

**THE INFLUENCE OF RESISTANCE TRAINING ON
MUSCULAR, GAIT AND PSYCHOLOGICAL
IMPAIRMENTS IN ADULTS WITH
FACIOSCAPULOHUMERAL, LIMB-GIRDLE AND BECKER
MUSCULAR DYSTROPHY**

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List of Abbreviations

BMD	Becker muscular dystrophy
FSHD	Facioscapulohumeral muscular dystrophy
LGMD	Limb-girdle muscular dystrophy
MD	Muscular dystrophy
NMC	Neuromuscular Centre
QoL	Quality of life
RT	Resistance training
MVC	Maximum voluntary contraction

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Abstract

Muscular dystrophies are inherited disorders that cause progressive muscle deterioration and weakness. Impaired walking and mental challenges are also recognised clinically, but there is little quantification of these in the literature. Resistance training was historically believed to be detrimental in this population, but the evidence for this is limited to anecdote and murine investigation. Potentially, as in healthy adults, resistance training could improve muscle strength in this population, together with physical function, gait and mental health.

Part A of this thesis aimed to describe lower-limb muscle strength, physical function, gait patterns and mental health profiles of adults with Facioscapulohumeral (9), Limb-girdle (6) and Becker (7) Muscular Dystrophy, compared to an age-matched control group (10). Part B of this thesis aimed to examine the effect of 12-weeks' resistance training on lower-limb muscle strength, kinematics and kinetics of gait and mental health in 17 ambulatory adults with muscular dystrophy.

Muscle strength, physical function, gait and mental health were impaired in the muscular dystrophy groups compared to controls. Mean adherence to the training programme was 96%. Isometric maximum voluntary contraction torque increased in 6 muscle groups by between 13% and 65%, along with improvements in functional movements such as a 23% decrease in stair descent time. Gait speed increased by 8% with additional improvements in gait abnormalities, such as a 4° reduction in the severity of knee hyperextension, a 2° increase in mean dorsi-flexion in the swing phase and a 9% increase in peak plantarflexion generation power in late stance. Perceived quality of life improved, with a 19% and 11% reduction in the severity of depression and trait anxiety and a 10% and 15% increase in self-esteem and physical self-worth.

This thesis described areas of predominant muscle weakness, gait abnormalities and poor mental health, previously un-reported in these muscular dystrophies. Resistance training was feasible and highly beneficial to muscle strength, gait and mental health. Thus, resistance training is an innovative approach to improving muscle strength and managing the physical and mental challenges of muscular dystrophy and in doing so, helping to maintain independence in this population.

Chapter 1

Introduction to

Muscular Dystrophy

1.1 Introduction

Muscular dystrophy (MD) embodies a broad collection of inherited muscle diseases which progressively weaken the muscles of the body to variable extents (Huml, 2015). MD is rare, relative to other neuromuscular diseases, with a collective prevalence between 19.8 and 25.1 per 100,000 individuals (Theadom et al., 2014; Norwood et al., 2009). However, this prevalence is ambiguous given that in excess of thirty subtypes of MD exist, all of which can be grouped into nine major types of MD (Terrill et al., 2013). These nine major types are Duchenne, Becker, Congenital, Distal, Emery-Dreifuss, Myotonic, Facioscapulohumeral, Limb-girdle and Oculopharyngeal MD (Huml, 2015), each of which differs by genetic phenotype, clinical signs and pathological criteria.

The discovery of MD is hard to pinpoint, as a direct consequence of the heterogeneous nature of MD. Various individuals have been credited with the initial description of MD. Some of these earliest descriptions were put forward by Giovanni Semmola, a physician at the Hospital of Incurables, who in 1834 presented a lecture on two boys with enlarged calf muscles. Sir Charles Bell wrote of muscle weakness in young boys in 1830 and Conte and Gioja documented cases of increasing muscle weakness in boys in 1836 (Huml, 2015). Importantly, MD was officially termed in 1886; it was named Duchenne MD after the French neurologist Guillaume Benjamin Armand Duchenne who was well known within the medical field. He documented 13 boys with progressive muscle weakness all of whom were unable to walk and died prematurely in their teenage years (Parent, 2014). Soon after this, the medical profession recognised that MD is not a homogenous condition and that in fact different types of MD exist, which are not exclusive to

young boys and differ in terms of weakness severity, location and rate of progression (Huml, 2015).

The variety of MD subtypes exhibit a diverse range of genetic mutations, yet all MDs ultimately cause progressive muscle deterioration and weakness that is detrimental to physical ability (Mercuri and Muntoni, 2013). Although the various types and subtypes of MD do not share the same genotype, they do share some common muscle histological features, including variation in myofiber size, myofiber degeneration and renewal, fibrosis (the replacement of muscle with connective tissue) and fat infiltration (Terrill et al., 2013). The exact mechanism of pathogenesis for every type of MD has not yet been described but it is known that each genetic defect results in either a problem with, or a lack of, one of the many proteins that are associated with muscles (Cohn and Campbell, 2000). These proteins are essential during different cellular functions in the muscle and therefore, each genetic mutation ultimately results in muscle cell and tissue death (Cohn and Campbell, 2000), albeit through a different pathway. The location of each protein deficiency can occur at a variety of molecular levels within the muscle, including the extracellular matrix, sarcolemma, cytoplasm, sarcomere and nuclear membrane, dependant on the protein in question (Terrill et al., 2013). Many of these MD related protein deficiencies, along with their location within a myocyte, are highlighted in Figure 1.1 (Murphy and Straub, 2015).

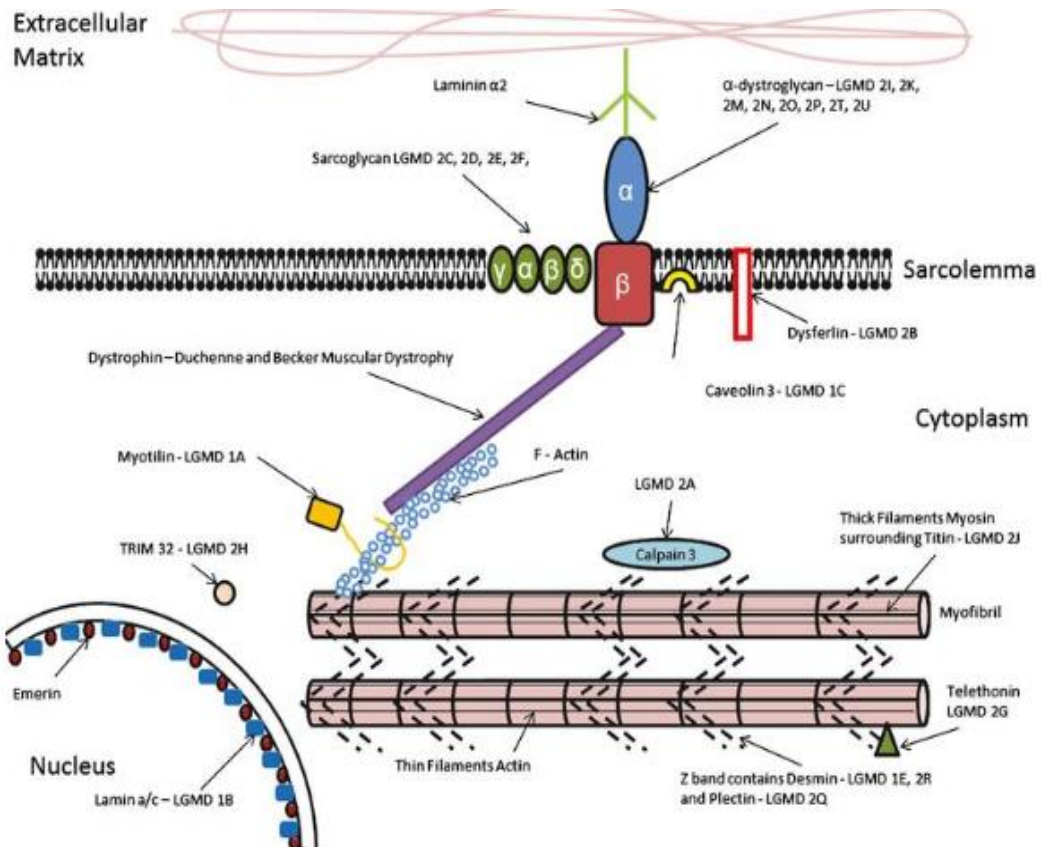


Figure 1.1: Molecular diagram of a myocyte, showing the proteins that are implicated in subtypes of MD. Diagram taken from Murphy and Straub (2015).

MD is notably variable in characteristics such as age of onset, pathway of inheritance and distribution of muscle weakness (Terrill et al., 2013), both within and between the different types of MD. In addition, MD can weaken the muscles to varying extents and severities. The age of onset of MD can vary between childhood and adulthood, with some cases of MD appearing in the third, fourth or even fifth decade of life (Mercuri and Muntoni, 2013). With regard to how MD is inherited, there are three potential pathways. The first, autosomal dominant inheritance occurs when one normal gene is inherited from one parent and one faulty gene is inherited from the other parent. Alternatively, autosomal recessive inheritance happens when both parents pass on the faulty gene and X-linked recessive inheritance arises when the mother carries and passes on the faulty gene (Huml,

2015). Alternatively, MD can also result from a de novo mutation. The distribution of muscle weakness is typically categorised per type of MD, but this will be discussed at length later within this review. It is important to note that the prognosis of MD also varies greatly, symptom expression can be mild, although progressive, or result in substantial disability and early death (Theadom et al., 2014).

Progressive muscle weakness is the main symptom of MD, but other symptoms can include reduced range of motion, pain, joint stiffness, cramps, fasciculation and pseudo-hypertrophy, whilst in certain forms of MD the respiratory muscles, swallowing muscles and cardiac muscles can also be affected (Mercuri and Muntoni, 2013). MD can be devastating for both the individual and their family, because despite its first description 15 decades ago, there remains no cure for MD (Huml, 2015). The current treatment options do however aim to manage symptoms, slow progression and prevent complications (Birkkrant et al., 2018). In recent years, the clinical management of MD has led to improved patient outcomes. In particular, life expectancy in young boys with Duchenne MD has improved from the teenage years to survival well into the twenties and possibly thirties nowadays (Birkkrant et al., 2018). To achieve this, a multitude of therapies including glucocorticoid steroid medication, cardiac management, respiratory management, sleep management and rehabilitation are employed (Huml, 2015). Physiotherapy is an important tool in this multidisciplinary approach, which helps maintain functional mobility and independence for those individuals living with MD.

One of the major defining stages in the progression of MD is the loss of physical function or ability to walk, and with that the individual's independence. This is

especially true for Duchenne MD, one of the most common types of childhood MD, with a reported prevalence of 8.2 per 100,000 individuals (Mercuri and Muntoni, 2013). Duchenne MD affects mostly males but on rare occasions x inactivation or other genetic modifications can mean that females present with Duchenne MD. It is of childhood onset and renders boys wheelchair bound by, on average, the age of 12 years old (Huml, 2015). However, adults with other types of MD are often able to remain ambulatory. The most common of these forms are Myotonic MD, Becker MD (BMD), Facioscapulohumeral MD (FSHD) and Limb-girdle MD (LGMD), which have a reported prevalence of 8.3, 7.0, 3.9 and 1.6 per 100,000 individuals, respectively (Mercuri and Muntoni, 2013; Di Fruscio et al., 2016; Mah et al., 2016). Myotonic MD is the most common overall, but it differs widely from the other eight MDs as the disorder affects nearly every system in body, even the endocrine and central nervous system (Hilbert et al., 2012). As the present thesis is concerned with ambulatory adults with MD, it will focus largely on the three most common types of MD where individuals are often able to remain ambulatory into adulthood (FSHD, LGMD and BMD), disregarding Myotonic MD due to the additional complications associated with it.

1.1.1 FSHD

The genetic mutation responsible for FSHD is unknown, but the site of the genetic defect is believed to be located in the D4Z4 DNA region (Emery, 2002). Two types of FSHD exist, the most common is termed type 1 and the second is termed type 2. Although not fully understood, a widely accepted explanation for both types of FSHD is incorrect expression of a retrogene named DUX4 (Sacconi et al., 2015).

DUX4 is typically suppressed in healthy muscle tissue as it is harmful to the muscle cells, but mis-expressed in cases of FSHD (Yao et al., 2014). Type 1 FSHD accounts for 95% of cases, which are transmitted as an autosomal dominant trait and the remaining 5% are inherited as type 2 FSHD (Huml, 2015). Type 1 FSHD exhibits a loss of microsatellite repeat arrays at chromosome 4 in the D4Z4 region (Yao et al., 2014), resulting in mis-expression of DUX4. Type 2 FSHD is due to a mutation in the SMCHD 1 gene on chromosome 18, leading to mis-expression of DUX4 (Statland and Tawil, 2014). Despite this knowledge, the consequence of DUX4 expression in skeletal muscle has not been established definitively. There are however, numerous propositions including cell apoptosis, altered expression of genes that are involved in RNA splicing and processing, obstruction of normal muscle regeneration and the possible inducement of an immune response (Tawil et al., 2014). A detailed explanation of each of these proposed mechanisms for the pathogenesis of FSHD is provided by Tawil et al. (2014).

FSHD is generally of adult onset with slow progressive manifestations commencing in the second or third decade of life; an earlier onset is largely accompanied by more rapid progression and severity (Sacconi et al., 2015). FSHD is described clinically as a primary weakness of the facial, scapula and humeral muscles (Emery, 2002), with weakness in the foot extensors accepted as a common characteristic (Huml, 2015), yet there is limited quantitative assessment of muscle strength in FSHD. Asymmetric muscle weakness, which is uncommon in other MDs, is recognised in clinical descriptions of FSHD as a possible characteristic (Sacconi et al., 2015). In rare cases, FSHD can also cause visual abnormalities, hearing loss and cardiac arrhythmias (Huml, 2015). In most cases the use of a wheelchair is only needed later in life,

although experimental descriptions of walking in this population are scarce. Indeed, the majority of wheelchair dependant FSHD individuals will express an early childhood onset (Sacconi et al., 2015).

1.1.2 LGMD

The LGMDs are a diverse group of at least thirty-four disorders (Nigro and Savarese, 2014; Liewluck and Milone, 2018) that are described clinically as sharing a weakness of the proximal limb musculature (Emery, 2002), although experimental descriptions of muscle weakness in these adults are extremely limited (Jacques et al., 2018; Lokken et al., 2016). Two main types of LGMD exist, which are further categorised into various sub classifications. LGMD type 1 is relatively rare and represents an autosomal dominant inheritance, whereas LGMD type 2 is much more common and is inherited through a recessive pathway (Vieira et al., 2014). Both types of LGMD are sub classified further according to the precise genetic defect: LGMD1 includes eight subtypes ranging from A-H and LGMD2 includes twenty-six subtypes ranging from A-Z (Liewluck and Milone, 2018).

A comprehensive list of the genetic mutation and associated protein deficiency for each subtype of LGMD has been provided by Liewluck and Milone (2018). The thirty-four LGMDs give rise to a complex network of genetic defects and consequential protein deficiencies. Thus it is currently extremely challenging to manage and to understand the pathogenesis of LGMD. To combat this, Liewluck and Milone (2018) resourcefully grouped all LGMDs into seven alternative subgroups, as a function of the defective protein or shared location. This simplifies the understanding of where on a molecular level each LGMD subtype influences skeletal muscle cells. These

seven subgroups include protein deficiencies that are located in the extracellular matrix, sarcolemma, cytoplasm, nucleus and sarcomere, the majority of which are demonstrated in Figure 1.1 and described below:

1) α -Dystroglycanopathies (LGMD 2I, 2K, 2M, 2N, 2O, 2P, 2S, 2T, 2U and 2Z) are due to a mutation in the DAG1 gene that encodes for a protein named α -Dystroglycan, or in genes that encode for other proteins that work together with α -Dystroglycan, such as Fukutin and Protein-O-mannosyl transferase-1. These proteins are located in the sarcolemma and help to maintain integrity of the sarcolemma and link the dystrophin-associated glycoprotein complex to the extracellular matrix.

