. However, Bonuccelli *et al.*, (2009) demonstrated that glucose appearance from the gut is almost identical when an OGTT is perfomed in the fasted or fed state. Presumably an intravenous glucose tolerance test (IVGTT), which measures the response to a glucose load injected directly into the blood (Hovorka *et al.*, 2002), would offer improved measurement of skeletal muscle insulin sensitivity as the infused glucose misses the liver at first passing. Therefore, future work should investigate the impact of upper body exercise on insulin sensitivity using either the IVGTT or gold standard euglycemic insulin clamp method. These techniques, with the combination of dual-tracer dilution methodology, would offer more information regarding the effects of insulin on glucose distribution/transport, uptake and endogenous production as a result of exercise training.

Perhaps the most notable consideration for **Chapter 6** is the relatively short nature of the intervention, meaning careful interpretation of the findings are required when drawing conclusions regarding long term adaptations.

7.4. RECOMMENDATIONS FOR FUTURE RESEARCH

The data presented in this thesis highlights potential areas for future research in persons with SCI. These include but are not limited to;

i) Incorporating the use of validated wearable PA monitoring devices and the provision of feedback to facilitate behaviour change and longer term benefits to metabolic health.
ii) The impact of manipulating functional electronic stimulation (FES) frequency on skeletal muscle adaptations to training.
iii) The potential additive effect of combining FES with moderate-intensity upper body exercise on whole-body insulin sensitivity.
iv) The effect of an energy deficit, created through exercise, diet or both, on metabolic flexibility, body composition and markers of systemic inflammation in persons with chronic SCI.

This section will briefly explore these issues, and where appropriate, propose experimental designs to answer these specific questions. Ambiguity also remains regarding the most appropriate exercise intensity to reduce the clustering of various CVD risk factors in this population. For example, high intensity interval training (HIIT) has been proposed in the able-bodied population as a potent time-efficient strategy to induce metabolic adaptations (Gibala & McGee, 2008; Babraj *et al.*, 2009; Gibala *et al.*, 2012). However, it is unlikely the smaller muscle groups of the arm would trigger the same disturbances to whole-body homeostasis as high intensity leg cycle ergometer exercise. Therefore, the appropriate dose would need to be considered and whether this is a feasible exercise modality for persons with SCI who experience increased shoulder pain and functional limitations. Furthermore a longer, more 'real world', PA intervention would be useful to examine (i) the adherence to certain behaviours, and (ii) whether certain metabolic health and CVD risk factors change after a period of several months rather than weeks.

7.4.1. The use of Wearable Physical Activity Monitoring Technology in Wheelchair Users

Besides providing accurate feedback on habitual PA, wearable devices could also be used to set and monitor various lifestyle goals. It has recently been suggested (Thompson & Batterham, 2013) that PA is highly heterogeneous and as such, there is no single outcome measure (Table 2.2) which captures all the relevant information about a given person. There are multiple ways of harnessing the protective properties of PA, because there are numerous dimensions to this behaviour that are all independently important. With technological advancements it is now possible to portray simple and/or sophisticated PA profiles to research participants, promoting a smorgasbord of personalised PA choices with options tailored to the individual's needs and preferences. This approach of maximising feedback to participants and the use of online platforms has been adopted in a recent study recruiting participants (aged between 40 – 70 years) who are at risk of CVD and T2DM (Peacock *et al.*, 2015). Potentially a similar approach could be taken with wheelchair users, using the accurate feedback from the Actiheart, validated and used in **Chapters 5** and **6**, respectively. Ding *et al.*, (2012), developed a physical activity monitoring and sharing platform (PAMS) especially designed to capture PA that is part of the everyday lives of wheelchair users. This information can be shared on social media and can motivate wheelchair users to become more physically active. These methods could be incorporated to promote long term adherence to health promoting behaviours by facilitating autonomy and choice in persons with SCI.