2) Caveolae associated, which includes LGMD1C and is due to a mutated Caveolin-3 gene. This mutation causes a deficiency in the Caveolin and/or Cavin proteins that play a major role in maintaining the stability of the sarcolemma membrane.

3) LGMD2B and LGMD2L with defective membrane repair. These are due to a mutation in the DYSF and ANO5 gene that typically encode for the Dsyferlin and Anoctamin-5 protein and are both critical for the repair of the muscle membrane following disruption and are located in the sarcolemma and cytoplasm.

4) LGMDs caused by a protein deficiency in the nuclear envelope. These include LGMD1B, LGMD1F, LGMD2X and LGMD2Z, which are due to a mutation in the LMNA gene that encodes for the protein LAMIN A/C, TNPO3 gene that encodes for the protein Transportin-3, POPDC1 gene that encodes for the Popeye domain containing protein 1 and TOR1AIP1 that encodes for the Lamin-associated protein 1, respectively.

5) Sarcoglycanopathies (LGMB 2C, 2D, 2E and 2F), which are due to mutations in gene loci that encode for Sarcoglycan proteins. These Sarcoglycan proteins are located in the sarcolemma within in a sub-complex of the dystrophin-associated glycoprotein complex. The role of Sarcoglycan proteins is similar to many other defected proteins in LGMD, which is to maintain the integrity of the sarcolemma and to connect the sarcolemma to the extracellular matrix.

6) Z-disk Proteinopathies (LGMD 1A, 1D, 1E, 2G, 2J, 2Q and 2R) are due to a mutation in genes that encode for proteins located in the Z-disk or proteins that facilitate the function of the Z-disk, such as Titin, Telethonin and Desmin. The z-disk defines the border of a sarcomere and is important for mechanical stability.

7) Other LGMDs (LGMD 1G, 1H, 2G, 2H, 2V and 2W) in which the exact protein deficiency and/or cellular location is currently unknown.

In short, it is difficult to outline one common pathway of pathophysiology for LGMD due to the variety of locations and functions of the defected proteins. However, Murphy and Straub (2015) highlight that the mechanism of pathogenesis for the majority of LGMDs is ultimately through sarcolemma membrane instability, which consequently leads to muscle fibre degeneration. Murphy and Straub (2015) also highlight two other mechanisms including a dysfunctional dystroglycan complex and errors in muscle repair, but they stress that these two additional mechanisms are also likely to lead to sarcolemma membrane instability and in turn muscle fibre degeneration, in the end.

The LGMDs have a far less uniform progression rate than other MDs, such as FSHD. They can progress rapidly resulting in a severe loss of independence, or at a much

slower rate allowing an ordinary life expectancy and activity capability (Di Fruscio et al., 2016). Interestingly, the severity and rate of progression can range between mild, moderate and severe even within individuals of the same family, due to the severity of the individual mutation affecting the gene (Nigro and Savarese, 2014). LGMD can manifest in early childhood, late childhood/adolescence after ambulation has been attained or milder variants may not appear until adulthood (Mercuri and Muntoni, 2013). Invariably, the milder adult onset variants are typically associated with the autosomal dominant forms (LGMD1), whilst the more severe childhood onset variants are generally caused by the more common recessive forms (LGMD2). According to clinical descriptions, muscle weakness primarily occurs in the proximal shoulder and/or pelvic girdle muscles (Vieira et al., 2014) and in some forms (1B, 1D, 2C, 2D, 2E, 2F, 2G, 2I, 2K, 2L, 2M, 2N and 2O) the disorder is associated with cardiac involvement (Mercuri and Muntoni, 2013). In instances of childhood onset, ambulation will be achieved but invariably lost by adolescence. Conversely, ambulation will generally be maintained at least until later life, in cases of adult onset (Mercuri and Muntoni, 2013), but experimental descriptions of gait are yet to emerge in this condition.

1.1.3 BMD

BMD is allelic with Duchenne MD, meaning that it is caused by a different mutation in the same gene as Duchenne MD, which is located on the Xp21 chromosome (Mercuri and Muntoni, 2013). Both disorders are inherited via the x-linked recessive pathway, rendering the conditions male oriented, unlike FSHD or LGMD (Coote et al., 2018). Whilst females who carry the condition usually present as asymptomatic,

roughly 2-8% can endure mild to moderate symptoms (Huml, 2015) or in rare cases symptoms as severe as boys with Duchenne MD, and are therefore labelled as manifesting carriers.

As the Duchenne MD gene is one of the largest recognised human genes, information on the pathogenesis of Duchenne and BMD is ample. In essence, dystrophin, which is a protein usually located in the sarcolemma and cytoplasm, is completely absent in those with Duchenne and either reduced or abnormal in those with BMD (Mercuri and Muntoni, 2013). Dystrophin is essential for muscle fibre cohesion, as it bonds to the dystroglycan proteins to form a physical link for actin fibres across the sarcolemma to connect the extracellular matrix to the cytoplasm (Figure 1.1) (Winder, 1997). This is termed the dystrophin glycoprotein complex and is essential for sarcolemma membrane function in order to cope with contractile stress (Robinson-Hamm and Gersbach, 2016). Absent or reduced dystrophin destabilises this dystrophin complex, and consequently results in muscle degeneration with a diminished or reduced regenerative capacity (Lapidos et al., 2004).

In BMD, the pattern of muscle weakness mimics that of Duchenne MD but with a lesser severity and rate of progression. Clinical descriptions of muscle weakness in BMD describe a predominantly proximal to distal muscle weakness pattern, impairing the proximal knee and hip extensor muscles first followed by the more distal leg muscles, and pseudohypertrophy of the gastrocnemius muscle is often evident (Emery, 2002; Huml, 2015). However, experimental investigations of muscle strength in adults with BMD are limited to grip strength, the knee extensors, the

plantar-flexors and the dorsi-flexors (Lokken et al., 2016; Jacques et al., 2018). The clinical characteristics of BMD are more variable than Duchenne MD, due to variability in the severity of the genetic defect (Coote et al., 2018). The age of onset in BMD is later than Duchenne MD, occurring anytime between childhood and adulthood. Loss of ambulation is also variable in BMD, ranging from adolescence onwards and in many cases ambulation is sustained well into adulthood (Mercuri and Muntoni, 2013), although experimental descriptions of ambulation do not exist. Cardiomyopathy occurs in some cases of BMD, with 70% of the combined Duchenne and BMD cases presenting with it (Coote et al., 2018). In addition, respiratory weakness typically parallels the severity of skeletal muscle weakness and is therefore more severe in Duchenne than BMD.

Chapter 2

Literature Review

2.1 Literature Review Aims

Previous research studies have investigated the muscular, biomechanical and/or psychological characteristics of individuals with muscular dystrophy (MD), compared to non-dystrophic individuals: no review has pooled this evidence. Accordingly, this literature review aims to identify, review, and synthesise the research surrounding MD, with a specific emphasis on Facioscapulohumeral MD (FSHD), Limb-girdle MD (LGMD) and Becker MD (BMD) in the following areas:

1. Muscle strength and physical function
2. Gait pattern characteristics
3. Mental health and wellbeing

This review also aims to unravel the evidence surrounding the role of resistance exercise training in individuals with MD, with a specific emphasis on FSHD, LGMD and BMD. This review will summarise what is known, identify knowledge gaps and outline where future research is required.

2.2 Muscle Strength in MD

Decreased skeletal muscle strength is a well-recognised feature of all MDs, to varying degrees and distributions of muscle involvement, and is a detriment to physical function (Huml, 2015). Previous investigations of muscle strength, the parameters associated with muscle weakness and physical function in MD, exist mostly in children with Duchenne MD (Mathur et al., 2010) or are limited to clinical assessment through manual muscle testing rather than quantitative measurement.

2.2.1 Muscle Weakness Distribution

The distribution of muscles that are weakened in the different forms of MD have been classified clinically and schematics that demonstrate these classifications, such as Figure 2.1 presented by Mercuri and Muntoni (2013), are often utilised to describe MD. Furthermore, these weakness patterns are often used, in combination with the suspected pathway of inheritance, during early medical consultations (Tawil et al., 2010; Mercuri and Muntoni, 2013). However, although clinical descriptions of weakness distribution in FSHD, LGMD and BMD are readily available, they are not based on quantitative data presenting muscle strength in these populations. Such data do not exist to any great extent or depth within the literature, rendering clinical classifications of FSHD, LGMD and BMD ambiguous. This is an important consideration given that subtype-specific patterns of muscle weakness are often used to inform and facilitate an initial MD classification, to

subsequently direct further diagnostic testing, and to inform the ongoing clinical management of MD subtypes.

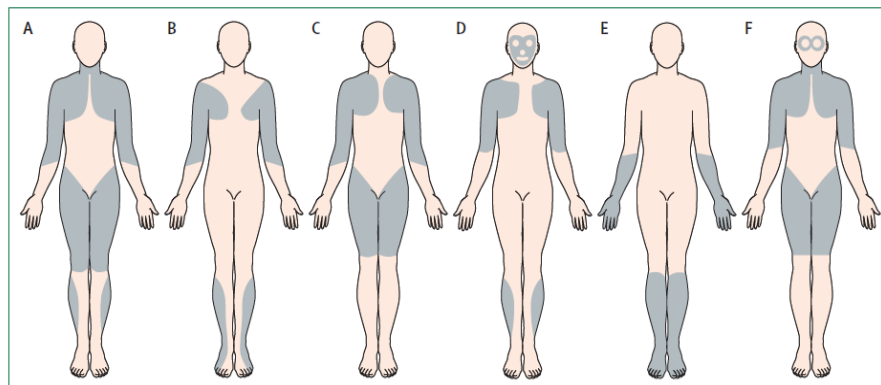


Figure 2.1: Patterns of predominant muscle weakness in six types of MD: Duchenne and Becker (A), Emery-Dreifuss (B), Limb-girdle (C), Facioscapulohumeral (D), Distal (E) and Oculopharyngeal (F). Shading = involved

Scientific quantification of muscle strength in the various forms of MD will either support or challenge the pre-existing clinical classifications, and in doing so facilitate rehabilitation or clinical management programmes. In particular, scientific quantification of lower-body muscle strength could help to direct interventions aimed at maintaining walking and/or functional ability. However, the majority of studies that have previously quantified muscle strength in MD have been undertaken in children with Duchenne MD. The results of these studies cannot be related to ambulatory adults with other forms of MD, given the reduced severity and progression rate compared to Duchenne MD. In other forms of MD, specifically those relevant to this thesis: BMD, LGMD and FSHD, only five studies have scientifically quantified lower-limb muscle strength in these populations (Bachasson et al., 2014; Jacques et al., 2018; Lokken et al., 2016; Skalsky et al., 2008; Marra et al., 2018), in four muscle groups (knee extensors, knee flexors, dorsi-flexors and plantar-flexors). Of these studies, two measured isometric maximum voluntary contraction (MVC) strength using the gold standard technique of isokinetic

dynamometry (Skalsky et al., 2008; Lokken et al., 2016), and the other three completed isometric quantitative muscle strength assessments using a strain-gauge (Jacques et al., 2018; Bachasson et al., 2014; Marra et al., 2018).

2.2.1.1 Quantitative Strength Data in FSHD

In FSHD, the weakness distribution is classified clinically as a primary muscle weakness in the facial, scapula and humeral muscles, along with distal weakness of the lower body (Figure 2.1) (Emery, 2002; Tawil et al., 2010; Mercuri and Muntoni, 2013). In accordance with this, Jacques et al. (2018) reported a 35% reduction in isometric MVC strength of the plantar-flexor muscles, in adults with FSHD compared to an age-matched control group. However, higher percentages of weakness have been reported in the proximal muscle groups, relative to matched control groups in this population. The strength of the knee extensor muscles in individuals with FSHD were reportedly 41.6% (Skalsky et al., 2008), 44.9% (Bachasson et al., 2014), 65.6% (Marra et al., 2018) and 24.9% (Jacques et al., 2018) lower than non-dystrophic control groups. In a second proximal muscle group, knee flexor strength was reportedly 56% lower in a group of children and adults with FSHD (10-64 years), compared to a sex, height and weight matched control group (Skalsky et al., 2008). However, the pre-existing clinical classifications (Figure 2.1) do not signify a predominant weakness of these proximal muscles in FSHD. The differences in the severity of knee extensor weakness between the experimental studies may be explained by differences in testing procedure, ambulatory status, participant ages and the variables used to match participant groups. Concerning the latter point, Marra et al. (2018) did not age-match the experimental to the control group,

rendering the control group an average 20.5 years younger, which may explain the greater differences in muscle strength. At the lower end of the scale, the differences are likely due to a combination of sex differences and measurement technique, as Jacques et al. (2018) studied an all-male group.

2.2.1.2 Quantitative Strength Data in LGMD

Clinical descriptions of LGMD demonstrate a predominantly proximal muscle weakness pattern (Figure 2.1) (Emery, 2002; Wicklund and Kissel, 2014; Mercuri and Muntoni, 2013). This is in part supported by experimental data, as Jacques et al. (2018) reported knee extensor muscle strength values that were 43% weaker than an age-matched control group. However Jacques et al. (2018) also reported a more severe relative weakness in the distal plantar-flexor muscles of 58%. Further evidence supports this distal muscle weakness in LGMD, with an approximate 42% reduction in plantar-flexor muscle strength and an approximate 31% reduction in dorsi-flexor muscle strength of adults with LGMD, compared to an age-matched control group (Lokken et al., 2016). Despite this evidence, distal muscle weakness is not represented as a predominant clinical classification of LGMD (see Figure 2.1).

2.2.1.3 Quantitative Strength Data in BMD

Clinical descriptions of BMD often group it together with Duchenne MD (Emery, 2002) (Mercuri and Muntoni, 2013) and whilst BMD is a less severe variant of Duchenne MD, the specific weakness distribution in BMD may differ due to the extended period of ambulation in BMD (Huml, 2015). Nevertheless, clinical classifications of BMD allude to a proximal followed by distal muscle weakness pattern, similar to children with Duchenne MD (Emery, 2002). That is, the proximal

leg muscles such as the knee and hip extensors weaken first, followed by the more distally located leg muscles such as the dorsi flexors. Jacques et al. (2018) reported strength reductions of 41% and 51% in the knee extensor and plantar-flexor muscles of adults with BMD, respectively, compared to an age-matched control group. The more severe relative weakness of the plantar-flexor muscles in comparison to the knee extensor muscles does not support the classic proximal to distal weakness distribution that is described clinically. In addition, Lokken et al. (2016) reported a similar reduction of 53% in plantar-flexor muscle strength and a reduction of 43% in dorsi-flexor muscle strength, of adults with BMD compared to an age-matched control group. It is possible that the prolonged ambulatory capacity of adults with BMD (Huml, 2015) may help to preserve strength in the proximal muscles and therefore explain the limited agreement with the classic proximal to distal muscle weakness distribution that has been described clinically.

2.2.2 Parameters Associated with Muscle Weakness

Limited insight exists into the parameters that are associated with muscle weakness in FSHD, LGMD and BMD. The production of strength encompasses both central (neural) and peripheral (muscular) mechanisms, both of which have received limited attention within these populations.

At the muscle level, disparity between research studies exists. Skalsky et al. (2008) demonstrated a direct association between reduced isometric MVC strength, and smaller lean muscle mass in the knee extensor muscle region of children and adults with FSHD, measured using a dual-energy x-ray absorptiometry body scanner. Marra et al. (2018) reported a significant association between physiological cross-

sectional area, measured using magnetic resonance imaging, and MVC strength in the quadriceps of adults with FSHD. In addition, Lokken et al. (2016) established a direct relationship MVC strength and muscle size (cross-sectional area) of the plantar-flexor muscle group, in adults with LGMD but not BMD. In partial agreement with the latter study, Jacques et al. (2018) reported no association between plantar-flexor isometric MVC strength and lean body mass or medial gastrocnemius muscle size (anatomical cross-sectional area), in adults with BMD, LGMD or FSHD. These differences are most likely confounded by use of whole body (bioelectrical impedance analysis) versus regional (dual-energy x-ray absorptiometry) composition measures, and by the use of ultrasound versus magnetic resonance imaging to assess muscle size. Although the measure of anatomical cross-sectional area via ultrasound allows investigation with the most severely affected MD individuals, due to the portability and accessibility of such equipment, the results may be confounded by the inclusion of non-contractile muscle tissue within this measure.

One known study has investigated the association between central mechanisms of muscle function to muscle strength, in adults with FSHD, LGMD or BMD. Interestingly, Bachasson et al. (2014) presented a higher voluntary activation percentage in individuals with FSHD (95.6%) compared to an age-matched control group (90.6%), which was inversely related to quadriceps MVC strength. This finding may reflect a potential compensatory mechanism of the central nervous system to increase muscle strength where peripheral limitations exist in FSHD.

Similar to an ageing population, disuse atrophy may also contribute towards muscle weakness and reduced functional ability in adults with MD. Jacques et al. (2018) recently established a direct link between current physical activity levels, measured using accelerometers, and knee extension isometric MVC strength and physical function (10 m walk time), in adults with BMD. Importantly, this highlights a potential direct translation of lifetime physical activity levels on parameters such as progression of muscle weakness in MD, and it may help to explain some of the striking differences seen in the amount and progression of muscle weakness between individuals with identical genetic mutations.

Overall, the precise parameters that are associated with muscle weakness in these populations of MD are most likely multi-fold, but investigations into these parameters remain relatively vague and confounded by differences in measurement techniques.

2.2.3 Physical Function

In this thesis, physical function describes an individual's ability to perform normal daily household tasks, work related and recreational activities. It is often assessed by timed functional tests such as the time taken to rise from a seated position, the time taken to walk a given distance or the time taken to ascend and/or descend stairs. A person's physical function can also be associated with their ability to ambulate safely without falling, which is important given the high risk of injury, fractures, hospitalisation and even death that is associated with falls in other populations (Gill et al., 2013; Spaniolas et al., 2010). Ultimately, physical function offers an insight into a person's level of physical independence and a meaningful

measure of how the condition is progressing. It can be presumed that muscle strength influences, to a considerable extent, the capacity to perform physical tasks, as demonstrated in ageing populations (Byrne et al., 2016). Therefore, investigation of physical function together with muscle strength may help to better understand the factors that put adults with MD at risk of losing their physical independence.

Direct relationships between muscle strength and functional ability have not been demonstrated to any great extent in BMD, LGMD or FSHD specifically, but studies have demonstrated associations in paediatric Duchenne MD and adult Myotonic MD populations. Lindeman et al. (1998) established a strong inverse relationship between knee extensor MVC strength and timed motor performances, including time to walk 50 m, time to rise from a chair, time to ascend stairs and time to descend stairs, in adults with Myotonic MD. Hammaren et al. (2014) reported a negative association between number of falls and ankle dorsi-flexor MVC strength, in Myotonic MD. Beenakker et al. (2005) established a negative correlation between time to run 9 m and the sum of the MVC strength of 4 proximal leg muscles (knee flexors, knee extensors, hip flexors and hip abductors), in children with Duchenne MD. However, given the differences in age and ambulation duration along with weakness severity, progression and distribution between these types of MD and those relevant to this thesis (Huml, 2015), the exact same associations cannot be assumed to exist in FSHD, LGMD and BMD.

In FSHD, LGMD and BMD specifically, only one study has investigated associations between muscle strength and functional performance. Jacques et al. (2018) presented a significant inverse relationship between both knee extensor and

plantar-flexor MVC strength and 10 m walk time. However, multiple linear regression analyses demonstrated that total time spent being physically active was the greatest predictor of 10 m walk time, indicating that an active lifestyle may better predict physical function than muscle strength itself, in these forms of MD.

Investigation into the independent and synergist role of lower-limb muscle weakness on common functional tasks, such as standing up from a seated position, ascending the stairs and walking, in addition to number of falls may help to identify functionally important muscle weakness and therefore facilitate rehabilitation and/or management programmes in FSHD, LGMD and BMD. This information will help to inform future therapies which muscles have the greatest influence over fall risk and loss of physical function and independence in adults with MD.

2.2.4 Recommendations

Few studies have quantified muscle strength in BMD, LGMD and FSHD and in those that have, only four muscle groups were measured. No quantification of muscle strength has been reported in the muscle groups of the hips (e.g. hip abductors, hip adductors, hip flexors and hip extensors). Furthermore, limited agreement exists between the pre-existing clinical classifications of weakness distribution and the quantified muscle strength data that do exist.

Previous studies that have quantified muscle strength in BMD, LGMD and FSHD are subject to some key limitations. Firstly, the methods of matching control groups to MD groups were overall well established but variable. Three studies did match (Bachasson et al., 2014; Lokken et al., 2016), or accounted for statistically (Jacques et al., 2018), the age of participants between the experimental and control groups,

whilst one study matched these groups by sex, height and weight (Skalsky et al., 2008), and another study failed to match the participant groups entirely (Marra et al., 2018). Due to the progressive nature of MD and the decline in muscle strength typical with ageing, the use of appropriately age-matched control groups within MD research is of paramount importance. Secondly, measurement technique of isometric MVC strength was variable. 40% of studies utilised an isokinetic dynamometer (Skalsky et al., 2008; Lokken et al., 2016); the gold standard in strength measurement, and the remaining studies utilised a portable strain gauge (Jacques et al., 2018; Bachasson et al., 2014; Marra et al., 2018). The latter technique is more practical to use within a MD population, but it is important to show that this measurement technique and the specific protocol used are reliable, which was only demonstrated in one study (Jacques et al., 2018). Finally, the maximum number of lower-limb muscles that were measured per study was two, which limits comparisons of relative muscle strength between different muscle groups in the same individuals. Thus, it is difficult to decipher which muscles are more severely affected than others, per subtype of MD.

The relationship between muscle weakness and physical function has received little attention in BMD, LGMD and FSHD. Investigation into potential associations between lower-limb muscle strength and functional ability may provide an insight into which muscles have the largest influence on functional ability in these forms of MD, along with parameters such as walking capacity and more stringent gait parameters. Ideally, the establishment of full or lower-body strength profiles may help to identify weakness thresholds or weakness patterns that dispose these

individuals to reduced functional ability, an increased risk of falling and/or loss of ambulation.

In summary, MD is repeatedly defined as a condition characterized by lower skeletal muscle strength, smaller muscle mass, and lower physical performance; yet the precise details and nuances of these parameters for FSHD, LGMD and BMD are not clearly quantified. Detailed investigations into the specific weakness patterns of these ambulatory forms of MD, together with physical function would benefit both classification endeavours and condition specific management approaches.

2.3 Gait in MD

It has been suggested clinically that the ability to walk in individuals with MD often diminishes in conjunction with disease progression, and in many cases the ability to walk is eventually lost (Huml, 2015). Children with Duchenne MD typically become wheelchair bound by the age of 12 years old (Bushby et al., 2010), whilst individuals with FSHD, LGMD and BMD may remain ambulatory (Emery, 2002) but precise measures of age at loss of ambulation are not available. Ambulation may be maintained in adults with FSHD, BMD and LGMD but it is recognised that walking abnormalities are often observable. A major goal of individuals with MD and their physiotherapists is for them to remain ambulant and preserve function for as long as possible. In order to facilitate this, the gait patterns of adults with MD must be measured and analysed quantitatively, and the primary causes of the abnormalities understood.

In clinical environments, walking ability in individuals with MD is typically assessed using the 6-minute walk test, an outcome measure that is often utilised to inform

the effectiveness of clinical trials in MD (McDonald et al., 2010). Although this test demonstrates reduced walking speed in adults with MD (Bachasson et al., 2016), it offers no insight into the detailed gait abnormalities that exist. Investigation of spatial-temporal variables, joint kinematics, joint kinetics, muscular activity and the energetics of gait may facilitate the understanding of the biomechanical mechanisms behind reduced walking speed in MD. However, investigation of these parameters is currently limited to children with Duchenne MD, adults with Myotonic MD and minimal studies of adults with FSHD.

The number of studies that have assessed at least one detailed gait parameter (kinematic, kinetic, muscle activity or energetics) in individuals with MD compared to a control population or with increasing disease progression amount to seven observations of children with Duchenne MD, five of adults with Myotonic MD and four of adults with FSHD. Although sustained walking ability is equally important in individuals with LGMD and BMD, quantitative analysis of gait in these populations compared to non-dystrophic control participants are yet to emerge.

Before discussing the aforementioned studies, the following section of this review will briefly describe the phases of gait and important terminology for reference.

2.3.1 The Gait Cycle

Human walking is the bipedal movement that occurs due to the forward progression of the feet. Support and propulsion are provided by alternative movements of the feet. The term gait is used to refer to the manner of walking. One gait cycle (Figure 2.2) consists of two successive instances of initial foot contact with the ground, on the same side (ipsilateral; Figure 2.2). Two phases make up the gait cycle: the stance phase and the swing phase. The stance phase is when the foot is in contact with the ground (typically around 60% of the gait cycle) and it begins with initial contact and ends with toe-off. The swing phase is when the foot is in the air and passes the support leg ready to contact the ground again (around 40% of the gait cycle).

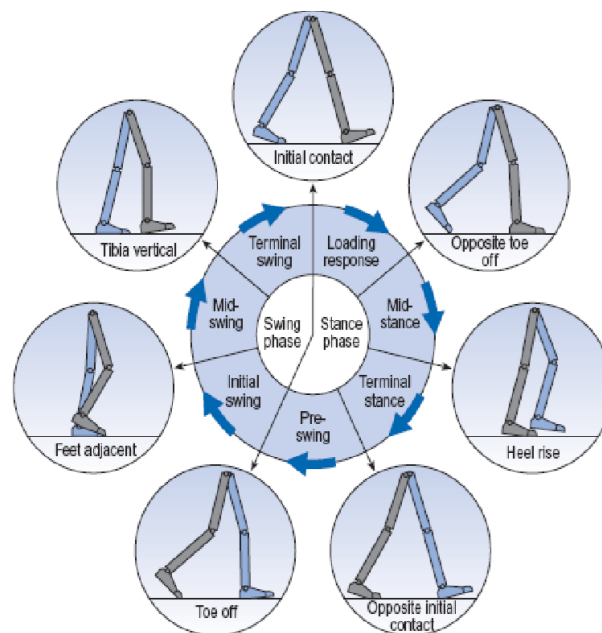


Figure 2.2: One gait cycle from initial contact to the next contact on the same side (Whittle, 1991)

Spatial-temporal variables and kinematic and kinetic variables are most often used to describe gait in research. Spatial-temporal variables describe parameters of distance and time, kinematics describe the angular displacement of joints and kinetics describes forces, joint moments and joint powers.

2.3.2 Spatial-Temporal Variables

Authors consistently report slower self-selected walking speed and reduced stride length in children with Duchenne MD (D'Angelo et al., 2009; Doglio et al., 2011; Gaudreault et al., 2009; Gaudreault et al., 2010; McDonald et al., 2010; Ropars et al., 2016; Sutherland et al., 1981), adults with FSHD (Aprile et al., 2012; Iosa et al., 2007; Iosa et al., 2010; Rijken, van Engelen, de Rooy, et al., 2015; Rijken, van Engelen, Geurts, et al., 2015) and adults with type 1 Myotonic MD (Bachasson et al., 2016; Galli et al., 2012; Radovanovic et al., 2016; Tiffreau et al., 2012; Wright et al., 1995), compared to control participants or with increasing disease severity. In addition, increased step width (Galli et al., 2012; Sutherland et al., 1981) and stance duration (Iosa et al., 2007) have also been reported in individuals with MD. Variable results have been reported for walking cadence, with some studies reporting no difference (D'Angelo et al., 2009; Gaudreault et al., 2010; Gaudreault et al., 2009) and others reporting either reduced (Ropars et al., 2016; Sutherland et al., 1981; Iosa et al., 2010; Bachasson et al., 2016) or increased walking cadence (Doglio et al., 2011).

In general, the research indicates that reduced walking speed in MD is primarily a function of reduced stride length, at least in the 3 types of MD mentioned above (Duchenne, FSHD and type 1 Myotonic MD). However, a study that included an additional type of MD, other than those mentioned above, contradicts this. Radovanovic et al. (2016) observed slower walking speed in both type 1 and type 2 Myotonic MD, yet those with type 2 did not differ in stride length compared to healthy controls. Unfortunately, cadence was not reported, but it can be deduced

that reduced speed must instead be due to reduced cadence in these participants. This discrepancy in stride characteristics is perhaps the result of different lower-limb weakness distributions between type 1 and type 2 Myotonic MD, which was confirmed via manual muscle testing in the study (significantly weaker distal muscles in type 1 and weaker proximal muscles in type 2). Hence, the current author suggests that the mechanism behind reduced walking speed in MD is a direct function of weakness distribution. It could be theorised that lower extremity distal muscle weakness causes an inability to fully weight-bear over the forefoot and create adequate progression during late stance, resulting in shorter strides, whilst predominantly proximal lower extremity muscle weakness may, or may not, preserve this function. To clarify this, future descriptions of spatial-temporal variables during gait in MD should be undertaken in additional types of MD, those that may exhibit a predominantly proximal muscle weakness distribution pattern in the lower extremities, such as LGMD. Although weakness distribution patterns may be unpredictable, given the limited quantitative assessment of muscle strength already discussed in *section 1.2*.

2.3.3 Kinematics and Kinetics

Several techniques have been employed to assess the kinematics and kinetics of MD gait, including 2D and 3D motion analysis, ground reaction force measurements and accelerometry. Assessments have taken place in adults with Myotonic MD, children with Duchenne MD and adults with FSHD. To date there appear to be no published studies that have measured the kinematics and kinetics of gait in humans

with LGMD or BMD. The data will be discussed separately for the individual types of MD.

2.3.3.1 Myotonic MD

In individuals with Myotonic MD (type 1), joint motion abnormalities have been reported at all levels (pelvis, hip, knee and ankle). Galli et al. (2012) reported an excessive anterior pelvic tilt throughout the entire gait cycle, inadequate hip extension during terminal stance, hyperextension of the knee during mid-stance, additional knee flexion during swing and reduced plantarflexion during terminal stance. Similarly, Wright et al. (1995) also observed abnormal hip motion during the stance phase (irregular oscillations compared to a smooth continuous hip motion typical of healthy gait), but the total range of motion at the hip, knee and ankle were not significantly different between Myotonic MD and control participants. This apparent discrepancy is likely due to the comparison of overall range of motion throughout the gait cycle rather than within specific phases or at key moments, such as the stance phase or at initial contact. In addition, using triaxle accelerometers on the trunk, Bachasson et al. (2016) observed greater trunk acceleration in the medial-lateral direction during the 6-minute walk test, in individuals with Myotonic MD compared to a healthy control group.

Regarding gait kinetics in adults with Myotonic MD (type 1), Galli et al. (2012) established that maximum plantarflexion power generation, representative of push-off ability, was lower in MD than control participants, but that maximum hip power generation during loading was higher in the MD than the control group, with no difference in maximum knee power generation. This highlights a predominant

contribution of hip power during gait in this disorder. Regarding joint moments, Tiffreau et al. (2012) reported differences in the knee extension joint moment between MD and control participants, but the direction of this difference was not stated. It is important to note that this assessment was completed on a treadmill. The influence of a moving treadmill belt on the gait of individuals with MD has not yet been established and as such, the differences presented by Tiffreau et al. (2012) may diminish or increase during over-ground gait.