The feasibility of combining sensors should be explored. For example the combination of GPS and accelerometer outputs could provide more detailed information on where a specific behaviour has been performed and its context. Information about the location and purpose of activity behaviours is desirable in surveillance because public health objectives frequently focus on specific types of activity. This is even more pertinent to wheelchair users in order to understand specific barriers to exercise; information regarding these features could provide extremely useful recommendations. Future research could assess whether the incorporation of a tri-axial accelerometer worn on the most sensitive anatomical location (wrist) and individually calibrated heart rate would further improve the PAEE estimation error in wheelchair users. It would be advisable to

develop branched model equations, similar to those used by the Actiheart, to minimise the strengths and weaknesses of these two techniques when used independently.

7.4.2. Neuromuscular Electrical Stimulation or Functional Electronic Stimulation

Surface neuromuscular electrical stimulation (NMES) can be used to stimulate single or multiple muscle groups, with no intention of producing a functional or coordinated movement. Whereas functional electronic stimulation (FES) is a form of NMES that provides stimulation of selected muscles in a coordinated manner resulting in functional movement patterns, such as cycling or rowing. Researchers have advocated SCI specific PA guidelines (Ginis *et al.*, 2011), or encouraged persons with SCI to meet able-bodied guidelines (Cowan & Nash, 2010) when it comes to voluntary upper extremity exercise. However, at present there is no consensus regarding stimulation parameters (amplitude of current, frequency and pulse durations) or the training duration and frequency of NMES or FES in order to exercise paralysed muscles. When summarising the literature to date with regards to the impact of NMES and FES on body composition, Gorgey *et al.*, (2015) suggested LM or FFM of the legs is likely to increase by 10%. The duration of these summarised studies ranged from 6 weeks to 2 years. This increase is likely to off-set the loss in LM (-0.2 kg) in the legs observed in **Chapter 6** over a six week period. Reversing or preventing the process of skeletal muscle atrophy is a desirable outcome, considering that skeletal muscle accounts for approximately 85% of glucose disposal during euglycemic clamp studies (Defronzo *et al.*, 1981). FES leg cycle exercise three time per week for 8 weeks, has been shown to increase GLUT-4 protein levels in paralysed skeletal muscle (+ 72%) (Chilibeck *et al.*, 1999) and improve whole-body glucose utilisation and insulin sensitivity (Jeon *et al.*, 2002).

A recent acute electrical stimulation study (Petrie *et al.*, 2015), found no differences in key metabolic transcription factors or induced fatigue between a 5- or 20- Hz electrical stimulation protocol. A logical extension of this would be to assess the '*Impact of the frequency of electrical stimulation on whole-body glucose utilisation and insulin sensitivity with training in persons with chronic SCI*'. Skeletal muscle in persons with chronic SCI is highly fatigable due to a shift in muscle fibre types and high susceptibility to muscle damage below the level of injury. Consequently this may result in a decline in

evoked torque 48 – 72 hours following an acute NMES bout (Mahoney *et al.*, 2007). As such, there may not be an additional benefit of frequent exercise sessions. Several previous studies have encouraged the feasibility of home-based NMES or FES to overcome transportation barriers (Dolbow *et al.*, 2012a; Dolbow *et al.*, 2012b; Dolbow *et al.*, 2013). Therefore, an 8-week home-based electrical stimulation RCT (frequency of exercise session 3 time per week) with two groups, using different stimulation frequencies (5 and 20 Hz) would be a suitable study design. It would be optimal to use the gold standard hyprerinsulinemic euglycemic clamp or IVGTT to assess insulin sensitivity pre-post intervention. The application of tracer technologies during the hyperinsulinemic clamp to track the uptake/utilisation of glucose would provide extremely useful mechanistic data. Furthermore, peripheral quantitative computed tomography (PQCT) could be used to quantify lower extremity skeletal muscle density and cross-sectional area. The low-force training frequency might hold the potential to improve metabolic health without increasing the risk of bone injuries using NMES or FES in persons with chronic SCI.