2.3.3.2 Duchenne MD

In children with Duchenne MD, assessments of gait kinematics have typically been conducted in the sagittal plane, but some investigation of frontal and transverse plane motion has also taken place. Postural abnormalities of lumbar lordosis and excessive anterior pelvic tilt are evident throughout the whole gait cycle (Doglio et al., 2011; D'Angelo et al., 2009; Sutherland et al., 1981). At the hip joint, extension is reduced during the stance phase (Sutherland et al., 1981; Gaudreault et al., 2010) with excessive flexion during the swing phase (D'Angelo et al., 2009; Gaudreault et al., 2010; Sutherland et al., 1981) compared to control participants. The latter appears to be a compensatory mechanism for reduced dorsi-flexion observed in the swing phase and at initial contact (D'Angelo et al., 2009; Doglio et al., 2011; Sutherland et al., 1981). At the knee joint, there is a lack of flexion during initial stance (D'Angelo et al., 2009) and in some children hyperextension of the knee is evident (D'Angelo et al., 2009), along with excessive knee flexion in the swing phase (D'Angelo et al., 2009; Doglio et al., 2011). Doglio et al. (2011) also assessed pelvic and hip motion in the frontal and transverse plane, reporting increased external

pelvic rotation, increased pelvic obliquity and early abduction of the hip during the stance phase. Furthermore, Gaudreault et al. (2010) found that hip abduction started much earlier during the stance phase in children with Duchenne MD, compared to control children. This motion signifies that the contralateral pelvis was lifted by the hip abductor muscles in combination with a lateral trunk lean towards the supporting limb, which the authors reported was confirmed via video.

Abnormalities in gait kinetics in Duchenne MD reflect both proximal and distal muscle weakness in the lower body. Smaller joint powers compared to control populations have been reported at all levels, including a smaller hip flexor power generation in late stance, sometimes referred to as the pull-off, (Gaudreault et al., 2010), a smaller knee power absorption in late swing (Gaudreault et al., 2009) and smaller plantar flexion power generations at push-off (D'Angelo et al., 2009; Gaudreault et al., 2009; Gaudreault et al., 2010). In terms of ground reaction forces, the magnitudes of the vertical, anterior and posterior peak forces were found to be lower in children with Duchenne MD than a control group walking at a self-selected pace, but no differences were evidence when the controls walked at a slow pace (Gaudreault et al., 2010). On the other hand, medial peak forces were significantly higher in the MD than the control group regardless of walking pace.

2.3.3.3 FSHD

Research into FSHD gait is far less comprehensive than that conducted on Duchenne MD. Two research studies have described lower-limb joint kinematics and/or kinetics during gait in adults with FSHD (Iosa et al., 2007; Rijken, van Engelen, de Rooy, et al., 2015) but only one of those compared gait to a control population (Iosa

et al., 2007). Additionally, two studies measured dynamic stability during gait in FSHD (Iosa et al., 2010; Rijken, van Engelen, Geurts, et al., 2015). Lower-limb kinematics and kinetics will be discussed first, followed by those studies that focused on dynamic stability.

2.3.3.3.1 Lower-limb kinematics and kinetics

Iosa et al. (2007) assessed sagittal plane kinematics and kinetics of the hip, knee and ankle joint during self-selected walking in 12 adults with FSHD, compared to 12 non-dystrophic control participants; it is unknown whether the groups were matched. In addition, MRI images of various lower-limb muscles were scored according to the quantity of fat infiltration present (ranging from no infiltration at 0 to whole muscle replacement at 3). The authors reported reduced ankle dorsi flexion at initial contact which was positively correlated with the MRI score in the tibialis anterior muscle, indirectly alluding to a relationship between tibialis anterior muscle strength and ankle angle during gait. Furthermore, insufficient knee flexion during the stance phase was reported and reduced hip extension at push-off. The latter abnormality was positively correlated with the MRI score in the hip extensor muscle, again alluding to an indirect association between hip extensor muscle strength and hip angle during gait. In some participants, a reduction in the knee flexion moment after foot-strike, reduction in hip extensor moment before toe-off and smaller peak plantarflexion power generation were evident, but none of these kinetic variables reached significance. The study was limited to participants with mild-moderate FSHD, which was evidenced by all MRI scores less than 1.5 and that no participants required the use of walking aids. The latter point was not directly

reported but is assumed based on the Ricci clinical severity scale scores, which were all less than or equal to 3.5 (use of walking aids is associated with a score of 4 or above). Thus, it is unclear whether differences in joint moments and/or powers may exist in more severe presentations of FSHD.

Rijken, van Engelen, de Rooy, et al. (2015) assessed gait in a group of adults with FSHD that included a wide range of severities, including 3, 3.5, 4 and 4.5 on the same Ricci clinical severity scale. Self-selected and maximum walking speed, joint powers and the percentage of contractile tissue left within the gastrocnemius, iliopsoas and gluteus maximus muscles (measured using MRI) were assessed. Reportedly, self-selected walking speed was 29% lower than normal values for healthy control populations. From self-selected to maximum walking speed, peak plantarflexion power at push-off increased by 28% and peak hip flexor power at push-off increased by 66%. This suggests that individuals with FSHD utilise hip power to a greater extent than ankle power to generate greater propulsive forces at push-off in order to walk at a fast pace, but it is unclear if this strategy differs to that used by control populations. At self-selected walking speeds, a positive correlation was established with ankle power at push-off (i.e. faster walkers generated more ankle power) but not with hip-power at push-off, despite greater contractile tissue remaining in the iliopsoas muscle (89%) than the gastrocnemius muscle (57%). Thus, the participants utilised an ankle push-off strategy for propulsion rather than a hip push or pull-off strategy, at a comfortable walking pace.

Comparison of kinematic and kinetic gait abnormalities in FSHD to control groups are limited in depth and numerous gaps in the literature are apparent. Investigation

of angular displacements and joint moments at the hip, knee and ankle joint are limited to the sagittal plane and adults with mild-moderate presentations of FSHD. In addition, ground reaction forces and joint powers in FSHD compared to control populations remain unreported. A more comprehensive description of joint kinematics and kinetics across a wider range of FSHD severities would be advantageous in this population.

In addition to the research gaps identified above in FSHD, several other points should be considered by researchers. Firstly, previous assessments of gait have taken place during barefoot ambulation. Whilst this is standard in laboratory-based gait analysis, it introduces significant practical issues (health and safety) in a MD population and gait abnormalities between MD and control participants may vary between barefoot and shod walking. Adults with MD are usually habituated to walking with shoes on, so walking without shoes goes against what is normal in this population. Future research should consider gait assessments whilst shod in MD as this better represents everyday life for these individuals. Secondly, it is often assumed that muscle weakness is the main contributor to gait alterations in MD, and although this reasoning is logical it has not been directly verified. Associations between joint angles and fat infiltration do not directly verify a relationship between joint angles and muscle strength. Whilst muscle strength may be associated with the severity of fat infiltration in that muscle it is not a direct measure of muscle strength. Future investigations interested in these potential relationships should utilise a direct measure of muscle strength.

2.3.3.3.2 Postural Control

Maintaining postural control is imperative to avoid falling over, a hazard that has been shown to increase 5-fold in individuals with FSHD (Horlings et al., 2009), with the majority of falls occurring in the forward direction. Although it seems likely that individuals with BMD and LGMD are also at an increased risk of falling over, this is yet to be confirmed.

Postural control in standing and during ambulation have previously been measured in adults with FSHD, whilst nothing is known about the postural control of adults with LGMD or BMD during gait. Postural control during barefoot stance was assessed in 15 adults with FSHD (Aprile et al., 2012). Centre of pressure data were collected over 30 seconds of quiet standing with eyes closed and eyes open, via a baropodometric platform. Compared to a healthy control population, FSHD participants exhibited significantly greater centre of pressure sway in both the eyes closed and eyes open condition, and centre of pressure sway velocity was greater in both the anterior-posterior and medial-lateral directions. Whilst this supports the notion of reduced postural control in adults with FSHD in stance, assessment during gait itself may provide greater insight into the loss of stability whilst walking.

With regards to postural control during the task of walking, two studies have considered this in adults with FSHD. Iosa et al. (2010) tracked the movement trajectories of the head and upper trunk during a stride, in the medial-lateral and anterior-posterior directions. Wider displacements of both the head and trunk were found in both directions compared to a control group, suggesting that the control of upper body and head movement during gait is reduced in adults with FSHD.

However, this finding does not directly represent stability with regards to controlling the body centre of mass. Alternatively, Rijken, van Engelen, Geurts, et al. (2015) calculated the margin of stability during walking, in adults with FSHD. The margin of stability refers to the distance between the centre of mass and the edge of the base of support (Hof et al., 2005) during single limb stance phases of gait. Thus, the distance represents how close a person is to falling over. The margins of stability in the anterior-posterior direction and medial-lateral direction are visually demonstrated in Figure 2.2 (Rijken, van Engelen, Geurts, et al., 2015).

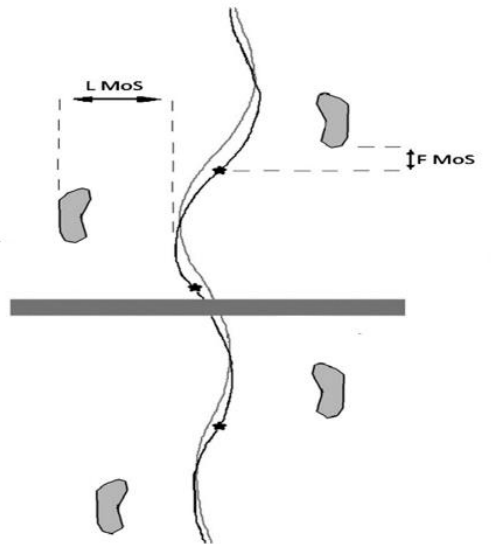


Figure 2.3: Schematic of the measurement of the medial-lateral margin of stability (L MoS) and the anterior-posterior margin of stability (F MoS), adapted from Rijken, van Engelen, Geurts, et al. (2015). * represents heel-strike. The grey line represents the centre of mass trajectory and the black represents the extrapolated centre of mass trajectory.

Rijken, van Engelen, Geurts, et al. (2015) calculated the margins of stability in adults with FSHD, compared to a non-dystrophic control group. In the anterior-posterior direction this was calculated as the anterior distance between the heel marker and the centre of mass at heel strike. In the medial-lateral direction it was calculated as the lateral distance between the centre of mass and the ankle marker throughout

the stance phase (Figure 2.2). The authors found no difference in either the anterior-posterior or the medial-lateral margin of stability during level walking between the FSHD and non-dystrophic control group (Rijken, van Engelen, Geurts, et al., 2015). This finding does not reflect the increased frequency of falls that has previously been reported in adults with FSHD (Horlings et al., 2009).

The previous research in MD suggests that no limitation in postural control during gait exists in adults with FSHD, but this may be due to the method used for calculating postural control. As already mentioned, to calculate of the margin of stability Rijken, van Engelen, Geurts, et al. (2015) utilised the distance between the centre of mass and the edge of the base of support (i.e. the position of the heel and ankle marker). However, Terry et al. (2014) proposed a technique that utilises the position of the measured centre of pressure to define the base of support instead of the position of markers on the foot. This technique considers the position and movement of the centre of pressure which varies as stance progresses, therefore allowing for adjustments in the position of the base of support with movement progression. This method has previously demonstrated deficient stability in a clinical population of adults with diabetic neuropathy (Brown et al., 2015). Thus, this technique may also prove useful in detecting postural control deficits in adults with FSHD, LGMD and BMD.

2.3.4 Muscle Activation

Investigation of muscle activation during gait in MD is limited to adults with Myotonic MD and children with Duchenne MD. Abnormalities in the timing of muscle activation have been established in each phase of the gait cycle. Galli et al.

(2012) reported no abnormality in the activity of the rectus femoris muscle in Myotonic MD, whereas Ropars et al. (2016) reported increased co-contraction of the rectus femoris with the medial hamstring muscle throughout the entire gait cycle, in DMD children. Furthermore, Galli et al. (2012) found prolonged activity of the tibialis anterior and delayed activity in the semitendinosus and gastrocnemius-soleus muscles during the stance phase in Myotonic MD. Additionally, both Galli et al. (2012) and Ropars et al. (2016) observed excessive co-contraction of the distal leg muscles during the swing and stance phase of gait, respectively, in Myotonic and Duchenne MD children compared to control populations. This research implies that different compensatory movement strategies may be utilised between the MDs, which is likely related to differing weakness distributions. However, there are limited data available to support this assertion and as such, further exploration of this is required.

In addition to the timing of EMG signals, the relative magnitude of EMG signals are important in gait analysis (Rosati et al., 2017). Only one study has measured this in MD, reporting a higher percentage of activation in the rectus femoris, medial hamstrings and tibialis anterior muscles in children with Duchenne MD compared to a control group (Ropars et al., 2016). However, to compare the magnitude of EMG signals between different participants, different muscles and/or different testing sessions, normalisation of the EMG signal is paramount (Burden, 2010; Lehman and McGill, 1999). This is because technical, anatomical and physiological elements are known to influence EMG magnitude (De Luca, 1997). Normalisation is achieved by dividing the EMG signal of the task (e.g. gait) by the mean or maximum EMG signal of a reference contraction in the same muscle (Burden, 2010). Ropars

et al. (2016) normalised EMG signals collected during gait, to a percentage of the maximum EMG signal that occurred during that same gait cycle. Arguably, this method does not permit comparison between different participants, as the EMG signal used as the denominator was obtained during the task under investigation (gait) and not a standardised reference contraction (Burden, 2010). For this reason, a valid comparison of the magnitude of muscle activation during gait between MD and control participants has not been undertaken. Future research should seek to rectify this.

There are numerous recognised methods to normalise EMG signals during gait. The Journal of Electromyography and Kinesiology and the SENIAM project (Merletii et al., 1999) both advocate the use of EMG associated with either an isometric or a dynamic MVC for normalisation purposes, in healthy participants. However, there is no precedent for EMG normalisation in pathological populations. Normalisation of EMG using a MVC may not be appropriate in individuals with neuromuscular disorders, due to potential problems with muscle fibre recruitment. Although, MD may not come under this bracket as it is characterised by muscle weakness rather than complications at the level of nerve cells. Consequently, individuals with MD may be able to elicit a maximum voluntary muscle contraction close to their maximum possible activation level, as in healthy individuals. It should firstly be established if a MVC is feasible in individuals with MD and if not, an alternative method of normalisation should be established that will allow comparison of muscle activation magnitude between MD and healthy control individuals.

2.3.5 Energetics of Gait

Walking capacity is essential for independent living and the completion of everyday activities. Deficits in the biomechanics of gait, such as reduced stride length or cadence, may increase the energy requirements of walking (Katzel et al., 2012), which presents as a higher oxygen consumption. Reduced economy of gait is often witnessed in other clinical disorders such as Parkinson's Disease (Katzel et al., 2012). Given the gait abnormalities previously presented in individuals with MD (as described above), the assessment of the energy requirement of gait is of particular interest, yet only one study has measured this in adults with MD compared to a control group. Tiffreau et al. (2012) reported no difference in oxygen consumption between adults with Myotonic MD and a healthy control group whilst walking on a treadmill. However, it was not clear if walking speed was matched between the participant groups and as Myotonic MD differs vastly from the other types of MD, these results cannot be generalised to other types of MD.

2.3.6 Recommendations

Despite the previous research that has investigated gait in individuals with MD, more research is required. Future studies should assess additional types of MD, a broader range of severities within the participant groups and examine gait in more depth and breadth. The current author suggests the following recommendations:

Additional types of MD, such as LGMD and BMD, require investigation. Kinematic and kinetic gait abnormalities in these conditions may be similar to those already described in other types of MD, but this is yet to be confirmed. In addition, in FSHD, kinematic and kinetic analysis is limited to the sagittal plane and to the less severe presentations of FSHD. Future research should include participants who rely on

walking aids to facilitate the understanding of gait in more severe presentations of FSHD.

There is relatively limited research concerning muscle activation patterns during gait in individuals with MD. There remains no investigation into participants with FSHD, LGMD or BMD. Future research should seek to establish both the timing and magnitude of the individual muscle activations during gait, in all types of MD. However, it must first be established whether normalisation of EMG signals to MVC are appropriate in individuals with MD and if not, an alternative normalisation technique sought.

There is a clear lack of research concerning the energetics of walking in all types of MD. Given the importance this review places on ambulation and physical function in everyday life, the economy of walking is of interest. Indeed, to minimise fall risk, metabolic gait assessments in MD should be completed during over-ground ambulation, opposed to the typical method of treadmill ambulation which more easily enables investigators to standardise walking speed. To enable metabolic assessments at a self-selected speed in MD, the calculation of walking cost should be employed by future studies. Walking cost is the amount of oxygen consumed per minute (ml/kg/min) normalised to the distance walked (ml/kg/m).