Acute exercise studies demonstrate an increased physiological demand during FES hybrid exercise compared to upper body exercise only (Bakkum *et al.*, 2013; Deley *et al.*, 2015). Upper body exercise targets a smaller muscle mass, which is already relatively well adapted to exercise, potentially reducing the potency of a therapeutic stimulus. Comparatively FES-cycling stimulates paralysed and larger muscle groups of the lower extremity. Yet, Bakkum *et al.*, (2015) noticed no additional benefits of performing hybrid exercise (FES-induced leg and handcycling) compared to handcycling in reducing CVD risk factors over 16 weeks of training. The authors concluded that the relatively small muscle mass available during handcycling is not a limiting factor for the improvement of CVD risk factors. However, the relatively untrained lower extremity skeletal muscle of participants in the hybrid group may have been a limiting factor. It is possible that during hybrid cycling, as skeletal muscle became fatigued, the legs were passive in the movement with propulsion being driven solely by the arms. This may explain why there were no noticeable differences between groups. To investigate the independent effects of FES and upper body exercise on metabolic health and body compositions the research design shown in Figure 7.1 has been proposed.

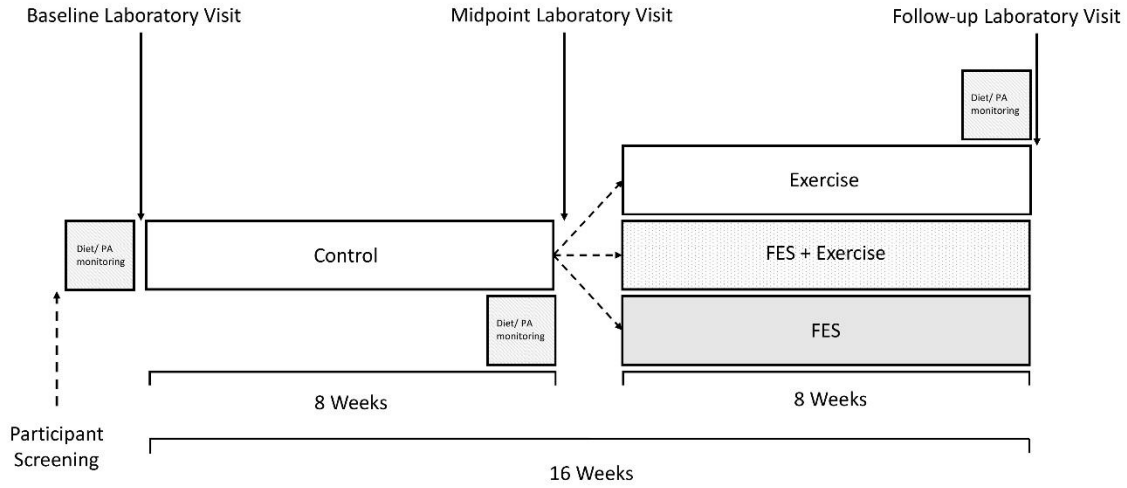

Figure 7.1: Schematic of a possible study design to assess chronic adaptations to upper body exercise, FES and combined

Briefly, participants will be eligible for this study if they are classified as inactive at baseline (PAL $\leq$ 1.60) using the Actiheart validated in **Chapter 5**. Fasting measurements, insulin sensitivity (assessed via clamp method), body composition and aerobic capacity will be assessed pre-post an initial 8-week lifestyle maintenance control period. Diet and activity levels will be assessed in the final week to ensure PA behaviours and nutritional status have not changed. Then participants will be randomly assigned to one of three groups; ACE exercise (65% $\dot{V}O_2$ peak), FES leg exercise (chosen frequency dependent on findings from previous study) and FES leg exercise plus ACE. It would be interesting to see if the combination of upper body moderate-intensity exercise and FES, maintaining or potentially increasing LM in the leg, might lead to greater improvements in insulin sensitivity. Due to the potential limitation with hybrid cycling (skeletal muscle in the legs being highly fatigable and an increase reliance on the arms) the FES and upper body exercise will be performed separately. There are of course practical limitations to such a design; it is relatively resource/time heavy which would place a considerable burden on the participants. If it was home-based, the study would require considerable financial support to purchase exercise equipment. Furthermore, matching the energy expenditure in each group could be problematic. Overall, the potential to quantify the independent therapeutic effects of FES and upper body exercise, and the combination of the two, means it could be worth the associated time and resources.