Relationships between muscle weakness and specific gait abnormalities in MD are unknown. Some investigations presented relationships between measures of fat infiltration within a muscle and specific gait abnormalities, but such relationships are indirect and only allude to an association between muscle strength and gait abnormalities. Future research should seek to identify direct relationships between

gait abnormalities and muscle strength, ensuring quantitative measures of muscle strength are utilised.

Finally, the assessment of dynamic stability in adults with FSHD, LGMD and BMD is limited to one study in FSHD. Future investigations should seek to examine dynamic stability during gait in these populations.

2.4 Quality of Life and Mental Health in MD

Individuals living with long-term clinical conditions are often faced with additional physical and mental challenges, as a direct consequence of their chronic disease. These additional challenges may have an impact on their quality of life and psychological state.

Quality of life is a notion that is hard to describe but on a subjective level it is instinctively understood. The World Health Organisation defines global quality of life as “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” (Khanna and Tsevat, 2007) In the framework of health and illness, health-related quality of life (hereafter referred to as QoL) is “the extent to which one’s usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment” (Khanna and Tsevat, 2007). An individual’s psychological state is concerned with aspects of his or her mental health and is inclusive of psychological concepts such as depression, anxiety and self-esteem.

In comparison to other chronic diseases, relatively few studies have assessed QoL or concepts of mental health in individuals with MD (Winter et al., 2010). Most studies that have, were conducted in children or adults with Duchenne MD, whilst

individuals with FSHD, LGMD and BMD have received little attention. The results of studies in children and adults with Duchenne MD cannot be generalised to adults living with other types of MD. This is because of the severe childhood onset and early loss of ambulation in Duchenne compared to other MDs, in which individuals may have lived any number of years unaffected by, or unaware of, their MD condition and in many cases are able to remain ambulatory.

2.4.1 Quality of Life in MD

In recent years, improving QoL has become a major goal of long-term disease management. This is because chronic conditions can impact on QoL, as shown in individuals with a variety of different muscle diseases (Graham et al., 2011).

In MD specifically, a limited number of studies have assessed QoL, and most studies that have been conducted in individuals with Duchenne MD (Davis et al., 2010; Uzark et al., 2012; Landfeldt et al., 2016; Lue et al., 2016; Kohler et al., 2005; Elsenbruch et al., 2013; Pangalila, van den Bos, Bartels, Bergen, Kampelmacher, et al., 2015). In any case, the literature is controversial. Some studies have reported reduced QoL in MD, compared to control groups or normative reference values. Whereas other studies report that whilst physical aspects of QoL are impaired, QoL in the mental health domain is similar between individuals with MD and control groups or normative reference values. Accordingly, reduced QoL in both physical and mental health subscales have been found in children with Duchenne MD (Davis et al., 2010; Uzark et al., 2012; Landfeldt et al., 2016), children and young men with Duchenne MD (Lue et al., 2016), a combined group of children and adults with Duchenne MD, BMD and LGMD (Grootenhuis et al., 2007), adults with Myotonic MD

(Antonini et al., 2006) and adults with FSHD (Winter et al., 2010; Padua et al., 2009). On the other hand, several authors report no difference in QoL, although interestingly these studies included no examinations of FSHD, LGMD or BMD. These studies included a mixed group of children and adults with Duchenne MD (Kohler et al., 2005) and adults with Duchenne MD (Pangalila, van den Bos, Bartels, Bergen, Kampelmacher, et al., 2015; Elsenbruch et al., 2013).

Those research studies discussed above, that report a positive QoL in individuals with Duchenne MD, concur with the disability paradox phenomenon (Albrecht and Devlieger, 1999). This occurs when individuals report a good QoL in spite of long-term disease and disability, which often seems counterintuitive to healthy individuals (Pangalila, 2016). However, these studies are limited to Duchenne MD, and therefore, the disability paradox is potentially exclusive to Duchenne MD. This is important to note, as boys with Duchenne MD are subject to a severe childhood onset and early loss of ambulation, leaving them little to no experience of a life without disability. This may influence how they perceive their QoL both in the physical and mental health domains, compared to other types of MD with a much later disease onset. Thus, the disability paradox, and therefore a high perceived QoL, may be exclusive to Duchenne MD or it may exist in adults with other types of MD, such as FSHD, LGMD and BMD, but more research studies quantifying QoL in these populations are required to determine this.

The relationship between disease and QoL in people with MD is clearly complicated and may be related to additional factors. These could include disease-specific parameters such as age at onset, disease severity, disease duration or specific

muscle involvement or it could be related to more personal factors, such as self-perceptions and aspects of mental health. This would be expected as in other neuromuscular disorders, QoL has shown a strong relationship to disease-specific parameters, such as disease severity, pain and fatigue, in addition to aspects of mental health, such as mood (Graham et al., 2011). In MD specifically, investigation into the factors associated with QoL has been limited, but some studies have investigated this. However, the focus of these studies is on disease-specific parameters, with little consideration of mental health.

2.4.2 Parameters Associated to QoL in MD

Disease-specific parameters that may be associated with QoL in individuals with MD have been investigated in Duchenne MD mainly, but some studies have included FSHD. These studies have shown that numerous parameters are negatively related to QoL, mainly in the physical domains. These include, age (Uzark et al., 2012), disease severity (Landfeldt et al., 2016; Padua et al., 2009; Otto et al., 2017), functional status (Lue et al., 2016) and wheelchair use (Wei et al., 2016). Other parameters are negatively associated with all domains of QoL, inclusive of pain (Padua et al., 2009; Abresch et al., 2002) and fatigue (Wei et al., 2016; Kalkman, 2005; Pangalila, van den Bos, Bartels, Bergen, Stam, et al., 2015). A more recent study did investigate individuals with LGMD (Peric et al., 2018) and reported negative associations between age at disease onset, current age, fatigue and use of assistive walking devices, with overall QoL score. Additionally, and of most interest, the authors assessed the strength of various muscle groups (shoulder abductors, elbow flexors, wrist extensors, hip flexors, knee extensors and dorsi-flexors) and

reported a positive correlation between hip flexor strength and overall QoL. This study is unique in its assessment of QoL in LGMD and it is the only study to assess potential relationships between the strength of various muscle groups and overall QoL. This is extremely practical, as unlike other parameters such as graded disease severity, the results can be used directly to inform future intervention programmes, such as which muscles to target during an exercise training programme.

Interestingly, the influence of mental health on QoL in MD has only been considered in three studies, in individuals with Myotonic MD, Duchenne MD and LGMD. Antonini et al. (2006) not only established a negative association between disease severity and duration with the physical domain of QoL, but also a negative association between depression and anxiety to QoL, in both the physical and mental health domains. Similarly, in Duchenne MD, Pangalila, van den Bos, Bartels, Bergen, Stam, et al. (2015) also found an inverse relationship between anxiety and both domains of QoL and between depression and the physical domain of QoL. What is more, the frequency of fatigue, anxiety and depression was higher in those categorised as having poor QoL, than those categorised as having a good QoL. More recently, Peric et al. (2018) established a negative association between depression and total QoL score, in adults with LGMD. Unfortunately, the only psychological variable that the authors considered was depression and details regarding which specific QoL domains depression was associated with were not provided.

Thus, it appears that depression and anxiety are related to QoL in MD. However, other aspects of mental health, such as self-esteem, may also influence QoL in MD and should be considered by future investigators in all types of MD.

2.4.3 Recommendations

Overall, quantification of QoL in MD is controversial, and dominated by studies investigating Duchenne MD. The disability paradox may or may not be present in adults with other types of MD, but more quantifications of QoL in other types of MD are required to know this definitively.

It is clear that numerous disease-specific parameters influence QoL in MD, but more specific measures related to the disease, such as muscle strength in various muscle groups, may prove more useful. Furthermore, investigation into psychological concepts that may be related to QoL is limited to three studies. Nevertheless, the available evidence does suggest that both depression and anxiety can influence QoL in Duchenne and Myotonic MD, and that depression is associated with QoL in LGMD. Thus, both depression and anxiety may influence QoL in individuals with FSHD and BMD too, and anxiety may also be associated to QoL in LGMD, but investigations into these specific populations are required. Additional aspects of mental health, such as self-esteem, may also be associated with QoL and therefore, investigation of this is warranted in all types of MD.

Understanding QoL and the factors associated with QoL, will facilitate treatment and management programmes and potentially reduce the burden of disease on health. Future research should seek to quantify QoL in individuals with FSHD, LGMD and BMD specifically, and to investigate the association between muscle strength in various muscle groups and psychological state with QoL in these populations. In particular, the psychological parameters that may represent barriers to physical activity, such as depression, self-esteem and anxiety are of interest.

2.4.4 Mental Health in MD

The prevalence of poor mental health is considerably higher in individuals with a long-term physical disease (Katon, 2011). Specifically, patients with a physical disease are three times more likely to experience depression and/or anxiety, compared to individuals without disease (Moussavi et al., 2007). Hence, it is unsurprising that between 9.3% and 18.1% of patients with a physical condition present with depression, which is significantly higher than the 4.4% of the general population with no physical condition (Moussavi et al., 2007). Interestingly, the evidence suggests that those with a long-term disease in combination with depression and/or anxiety, have an inferior health status to those with depression or anxiety alone, or those with multiple physical diseases (Panagioti et al., 2014). What's more, a study of more than 30,000 patients with a physical disease in combination with depression, found reduced functional capacity in these individuals, signifying a relationship between mental health and physical function (Egede, 2007).

It is often recognised subjectively, that the physical burden of MD may have an impact on the psychological health of both the individual and, in many cases, their families (Huml, 2015). Yet the investigation of psychological health in individuals with MD is scarce, compared to other long-term clinical conditions, such as stroke (Burton et al., 2013), multiple sclerosis (Marrie et al., 2015) and cerebral palsy (Van Der Slot et al., 2012). Indeed, the progressive nature of MD prioritises medical and rehabilitation interventions over psychological management, to maintain the physical autonomy of patients. However, as stated by the World Health

Organisation 'there can be no health without mental health' (World Health Organisation, 2005). Thus, investigation of psychological health should be a priority and will help to ascertain the necessity for psychological intervention/management in MD. This is especially pertinent, given that (as discussed above) mental health may be related to perceived QoL and functional disability.

Mental health management is encouraged as part of the primary care and disease management for children with Duchenne MD, as discussed in the US Centres for Disease Control and Prevention clinical care recommendations (Bushby et al., 2010). However, investigation into the different components of mental health, risk factors and subsequently, potential interventions for poor mental health remain under-investigated in MD. In contrast, no such guidelines or framework for the management of adults with Duchenne MD or other types of MD were provided, other than the recommendation for a transition into the usual mental health care pathway, together with the general population (Bushby et al., 2010). This is despite the likely heightened occurrence of poor mental health in MD and the additional burden of the primary disease in these individuals too.

The psychological characteristics of individuals with FSHD, LGMD and BMD are relatively unknown, but three psychological concepts that have received some attention in individuals with MD are depression, anxiety and self-esteem. These are explored in the following sections.

2.4.4.1 Depression and Anxiety

The World Health Organisation classifies common mental disorders into two main categories; depressive disorders and anxiety disorders, with symptoms ranging

from mild to moderate to severe (World Health Organisation., 2017). Depression is defined as “a mental health disorder characterised by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feeling of tiredness, and poor concentration. Depression can be long lasting or recurrent, substantially impairing an individual’s ability to function at work or school or cope with daily life” (World Health Organisation., 2017). Anxiety on the other hand, is characterised by excessive and inappropriate worrying, intrusive thoughts, tension and concerns, along with physical symptoms such as sweating and trembling (American Psychological Association, 2019). In research, anxiety is often separated into two distinct constructs (state and trait anxiety), which were originally proposed by Cattell and Scheier (1961). State anxiety is a temporary state of anxiety that is related to a particular situation, whereas trait anxiety is a predisposition to long-lasting and persistent feelings of anxiety that are not restricted to particular circumstances (Spielberger et al., 1983).

Globally, it is estimated that 4.4% and 3.6% of the world population suffer with depression and anxiety disorders respectively, and many individuals suffer with them both together (World Health Organisation., 2017). The increased presence of depression and anxiety in individuals with chronic disease (Moussavi et al., 2007) (between 9.3 and 18.1%) may stem from several origins. The burden of the disease itself may cause enough stress to prompt or exacerbate a psychiatric disorder or conversely, there may be a joint pathway between the pathogenesis of a disease and psychiatric disorders. In MD, both options are viable and may be interchangeable between the different types of MD, due to the varying pathogenesis between them.

Research studies investigating anxiety and/or depression in individuals with MD, compared to control or normative reference data are sparse. Investigation has taken place in children and adults with Duchenne MD (Pangalila, van den Bos, Bartels, Bergen, Stam, et al., 2015; Elsenbruch et al., 2013). In FSHD, BMD and LGMD specifically, one study utilised assessments of mental health from caregivers of non-ambulatory males with BMD (Latimer et al., 2017), and two studies compared levels of depression between different MD populations. This was between BMD and LGMD (Melo et al., 1995) and between Myotonic MD and FSHD (Alschuler et al., 2012). Finally, only one study assessed depression in one of the target populations (FSHD) independently. Padua et al. (2009) investigated factors that may be associated with depression (inclusive of age, clinical severity and muscle region involvement), in individuals with FSHD.

Pangalila, van den Bos, Bartels, Bergen, Stam, et al. (2015) found that depression and anxiety were present in 19% and 24% of adults with Duchenne MD respectively, and that the severity of both concepts were negatively associated with QoL. The frequency of anxiety and severe depression were in line with the reference population, but moderate depression was higher than in the reference population (18% versus 8%). In contrast, Elsenbruch et al. (2013) reported that a small proportion of adults with Duchenne MD presented mild-moderate depressive symptoms (between 11-17 on The Beck Depression Inventory) but the mean score was not clinically relevant (4.1).

In FSHD, LGMD and BMD, depression and anxiety may or may not have an increased frequency, but the research is inconclusive. In a study relating to children and adults

with Duchenne and BMD (Latimer et al., 2017), 209 caregivers completed a survey examining secondary conditions. Depression and anxiety were reported in 26% and 18% of BMD participants, respectively. However, incongruity between caregivers and MD patient reports have previously been demonstrated in ratings of perceived QoL (Wei et al., 2016) and therefore, these results may not represent the perceptions of the individuals with BMD themselves. Melo et al. (1995) reported no difference in the frequency of anxiety and depression between adults with BMD and LGMD, indicating no effect of genotype on mental health in these conditions, but comparison to a non-dystrophic control group or reference values was not conducted. In contrast, however, Alschuler et al. (2012) did report significantly less depression in adults with FSHD compared to adults with Myotonic MD, despite significantly higher levels of pain and lower physical functioning, with no difference in fatigue or age between the groups. Thus, depression may be higher in particular genotypes of MD, but this is hard to determine as other variables such as age at onset and disease duration may have differed between the groups. Furthermore, it is well known that Myotonic MD differs from the other 8 types of MD, as nearly every system in the body is involved (Huml, 2015). Hence, the increased frequency of depression within this population compared to FSHD is fairly meaningless. Finally, Padua et al. (2009) established that depression was positively associated with age in adults with FSHD, and that participants with both upper and lower limb involvement had significantly higher depression scores than those with upper limb involvement only. This type of information could direct the design of future intervention programmes aimed at increasing muscle strength. However, it is unclear whether the accumulation of having more muscles involved was the

mediating factor in depression, or whether lower limb muscle involvement specifically was more important. For this reason, investigation towards the influence of individual muscle groups would facilitate the design of future intervention programmes, particularly those designed to target muscle strength.

Overall, numerous problems with the research are evident. The frequency of depression and anxiety compared to non-dystrophic control or normative reference data is limited to investigations in Duchenne MD, which cannot be generalised to adults with FSHD, LGMD and BMD. This is because boys with Duchenne MD typically become wheelchair bound by the age of 12 years old. Therefore, their psychological characteristics may differ to adults with FSHD, LGMD and BMD, who are able to remain ambulatory into adulthood and have often experienced many years without disability. In addition, individuals with Duchenne MD are often treated with corticosteroids, which may influence aspects of mood, as discussed by Poysky (2007). Secondly, the factors that may be associated with depression and anxiety in FSHD, LGMD and BMD are largely unknown. Investigation has been limited to the parameters of age, clinical severity and muscle region involvement, in FSHD. Whereas other factors, particularly those that have the potential to directly inform future intervention programmes (such as the strength of individual muscle groups or physical activity levels) have not been investigated.

2.4.4.2 Self-esteem

Global self-esteem (hereafter referred to as self-esteem) has been defined as “an individual’s global, subjective and emotional evaluation of their perceived worth as a person” (Rosenberg, 1965). The presence or development of a chronic clinical

condition may be a driving force behind changes in self-esteem, as although reports of self-esteem before and after diagnosis are typically not possible, lower self-esteem has been reported in numerous clinical conditions, such as multiple sclerosis (Sarisoy et al., 2013), cerebral palsy (Riad et al., 2013), obesity (Abiles et al., 2010) and acquired brain injury (Kelly et al., 2013), compared to age-matched control populations. This is important given that self-esteem has been shown to be highly associated with measures of health-related QoL, in clinical conditions such as multiple sclerosis (Mikula et al., 2017). Furthermore, self-esteem has been identified as a crucial mediator in adherence to treatment programmes, such as exercise in diabetic patients (Knecht et al., 2001). Interestingly, it is well established within cross-sectional and longitudinal research studies that age is positively associated with self-esteem, from adolescence to adulthood (Huang, 2010), followed by a subsequent reduction in old age (Orth and Robins, 2014).

The assessment of self-esteem in MD is extremely limited. Only two studies, to this author's knowledge, have investigated self-esteem in individuals with MD. Specifically, these studies assessed children with LGMD (Miladi et al., 1999) and adults with Myotonic MD (Bertrand et al., 2015), compared to control and normative reference data, respectively. At present, no studies have investigated levels of self-esteem in adults with LGMD, BMD and FSHD. Miladi et al. (1999) measured self-esteem subjectively, in children and young adults (ranging from 10-22 years old) with LGMD, compared to an age and sex-matched control group of children referred to an outpatient clinic for emotional and behavioural difficulties. The children were shown projective cards that elicited realistic common interpersonal events with children and adults, and their self-esteem was scored

based on stories told by them in response to these cards. Overall, lower self-esteem was reported in children with LGMD than the control group. However, the investigator scoring self-esteem was not blinded to the groups, which is important given the subjective nature of this investigation. In adults with Myotonic MD, Bertrand et al. (2015) assessed self-esteem using the Rosenberg Self-esteem Scale. The authors reported no difference in self-esteem compared to normative reference data. However, there was a significantly lower self-esteem in the more severe MD group compared to the mild group, suggesting a potential relationship with disease severity or genotype.

The disparity in findings between the two studies that investigated self-esteem in MD, are perhaps a consequence of the different forms of MD and therefore the different pathogenesis of each disease, but there are multiple other potential explanations. The discrepancy may be due to the different measures of self-esteem utilised or the difference in age between the populations. As mentioned earlier, self-esteem increases from adolescence to adulthood across many different populations (Orth and Robins, 2014). Although the participants in both studies were compared to age-matched control or normative reference data, the additional impact of MD may be evident in children (due to the already inferior and vulnerable self-esteem), but dissipated in adults with MD. Alternatively, disease severity or duration may have influenced self-esteem in both studies, as naturally, the children and young adults in the former study had less time since MD onset. More MD research studies assessing global self-esteem, along with the factors that are associated with this are required. Global self-esteem may be lower, equal or even higher in adults with

LGMD, BMD and FSHD compared to age-matched controls, but research in these individuals specifically is required to determine this.

A major limitation of these studies is that investigation was limited to measures of global self-esteem. However, self-esteem is now considered to be multidimensional, with global self-esteem influenced by various domain levels of self-esteem, which are associated with different areas of the self (Raustorp et al., 2005), such as physical, academic, cognitive and social self-worth (Raustorp et al., 2005).

Self-esteem in individuals with a disease compared to individuals with no disease may differ in specific domains of the self, particularly those domains that are impacted by the disease. In MD for example, physical self-worth is of particular interest due to the characteristic effects of MD on physical function. The investigation of global self-esteem alone may conceal variances in self-esteem within this area. Hence, it is important to study self-esteem from this multifactorial perspective. This is particularly important when examining changes in self-esteem through a physical exercise intervention. The Physical Self-Perception Profile was developed by Fox and Corbin to enable measurement of physical self-worth in adults, and therefore this might be a useful measure in such studies (Fox and Corbin, 1989).

2.4.5 Recommendations

The degenerative aspects of MD mean that researchers prioritise medical interventions to maintain the physical autonomy of patients. However, psychological profiles of adults with MD, specifically FSHD, LGMD and BMD, would

be highly advantageous to discern the need for increased psychosocial support and counselling. Furthermore, previous psychological assessment has focused on the construct of depression, whilst there has been less investigation of other constructs such as anxiety and self-esteem. Furthermore, future researchers should look more deeply into domain levels of self-esteem in MD, with specific emphasis on self-esteem at the physical level.

Investigation into factors that may be associated with, and mediate, mental health in FSHD, LGMD and BMD would be highly beneficial to future interventions and management programmes, particularly those parameters that could be tackled directly by interventions, such as physical activity levels or muscle strength. In addition, the relationship between depression, anxiety and self-esteem with QoL in these populations is of interest.

2.5 Resistance Training in MD

Resistance training (RT) is a type of exercise that is endorsed by numerous health organisations, including the American College of Sports Medicine (Kraemer et al., 2002), who recognise that developing or maintaining muscular strength is pertinent for physical health and functional ability. In healthy populations, it is well established that RT increases skeletal muscle strength and lean body mass (Kraemer and Ratamess, 2004; Williams et al., 2007). These benefits are also evident in many other clinical populations often characterised with muscle weakness, such as stroke patients (Pak and Patten, 2008), elderly individuals (Morse et al., 2005), cerebral palsy children (Scholtes et al., 2010) and adults with multiple sclerosis (White et al., 2004), to name a few. Thus, RT may also benefit individuals living with a muscle

condition that progressively weakens and diminishes their skeletal muscle: namely, individuals with FSHD, LGMD and BMD, whose primary affliction is muscle deterioration and progressive weakness (Huml, 2015). However, investigation into the role of RT in MD has been extremely limited, due to historical fears that it may be detrimental to individuals with MD (Gianola et al., 2013). Specifically, for many years the medical domain believed that muscular effort might exacerbate the loss of muscle tissue and strength in individuals with MD (Ansved, 2001). This dated perspective has received limited scientific scrutiny and therefore, the value of RT in MD remains controversial, despite the arguments for a harmful effect being based on murine assessment of only one type of MD and anecdotal evidence (Ansved, 2001).

The murine evidence for a harmful effect of RT exists in mouse models of Duchenne MD, named mdx mice (Petrof, 1998). Weller et al. (1990) found that the mdx mice demonstrated more muscle fibres containing IgG, which is described as a biomarker for acute necrosis, following a bout of electrically stimulated eccentric contractions, compared to non-mdx mice. In addition, Petrof et al. (1993) reported an increased degree of sarcolemma membrane rupture in response to a range of *in-vitro* electrically stimulated maximal muscle contractions, in mdx compared to normal mice. However, multiple problems arise from generalising this evidence to both humans with Duchenne MD and other types of MD. Firstly, each type and subtype of MD differs via genetic mutation and subsequently, the defected protein or pathogenesis of the disease; It cannot be assumed that each type of MD will react to a stimulus such as RT in the same way. In addition, biological factors are present *in-vivo* that are most likely absent when muscles tissues are examined *in-vitro*,

which may influence the function and stability of the muscle cells. Furthermore, although mdx mice have the same genetic defect as humans with Duchenne MD (a mutated dystrophin gene), numerous differences exist between mdx mice and humans. Some of the most obvious differences include scale, tissue growth and development, and arguably one of the most important differences, that is often ignored, is that the mdx myopathy is not a precise replication of Duchenne MD (Partridge, 2013). Therefore, although suggestive, mdx mouse evidence should be treated circumspectly and a direct extrapolation to humans with MD should not be assumed.

An organisation heavily associated with MD recently recognised that some muscular exercise might benefit adults with some forms of MD (Muscular Dystrophy UK, 2014). However, due to the lack of research investigating RT in MD their guidelines are understandably, extremely vague. Thus, RT in MD remains underplayed, rendering it a potentially huge missed opportunity in the management of MD. The continuation of this limited research is likely due to how challenging this type of research is to undertake. There are an abundance of barriers to designing and implementing a RT study, for individuals with MD. These barriers include limited access to adults with MD, as a direct result of the rarity of the conditions. This forces researchers to employ less stringent controls over participant inclusion criteria concerning age, sex, condition severity, condition duration and rate of progression. Other barriers include the labour-intensive requirement for participant supervision to ensure movement quality, and the need to adapt regular exercises to allow completion by individuals with severe disabilities. Despite these barriers, research in this area is warranted.

Aside from the muscular adaptations typically associated with RT, there are other benefits of RT. Positive effects of RT on mental health and wellbeing are well documented in a variety of clinical populations. Perhaps of most interest are those studies demonstrating improved mental health in older adults, who similar to adults with MD, often experience inadequate muscle mass, strength and physical function (von Haehling et al., 2010). QoL has been shown to consistently improve post completion of a RT programme in a variety of clinical populations, including adults with Parkinson's disease (Ferreira et al., 2018), older adults (Kekalainen et al., 2018) and patients with chronic heart failure (Lans et al., 2018). With regards to the more detailed parameters of mental health, several reviews have been conducted into the effects of RT in numerous populations. O' Connor et al. (2010) conducted a systematic review and meta-analysis into the effects of RT on various aspects of mental health, including anxiety, depression and global self-esteem. Furthermore, Mead et al. (2010) meta-analysed studies that had measured the effects of RT in clinically depressed individuals and Spence et al. (2005) meta-analysed the influence of RT on global measures of self-esteem.

The effects of RT on the reduction of anxiety symptoms are positive. O' Connor et al. (2010) revealed a moderate effect (0.19 SD) of RT on the reduction of anxiety symptoms across older adults, breast cancer patients and adults with osteoarthritis, but a large effect of RT (0.54 SD) was established when those studies that included only older adults were meta-analysed (Tsutsumi et al., 1998; Jette et al., 1996; Damush and Damush, 1999; Cassilhas et al., 2007). Importantly, Strickland and Smith (2014) highlighted the importance of an intensity threshold, with the largest reductions in anxiety associated with RT programmes of moderate intensity.

The evidence with regards to the effect of RT on depression is supportive, on the whole. Mead et al. (2010) reported large reductions in the severity of depressive symptoms (1.34 SMD) amongst clinically depressed patients. Furthermore, consistent reductions in depressive symptoms amongst individuals with fibromyalgia (Jones et al., 2002; Hakkinen et al., 2001), spinal cord injury (Hicks et al., 2003) and osteoarthritis (O' Reilly et al., 1999) have been established, whilst results in older adults are inconclusive. Some studies have found a positive effect of RT in older adults, with reductions to the severity of depression (Cassilhas et al., 2007; Timonen et al., 2002; Singh et al., 1997), whilst other studies have reported no change to depression with RT in elderly populations (Jette et al., 1996; Sims et al., 2006; Chin A Paw et al., 2004; Penninx et al., 2002). It is unclear exactly which variables mediate the effect of RT on depression in older adults as many similarities in study design exist between the two groups, such as an age range from 68 to the mid 80's, programme durations between 10 and 24 weeks on both sides and exercise frequencies of 2 or 3 times per week on both sides. Logically, it could be assumed that the baseline severity of depression likely mediates the effect of RT in elderly adults, however, Penninx et al. (2002) showed no effect of RT in both highly depressed and non-depressed older adults. On closer inspection, it appears that adherence and compliance to RT programmes are the key mediators in whether RT influences depression in older adults. Adherence was reportedly high in those studies that reported a positive effect of RT (reported as above 75%, on average 90% and on average 93%) and low in those that reported no effect of RT (ranging from 58 % to 71%). What is more, after finding no effect of RT between depressed and non-depressed elderly adults, Penninx et al. (2002) found a significant effect of

RT when participants were re-grouped by compliance percentage, reporting a reduction in depression in the high compliance group only ($\geq 79\%$). Thus, it appears that RT does positively influence depression in elderly adults, as long as adherence to the programme is sufficient.

Investigation into the effects of exercise on self-esteem are typically focused on global measures of self-esteem. Spence et al. (2005) found a small effect (0.24 SD) of RT on improvements in self-esteem and O' Connor et al. (2010) concluded that randomised control trials exhibited a consistently positive effects of RT on global self-esteem across a range of populations, including elderly men and women (Tsutsumi et al., 1998; Singh et al., 1997), cancer patients (Courneya et al., 2007) and clinically depressed individuals (Ossip-Klein et al., 1989). More recently, improvements in global self-esteem together with larger improvements in physical self-perceptions have been demonstrated in a population of obese women, post 12-weeks of RT (Megakli et al., 2015). Physical self-perceptions may have a higher sensitivity to change than global measures of self-esteem following a programme of RT specifically, given the focus of RT on physical aspects and the multidimensional nature of self-esteem. Overall, RT may also elicit beneficial effects on aspects of mental health and QoL in individuals with MD.

In addition to the potential psychological health benefits of RT discussed above, RT might also influence the walking ability of individuals with MD. Evidence to suggest this stems from a positive relationship found between lower limb muscle strength and self-selected walking speed in older adults (Buchner et al., 1996). Habitual gait speed increased with leg muscle strength up to a threshold, after which no

advantage of muscle strength was evident (Buchner et al., 1996). This highlights the important role of lower limb muscle strength on gait performance, in individuals with initially weaker muscles. Further to this, in MD participants specifically, Lindeman et al. (1998) reported a strong correlation between quadriceps muscle strength and timed motor performances (the 6-minute walk test, descending and ascending stairs and rising from a chair), in Myotonic MD. RT programmes have proved successful in influencing a number of gait parameters, in other disorders that commonly exhibit gait deficiencies. For example, in individuals with multiple sclerosis, increased walking speed, increased stride length and decreased double support duration has been reported (Manca et al., 2017; Kierkegaard et al., 2016; Gutierrez et al., 2005). In children with cerebral palsy, positive effects of RT include increased ankle power at push-off and reduced minimum knee angle during the stance phase (Eek et al., 2008; Engsberg et al., 2006). Thus, RT may also influence walking speed and gait parameters in individuals with MD.

Essentially, there is viable potential for RT to improve muscle strength in MD, as shown in healthy individuals and other clinical populations, or for RT to stabilise the inherent decline in muscle mass and strength in MD. Furthermore, the benefits of RT in MD may go beyond muscle strength, yielding functional benefits in the physical and/or psychological domain. RT may be able to improve physical function and walking ability in MD, along with psychological health and wellbeing. Few research studies have considered the role of RT on muscle strength in MD, and even fewer studies have considered the potential for additional benefits of RT in individuals with MD.

2.5.1 RT on Muscle Strength in MD

Few research studies have investigated the influence of RT programmes on variables of muscle strength in MD. In FSHD, LGMD and BMD specifically, only one study has examined adults with FSHD (Van der Kooi et al., 2004) and another study has investigated a combined cohort of individuals with LGMD and BMD (Sveen et al., 2013). Gianola et al. (2013) conducted a systematic review and meta-analysis into RT in individuals with MD, in which only five studies were retrieved overall. The participants in those studies consisted of children with Duchenne MD (de Lateur and Giaconi, 1979), adults with Myotonic MD (Kierkegaard et al., 2011; Lindeman et al., 1995; Tollback et al., 1999) and adults with FSHD (Van der Kooi et al., 2004). Four of the studies measured isometric maximum voluntary contraction (MVC) torque (Lindeman et al., 1995; Tollback et al., 1999; Van der Kooi et al., 2004; de Lateur and Giaconi, 1979). The authors conducted a meta-analysis on those studies that measured MVC torque of the knee extensor muscles and found no significant effect of RT, but the direction of the effect was positive in all of them (Gianola et al., 2013). This non-significant outcome is likely due to the small number of participants that could be used in the meta-analysis (total of 37), which highlights the need for further research. It is pertinent to note that within these progressive conditions that the ability to maintain rather than significantly increase strength may be equally as meaningful, and future research should recognise this. The meta-analysis also considered the influence of RT on physical function (Gianola et al., 2013). Two studies that included multiple measures of physical function (Kierkegaard et al., 2011; Lindeman et al., 1995), such as time to ascend the stairs, time to descend the stairs and time to stand up from a seated position, were meta-analysed, but no

significant effect of RT was found. However shortly after this review, Sveen et al. (2013) demonstrated a ~60% and ~35% increase in elbow flexor and knee extensor muscle strength, respectively, following 24-weeks of RT in adults with LGMD and BMD. This latter study offers support for RT in adults with MD and justifies the need for continued research in this area to determine an outcome unequivocally.