7.4.3. The Effect of Diet and Upper Body Exercise

It is well established that combining diet with regular PA is the most effective treatment of obesity (Brochu *et al.*, 2000; Poirier & Despres, 2001). Despite the increased likelihood of obesity following SCI (Weaver *et al.*, 2007; Gater, 2007), it is surprising that there is such a paucity of research looking at the combination of PA and calorie restriction on body composition and metabolic health in persons with SCI. A large scale study (n = 316) in older (≥ 60 years) overweight or obese men and women lasting 18 months showed that diet-induced weight-loss resulted in greater reductions in inflammatory biomarkers compared to exercise alone or exercise plus diet (Nicklas *et al.*, 2004). This was perhaps explained by the much greater weight loss experienced in the diet group. Potentially the 6 weeks of moderate-intensity upper body exercise (**Chapter 6**) did not lead to significant reductions in inflammatory biomarkers as there were no significant changes in body mass, or more importantly FM. Achieving weight loss via upper body exercise alone is difficult, as the contracting skeletal muscle mass involved is smaller, resulting in a reduced whole-body oxygen uptake/PAEE. Donnelly *et al.*, (2009) suggested that body mass reduction requires an exercise energy expenditure in excess of 2000 kcal·week^{-1}. Extrapolated from our sample of inactive participants in **Chapter 6** this would equate to ~ 64 minutes of moderate-intensity arm crank per day (assuming there are no compensatory behaviours or substitution of PA). One option to reduce exercise time would be to increase the intensity of exercise to achieve the required energy expenditure. However, achieving significant weight loss via exercise interventions absent of calorie restriction for persons with SCI might be difficult.

Irrespective of how negative energy balance is achieved, be it through calorie restriction or increased exercise, Fontana *et al.*, (2007) noticed substantial and similar improvements in CVD risk factors in able-bodied overweight adults. It would be interesting to see if similar findings are observed in persons with chronic SCI. Hence, the schematic of energy deficit is proposed in Figure 7.2. The aim of this study would be: *'To assess the impact of an energy deficit, through exercise, diet or both, on metabolic flexibility, body composition and markers of systemic inflammation in persons with chronic SCI'.* It has been stated that total exercise duration (irrespective of relative exercise intensity) was the key factor in improving insulin sensitivity (Houmard *et al.*, 2004). Therefore, to ensure

participants performed the same total amount of training sessions in both exercise groups, exercise intensity would need to be manipulated accordingly to guarantee the same energy deficit is created. Furthermore, in order to promote weight loss through exercise alone, this would need to be of a vigorous intensity for it to be realistically achievable within the everyday lifestyle of previously inactive research participants.

Changes in fasting RER in **Chapter 6** was significantly different between groups, with a reduction and increase in the INT and CON group, respectively. This finding, would suggest a greater reliance on fat oxidation in the fasted state with exercise. However, to determine metabolic flexibility measurements of both fasting and postprandial RER are required, as metabolic flexibility is defined by the degree to which you can switch between the two. In our participants we noticed unremarkable levels of fasting TAG, only 20% were > 1.7 mmol·L^{-1}. Considering humans now spend most of their lives in the postprandial, not fasted, state, it would make sense to measure postprandial lipaemia (PPL) in response to a mixed meal. Particularly as researchers have shown exaggerated PPL in individuals with chronic paraplegia, despite also observing unremarkable concentrations of fasting TAG (Nash *et al.*, 2005; Emmons, 2009). This exaggerated PPL is an important stimulus for the development of atherosclerosis (Zilversmit, 1979), and non-fasting TAG has revealed a stronger association with CVD than fasting (Bansal *et al.*, 2007). It is possible that as a result of a more sedentary lifestyle, reduced skeletal muscle LPL slows postprandial TAG extraction from the circulation. Furthermore, the loss of sublesional muscle mass limits the ability to metabolise postprandial TAG as a fuel source (Cowan & Nash, 2010). To our knowledge, no studies have been conducted looking at impact of upper body exercise on the responses of metabolic flexibility and PPL to a mixed meal tolerance test in persons with chronic paraplegia. Therefore, we propose the use of a mixed meal tolerance test and these measures in this study design.