The previous studies of RT on muscle strength in individuals with MD share some common drawbacks. Firstly, authors typically did not include any further physiological measures of muscle mass or function within their investigations. Secondly, only a limited number of skeletal muscles were measured (the knee extensors, knee flexors, elbow flexors and ankle flexors), which limits comparisons of strength between different muscles in the same individuals. Furthermore, limited subtypes of MD were considered, with the majority conducted in participants with Myotonic MD, and measures of physical function were rare. Finally, a major barrier to detecting a significant effect of RT in previous studies is that the progressive nature of MD was sometimes overlooked. Appropriate control groups or periods allow comparisons between RT programme effects and the muscular changes that typically occur during the degenerative progression of the disease. This is possible by utilising control groups who have a similar disease type, severity and progression rate or by measuring a control period before participants complete the RT programme. Some of the previous studies either failed to include a control group/condition or utilised the participant's contralateral limb as a control condition. This overlooks the possibility that unilateral RT can cause cross-education (strength gain in the opposite untrained limb) and therefore may mask the normal progression of MD.

Of all the previous RT studies in MD presented above, exercise duration ranged from 12-52 weeks, with significant gains in knee extensor one-rep maximum strength reported after a 12-week programme (Tollback et al., 1999). More RT studies are required to establish whether RT is beneficial in various types of MD.

2.5.2 RT on Gait in MD

Few studies have investigated the influence of RT on gait in MD and those that have, combined RT with aerobic exercise. Furthermore, in adults with FSHD, LGMD and BMD specifically, only one study included adults with LGMD and BMD. A study focused on balance and gait in Myotonic MD, investigated the effects of a 6-week rehabilitation-training programme. This program consisted of stretching exercises, balance training on a wobble board, resistance exercise on an isokinetic dynamometer and aerobic treadmill training (Missaoui et al., 2010). Increases of 18% and 32% in peak knee extension and knee flexion torques, respectively, were reported. These strength increases were accompanied by an improvement in balance, measured via the berg balance scale, functional reach test and timed up and go test, along with a 6% increase in fast walking speed but not self-selected walking speed. Whilst this evidence offers some support for the use of RT towards improving gait speed and stability in MD, the more detailed gait parameters were not measured and the sole influence of RT cannot be separated from the additional elements of the exercise programme. In addition, Berthelsen et al. (2014) investigated the combined effect of aerobic (walking or running) and RT (squats, calf raises and lunges) in individuals with LGMD and BMD, using an anti-gravity treadmill. Participants underwent a 10-week control period followed immediately

by the exercise programme, which was completed three times per week for a total of ten weeks. All exercises were completed on a treadmill within a lower body reduced pressure compartment. This allowed participants to exercise at a reduced proportion of their bodyweight, which was progressive and individualised to each participant. The RT consisted of squats, calf raises and lunge exercises whilst the treadmill was at a standstill. Post training, an 8% improvement in the distance walked over 6 minutes was reported, compared to the control period. In addition, after completion of the exercise programme a 13% improvement in dynamic balance measured using an AMTI force platform was reported. Both the improvement in walking speed and dynamic balance in this study offer support for RT in individuals with MD, but a deeper insight into the mechanism behind the increased walking speed, and whether these balance improvements were transferred during the task of walking remain unknown.

The biomechanical mediators of increased walking speed associated with exercise interventions in MD remain unknown. To combat this, detailed gait parameters, such as joint kinematics, joint kinetics and powers, muscle activity, energetics and stability require investigation. Future work is required to explore the possibility that RT can firstly, increase muscle strength in the legs of individuals with MD, and subsequently induce improvements in the detailed gait deficits and functional capacity of individuals with MD.

2.5.3 RT on QoL and Mental Health in MD

The few studies that have investigated RT in individuals with MD have been generally limited to physiological and biomechanical outcome measures.

Investigations into mental health have been limited to measures of QoL. Kierkegaard et al. (2011) measured QoL via the Short-Form 36 Health Survey, following 14-weeks of RT in adults with Myotonic MD, but no change was found. In addition, Berthelsen et al. (2014) observed QoL in adults with LGMD and BMD, before completion of a 10-week combined aerobic and RT programme, but unfortunately the authors failed to measure it post RT, reporting it as a baseline characteristic only. The more detailed variables of psychological health (e.g. anxiety, depression and self-esteem) are yet to be investigated following a programme of RT in MD. This is a disappointing since mental health and wellbeing are an extremely important part of an individual's global health.

2.5.4 Recommendations

Overall, there is an insufficient number and quality of research studies investigating the effect of RT on muscular, biomechanical and psychological variables in adults with FSHD, LGMD and BMD. The clinical implications of this are that there remains no answer to whether RT is beneficial, null or detrimental to individuals with MD. The collection of previous research studies that have measured muscle strength post RT have numerous limitations, and future research should make certain to include a range of muscle groups, include additional physiological and functional measures and importantly, ensure that appropriate control groups or control periods are utilised. Furthermore, investigation into the effect of RT on walking ability in MD is extremely scant and the biomechanical mechanisms of how, if at all, RT improves gait in MD are completely unknown. Therefore, future research should prioritise more sophisticated biomechanical variables of gait as outcome measures.

Finally, the effect of RT on psychological health in MD is yet to be investigated to any great depth. Regardless of whether RT is beneficial to muscle strength in MD, as long as it is not harmful, RT may positively influence psychological health, which in itself is extremely important to health and warrants investigation.

2.6 Thesis Aims and Objectives

The overarching aims of the current thesis are:

- 1) To contribute towards the understanding of muscle strength, gait and psychological limitations in individuals with FSHD, LGMD and BMD.
- 2) To enhance the understanding of the potential role of RT as an intervention in adults with FSHD, LGMD and BMD.

More specifically, the thesis objectives are:

- 1) To compare the lower-limb muscle strength and function of ambulatory adults with FSHD, LGMD and BMD, versus non-dystrophic age-matched control adults.
- 2) To examine the effect of a 12-week RT programme on lower-limb muscle strength and function in ambulatory adults with FSHD, LGMD and BMD.
- 3) To compare gait, including spatial-temporal, kinematic and kinetic variables, of ambulatory adults with FSHD, LGMD and BMD versus non-dystrophic control individuals.
- 4) To examine the effect of a 12-week RT programme on gait in adults with FSHD, LGMD and BMD.
- 5) To compare the mental health of adults with MD (FSHD, LGMD and BMD) to non-dystrophic control adults, and to assess the relationship of these parameters to quality of life in MD.
- 6) To examine the effect of as 12-week RT programme on QoL and mental health in adults with FSHD, LGMD and BMD.

2.7 Thesis Outline

This thesis will present each data chapter in two parts. Part A is a between participant design that examines differences between a MD group and an age-matched control group, or between three MD groups (FSHD, BMD and LGMD) and an age-matched control group. Part B is a within participant design that examines the influence of a 12-week RT programme compared to a 12-week control period, in a MD population.

Chapter 3 examines MVC torque in eight lower-body muscles and physical function via a 6-minute walk test, in adults with FSHD, BMD and LGMD compared to a matched control group. Part B examines the influence of a 12-week RT programme on MVC torque in eight lower-body muscle groups and timed tests of physical function, inclusive of a 6-minute walk test, a sit to stand test, a balance test, a stair ascent and a stair descent test, compared to a 12-week control period in a group of adults with MD (FSHD, BMD and LGMD).

Chapter 4 describes joint kinematics during gait and the metabolic cost of walking in adults with FSHD, BMD and LGMD, compared to a matched control group. Part B of this chapter examines the effect of a 12-week RT programme on these variables compared to a 12-week control period, in a group of adults with MD (FSHD, BMD and LGMD).

Chapter 5 describes joint kinetics (joint moments, joint powers and ground reaction forces) during gait in three groups of adults with FSHD, BMD and LGMD, compared to a matched control group. Part B of this chapter examines the effect of a 12-week

RT programme on these variables compared to a 12-week control period, in a group of adults with MD.

Chapter 6 investigates the mental health and QoL profiles of a group of adults with MD, compared to a matched control group, along with the severity of kinesiophobia in adults with MD. In addition, associations between physical activity and numerous mental health factors to QoL were examined in the MD population. Part B examines the influence of a 12-week RT programme on mental health and QoL, compared to a 12-week control period in a MD population.

Chapter 7 provides an overall summary of the principal findings, the clinical implications, the main limitations, the recommended future research and the overarching conclusions from this thesis.

Chapter 3

Influence of resistance training on muscle strength and physical function in adults with Facioscapulohumeral, Limb-girdle and Becker muscular dystrophy

3.1 Introduction

3.1.1 Part A

MD encompasses a range of myogenic conditions, which are caused by a variety of genetic mutations (Huml, 2015). Such mutations give rise to a reduced or absent expression of intra-muscular proteins, which ultimately cause progressive weakening and deterioration of the muscles (Mercuri and Muntoni, 2013).

Duchenne MD is the most severe form of MD, characterised by an absence of the protein dystrophin (Koenig et al., 1989), early childhood onset, rapid progression, cardiac and respiratory complications, loss of ambulation during childhood and premature death (Bushby et al., 2010). Other types of MD vary between childhood and adult onset, progress slower and do not typically lose the ability to walk, at least until later in adulthood (Emery, 2002). Three common types of MD that match the latter description are FSHD, LGMD and BMD (Emery, 2002). Similar to Duchenne MD, BMD is also due to a defect in the dystrophin protein, but the protein is reduced or dysfunctional rather than absent (Koenig et al., 1989). BMD is described as a less severe variant of Duchenne MD, with the loss in ability to walk typically occurring from the second decade of life onwards (Mercuri and Muntoni, 2013). FSHD and LGMD are both heterogeneous conditions, with various subtypes in each condition affecting different proteins at several molecular levels of the muscle cell (Sacconi et al., 2015; Liewluck and Milone, 2018). FSHD and LGMD typically occur in adulthood, with the loss in ability to walk occurring much later in life (Emery, 2002), if at all.

Despite differences in genotype between FSHD, LGMD and BMD, they all ultimately gives rise to progressive weakening and deterioration of the skeletal muscles

(Mercuri and Muntoni, 2013). Alongside this, individuals experience a worsening ability to perform daily functional tasks (Emery, 2002) such as, standing up from a seated position, walking, climbing stairs, descending stairs and many more.

Distribution patterns of muscle weakness in MD have been described clinically and schematics, such as that presented by Mercuri and Muntoni (2013) in Figure 3.1, are often referred to within the literature to describe predominant weakness patterns. Although clinical descriptions of weakness distribution in FSHD, LGMD and BMD are readily available, they are not based on quantitative data presenting muscle strength in these populations. Such data does not exist to any great extent or depth within the literature, which is important as subtype-specific patterns of muscle weakness are often used to inform an initial MD classification, to direct diagnostic testing, and to inform the clinical management of a patient.

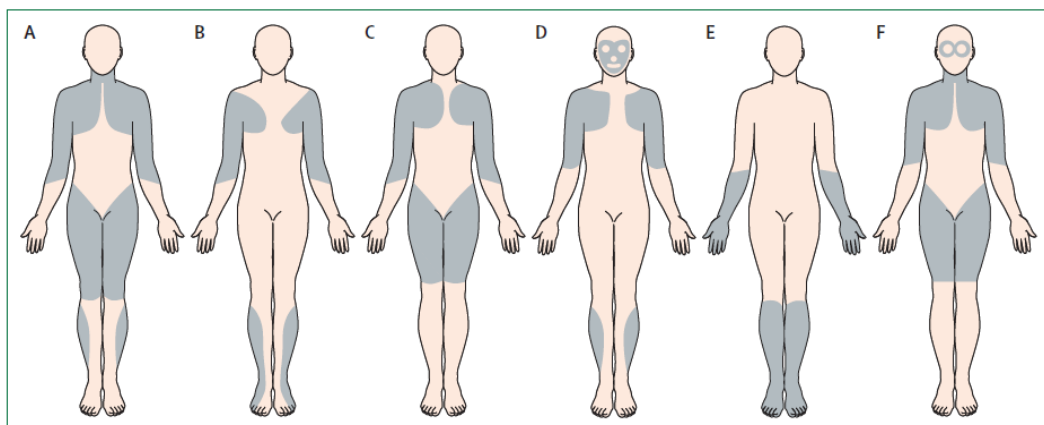


Figure 3.1: Pattern of predominant muscle weakness in MD: Duchenne and Becker (A), Emery-Dreifuss (B), Limb-girdle (C), Facioscapulohumeral (D), Distal (E) and Oculopharyngeal (F). Shading = involved muscles. Taken from Mercuri and Muntoni (2013).

In BMD, LGMD and FSHD only five studies have actively quantified lower-limb MVC torque (Bachasson et al., 2014; Jacques et al., 2018; Lokken et al., 2016; Skalsky et al., 2008; Marra et al., 2018), in four muscle groups: knee extensors, knee flexors,

dorsi-flexors and plantar-flexors. The number of investigations that have taken place for each muscle group per type of MD are demonstrated in Figure 3.2. From these five studies, some agreement with the pre-existing clinical classifications of muscle weakness distribution is evident (Figure 3.1). Accordingly, plantar flexor MVC torque was reportedly 35% weaker in adults with FSHD, and knee extensor MVC torque was 43% weaker in adults with LGMD, compared to non-dystrophic control adults (Jacques et al., 2018). These findings parallel the pre-existing clinical classifications of weakness distribution in FSHD and LGMD (Figure 3.1). However, numerous experimental studies have reported data that do not support such clinical descriptions.

Numerous experimental studies present results that challenge certain aspects of clinical classifications of muscle weakness distribution in FSHD, BMD and LGMD (Figure 3.1). Firstly, the knee extensor and knee flexor muscles are not recognised as a predominant region of muscle weakness in individuals with FSHD (Figure 3.1), yet studies have revealed knee extension MVC torques that were 41.6% (Skalsky et al., 2008), 44.9% (Bachasson et al., 2014) and 65.6% (Marra et al., 2018) weaker than non-dystrophic control groups, in these individuals. In addition, knee flexion MVC torque was found to be 56% weaker in FSHD than a non-dystrophic control group (Skalsky et al., 2008). Secondly, LGMD is described as presenting a primarily proximal muscle weakness pattern (Mercuri and Muntoni, 2013) (Figure 3.1), yet numerous studies have found significantly reduced muscle strength in the distal muscles of these individuals. In the plantar flexor muscles, MVC torque was found to be 58% weaker (Jacques et al., 2018) and 42% weaker (Lokken et al., 2016) than

a healthy control group, and in the dorsi flexor muscles MVC torque was 31% weaker (Lokken et al., 2016) than a control group. Finally, BMD is described clinically as presenting with descending proximal to distal muscle weakness (Emery, 2002). Jacques et al. (2018) reported that knee extensor MVC torque was 42% weaker in adults with BMD than a non-dystrophic control group, but Jacques et al. (2018) also reported a greater weakness, relative to the control group, of 51% in the distal plantar flexor muscles of the same individuals. This does not match with the proximal to distal muscle weakness classification that is described clinically for BMD (Emery, 2002). Thus, the clinical classifications of muscle weakness distribution in MD exhibit numerous discrepancies to the published strength data in FSHD, BMD and LGMD.