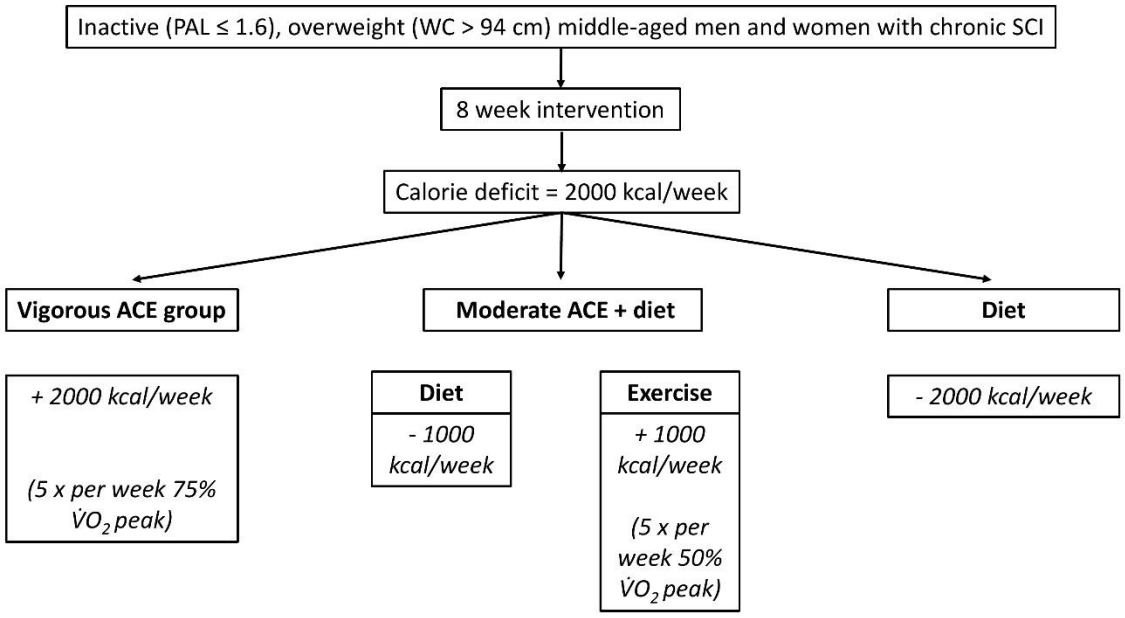

Figure 7.2: Schematic representation of the energy deficit, induced by vigorous ACE exercise alone, combination of moderate ACE and diet, or diet alone

7.5. CONCLUSIONS

In short, this thesis systematically developed and evaluated wearable PA monitoring devices to predict PAEE during free-living in wheelchair users. Our findings suggest the use of a multi-sensor device with individual heart rate calibration offers the most accurate prediction of PAEE in wheelchair users. There are relatively few examples in the literature where these tools and technologies have been incorporated into a controlled RCT. A prescribed moderate-intensity arm crank exercise intervention showed improvements in measures of metabolic health, but not other traditional CVD risk factors (lipid profiles and markers of inflammation). This was potentially because upper body exercise alone was not sufficient to promote substantial reductions in FM in persons with chronic paraplegia.

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