The MVC torque averaged from all previous investigations that have measured MVC torque of the knee extensors, knee flexors, plantar flexors or dorsi flexors, in individuals with FSHD, BMD and LGMD are presented in Figure 3.2, relative to non-dystrophic control groups. Within this schematic, the discrepancies between the pre-existing clinical descriptions of weakness distribution in MD and the quantitative data that are discussed above are evident.

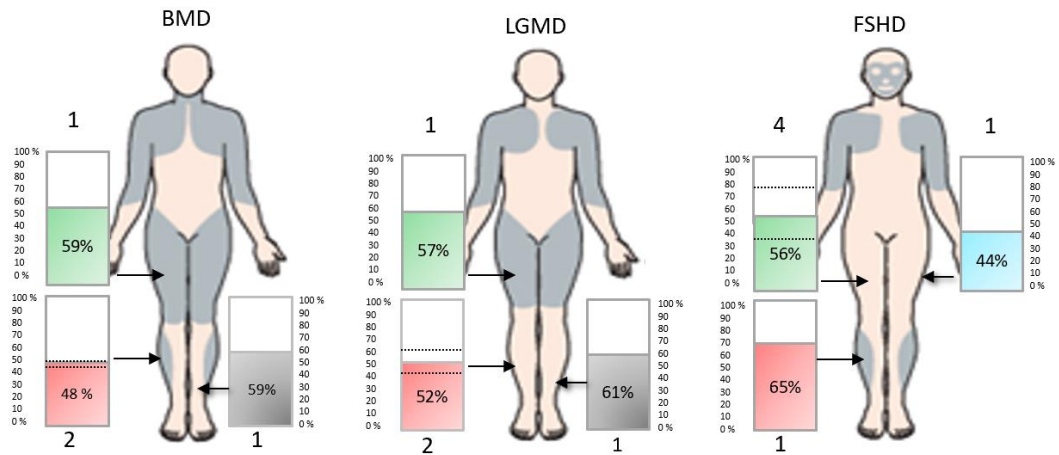


Figure 3.2: MVC torque per MD type in the knee extensors (green), knee flexors (blue), plantar flexors (red) and dorsi flexors (grey), as a percentage of MVC torque in control participants. Data was averaged from previously published data (Bachasson et al., 2014; Jacques et al., 2018; Lokken et al., 2016; Skalsky et al., 2008; Marra et al., 2018). Shading represents clinical classifications of weakness distribution (taken from Mercuri and Muntoni (2013)). Dashed lines represent the range across multiple studies. The number of assessments per muscle group are presented above or below the corresponding rectangle.

It is important to note that although experimental data in FSHD, BMD and LGMD highlight some discrepancies with the clinical classifications of weakness distribution, the previous studies are subject to numerous limitations. Firstly, only four muscle groups have been quantified overall, and no quantification of MVC torque has been reported in the muscle groups of the hips (e.g. hip abductors). The maximum number of muscles measured per study was two, which limits comparisons of relative muscle strength between different muscle groups in the same individuals. Three studies utilised a portable strain-gauge to measure MVC torque (Jacques et al., 2018; Bachasson et al., 2014; Marra et al., 2018), which is far more practical in this population than an isokinetic dynamometer; the gold standard of strength assessment. However, only one of those studies (Jacques et al., 2018) also demonstrated the reliability of their measurement technique and protocol. Finally, a major flaw of the previous research in this area is related to the method

of matching control groups to experimental groups. Three studies did match (Bachasson et al., 2014; Lokken et al., 2016) or accounted for statistically (Jacques et al., 2018) the age of participants between the groups. However, Skalsky et al. (2008) matched participants by sex, height and weight and Marra et al. (2018) did not match the participant groups, resulting in a difference of 20.5 years in the median age between the experimental and control group. Due to the progressive nature of MD and the decline in muscle strength with typical ageing, the use of appropriately age-matched control groups within MD research is of paramount importance.

Overall, five studies have quantified MVC torque in BMD, LGMD and FSHD and in those studies numerous limitations are evident. Therefore, the first aim of this study is to quantify the MVC torque of eight lower-body muscle groups and physical function in the form of a six-minute walk test, of adults with FSHD, BMD and LGMD, and compare to an age-matched control group.

3.1.2 Part B

In healthy populations it is well established that RT increases skeletal muscle strength and lean body mass (Kraemer and Ratamess, 2004; Williams et al., 2007). Furthermore, RT has proved highly beneficial in increasing MVC torque in older adults (Morse et al., 2005), a population that often presents with muscle weakness similar to MD. It would be highly valuable if RT offered similar benefits to adults with MD, but this is yet to be established.

For many years RT in adults living with MD was discouraged or disregarded by the medical domain. This was due to reservations that RT may damage muscle cells in

individuals with MD (Ansved, 2001). However, the evidence for this is limited to anecdotal case reports of overwork weakness in FSHD (Johnson and Braddom, 1971) and scapulooperoneal MD (Wagner et al., 1986) and murine evidence in MDX mice (Weller et al., 1990; Petrof et al., 1993). MDX mice represent one type of MD only (Duchenne) and in any case, the replicability of the MDX mutation to Duchenne MD is limited (Partridge, 2013). Given the stark differences in genotype and severity of Duchenne MD to other types of MD, along with questionable applicability of MDX mice results to humans, it is illogical to assume that RT should be avoided in all types of MD. Yet, there remains a lack of experimental investigation into RT in individuals with MD.

A meta-analysis conducted by Gianola et al. (2013) was unable to determine whether RT was beneficial or not in MD, as only four studies had previously measured MVC torque following a period of RT in individuals with MD (Lindeman et al., 1995; Tollback et al., 1999; Van der Kooi et al., 2004; de Lateur and Giaconi, 1979). Nevertheless, the authors did establish that despite no overall effect of RT, the direction of the effect in each of those studies was positive (Gianola et al., 2013). Shortly afterwards, Sveen et al. (2013) reported an approximate 60% and 35% increase in elbow flexor and knee extensor muscle strength (one-repetition maximum), following 24-weeks of RT in adults with LGMD and BMD. This research provides support for a beneficial effect of RT on muscle strength in adults with LGMD and BMD. However, more research, in more muscles, is required to determine this unequivocally.

It is pertinent to note that within this progressive condition (MD), the ability to maintain rather than increase muscle strength may be equally as meaningful. A major flaw of previous investigations into RT in MD is the lack of appropriate control groups or control periods within study designs. This limits comparison between the RT programme and the typical deterioration that may occur over an equal time period, due to the progressive condition. One possible approach to combat this is through the use of a within participant control design. These have previously been adopted to account for participant variance within small cohort training studies. In addition, limited attention has previously been paid to the influence of RT on functional performance in adults with FSHD, BMD or LGMD (Gianola et al., 2013). Whilst muscle strength is an important variable, the influence of RT on everyday life and physical function is of particular importance to prolonging independence in this population.

Therefore, the second aim of the present investigation was to determine the effect of a 12-week, twice a week, RT programme, compared to a 12-week control period, on isometric MVC torque and timed functional tasks.

3.2 Method

3.2.1 Study Design

The experimental design for this study was based around two parts. Part A was conducted to allow group comparisons between adults with muscular dystrophy (MD) and adults without MD (hereafter referred to as controls). Part B was a within-participant design involving a subgroup of adults with MD, and included 12 weeks of observation, followed by 12 weeks of resistance training (RT).

In part A, ten control and twenty-two MD participants attended the laboratory at MMU to complete one baseline testing session (PRE1). Data from this testing session correspond to baseline comparisons. A subset of 17 MD participants also completed part B. In total, part B participants completed three testing sessions including PRE1, followed by a second testing session 12-weeks after a control period (PRE2) and a third testing session within two weeks of completing a 12-week RT programme (POST, Figure 3.1). During the 12-week control period, MD participants were asked to maintain their habitual physical activity levels. The 12-week supervised RT programme took place at the Neuromuscular Centre (NMC), twice a week. Data collection at each testing session (i.e. PRE1, PRE2 and POST) remained identical. One additional testing session, MID-Train, took place halfway through the RT programme, which consisted of functional test measures.

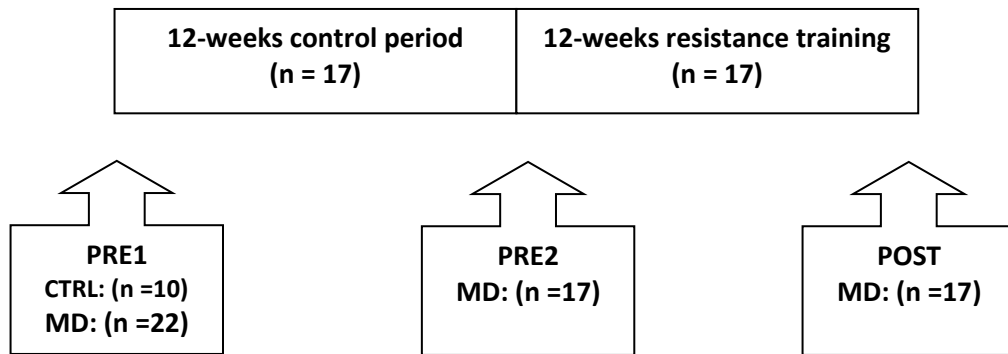


Figure 3.1. Schematic of study design. CTRL= control, MD = muscular dystrophy, PRE1 = testing session 1, PRE2 = testing session 2, POST = testing session 3.

3.2.2 Participants

Twenty-two adults with three distinct variants of MD; 7 with Becker (BMD), 9 with Facioscapulohumeral (FSHD) and 6 with Limb-girdle (LGMD) completed part A, along with 10 controls matched by age, stature and body mass (Table 3.1). Seventeen adults with three distinct variants of MD: 5 with BMD, 6 with FSHD and 6 with LGMD completed part B (Table 3.2).

All participants were between 26 and 64 years old, had not previously undertaken structured RT and were of sound intellectual status. All participants were untrained but functionally active (ambulatory) and self-reported that they did not undertake more than one hour of intense physical activity or three hours of low-moderate physical activity each week. Control participants were free from any known significant health problems, illness or musculoskeletal injuries. MD participants were able to walk at least seven metres with or without assistive walking devices, were in otherwise good health and without any uncontrolled co-morbidity or cardiac issues. All MD participants had previously received a laboratory confirmed diagnosis of MD via genetic testing at specialist clinics. MD participants were recruited from the NMC

(Cheshire, UK), a centre of excellence for adults with MD, where they regularly (weekly, bi-weekly or monthly) receive physiotherapy to maintain function and independence.

Manchester Metropolitan University (MMU) Ethics Committee granted ethical approval and all participants provided written informed consent, prior to participation.

Table 3.1: Participant characteristics for part A, presented as mean \pm SD.

	CTRL	MD	BMD	FSHD	LGMD
n	10	22	7	9	6
Male/Female	5/5	16/6	7/0	6/3	3/3
Age (years)	46.8 \pm 10.2	45.5 \pm 9.4	42.1 \pm 7.6	46.7 \pm 11.2	47.3 \pm 11.3
Stature (cm)	174.4 \pm 7.5	178.1 \pm 9.0	179.9 \pm 9.4	181.4 \pm 6.3	170.9 \pm 9.0
Mass (kg)	79.4 \pm 12.3	88.0 \pm 17.	93.0 \pm 16.7	88.2 \pm 18.4	82.0 \pm 19.4

CTRL= control, MD= muscular dystrophy, BMD= Becker, FSHD= Facioscapulohumeral, LGMD= Limb-girdle.

Table 3.2: Participant characteristics for part B, presented as mean \pm SD.

	MD	BMD	FSHD	LGMD
n	17	5	6	6
Age (years)	43.6 \pm 10.8	40.0 \pm 8.0	43.3 \pm 12.8	47.0 \pm 11.5
Stature (cm)	176.8 \pm 8.3	180.2 \pm 8.1	179.9 \pm 4.4	170.9 \pm 8.2
Mass (kg)	87.9 \pm 16.7	92.3 \pm 17.0	90.1 \pm 13.6	82.0 \pm 17.7

MD= muscular dystrophy, BMD= Becker, FSHD= Facioscapulohumeral, LGMD= Limb-girdle.

3.2.3 Procedures

All participants were screened for eligibility during a face-to-face meeting or via email. All testing sessions were identical, as time of day, equipment and order of data collection remained consistent, both between participants and between testing sessions. Participants attended the laboratories at MMU for a total of four hours per testing session, having refrained from consuming caffeine and alcohol in the 12 hours prior to the start of testing. Anthropometric and body composition measures were taken first, followed by strength tests in the knee flexor and knee extensor muscles using a Cybex dynamometer and six additional lower-limb strength tests measured using a load-cell, gait analysis and finally, a 6-minute walk test was completed. Participants also completed four timed functional tests at the NMC and seven questionnaires, within one week of each testing session.

3.2.3.1 Anthropometry

Stature (m) and body mass (kg) were measured using a stadiometer that was wall mounted and digital scales (Seca model 873, Germany). The dominant limb was determined via self-report, in answer to the following question: *which leg would you use to stop a football that was rolling towards you?* Leg length (mm; measured from the anterior superior iliac spine to the medial malleolus) was measured using a tape measure whilst the participant stood up. Knee width (mm; width of the knee from the medial to the lateral epicondyles of the femur) and ankle width (mm; medial-lateral distance across the malleoli) were measured bilaterally using callipers, whilst the participant stood up. Sole delta (mm; the difference in thickness

of the sole of the shoe at the toe and at the heel – positive indicates that the heel is raised compared to the toe) was measured whilst participants were seated.

3.2.3.2 Body Composition

Body composition, including fat mass and lean mass were measured using a bioelectrical impedance (BIA) device (Model 1500: Bodystat, Isle of Man, UK), whilst participants lay supine on a physiotherapy treatment bed. They were positioned with their arms slightly abducted from their sides and their legs separated marginally. Adhesive surface electrodes were placed on the right limb: on the dorsal surface of the hand at the metacarpals and at the distal prominences of the radius and ulna and on the dorsal surface of the foot at the metatarsals and between the medial and lateral malleoli. BIA was used as a substitute to a dual energy x-ray absorptiometry scan, because of the reduced functional movement ability in MD participants. BIA has previously been reported as a valid and reliable measure compared to dual-energy X-ray absorptiometry in adults with a wide range (19-38 kg/m²) of body mass indices (von Hurst et al., 2016).

Lean mass was determined using the following equation:

$$\textit{Lean mass (kg)} = \textit{body mass (kg)} - \textit{fat mass (kg)}$$

3.2.3.3 Knee Extensor and Knee Flexor Torque

Isometric maximal voluntary contraction (MVC) torque during knee extension and knee flexion were measured using an isokinetic dynamometer (Cybex Norm, Cybex International Inc., NY, USA). Participants sat on the dynamometer chair with a hip angle of 85° and were secured with straps around the shoulders, hips and thigh

(Figure 3.2). The axis of rotation of the dynamometer was aligned with the knee joint centre of rotation by visual inspection and the dynamometer and chair settings (lever arm length, back angle, chair fore-aft position, dynamometer rotation and dynamometer height) were noted and remained consistent between testing sessions. The cuff of the lever arm was attached proximal to the medial malleolus on the dominant leg.

Participants completed a set of five submaximal warm-up contractions of knee flexion, followed by a set of five submaximal warm-up contractions of knee extension. Subsequently, at an angle of 70° knee flexion, participants completed two maximal contractions of knee flexion, followed by two maximal contractions of knee extension, on the dominant leg. Participants were instructed to contract maximally for approximately 4 seconds, until verbally cued to relax. Verbal encouragement was given during MVCs and a three-minute rest period was given between each MVC. MVC torque was visible to participants during the contraction on a computer (Macintosh) and was recorded on an Apple computer (Cupertino, CA, USA) via an A/D converter (Biopac Systems, Santa Barbara, CA).

Torque measurements were processed offline using Acknowledge software (Version 3.9.2). Baseline torque was removed from the trace and then peak torque was measured. The highest torque produced during Knee extension and knee flexion was taken as MVC peak torque.



Figure 3.2: Example of participant set-up for measurement of knee extension and knee flexion MVC torque.

3.2.3.4 Strength Tests

The research team developed seven isometric strength tests, which were initially piloted in individuals with MD. Due to the limited mobility, fatigue and severe muscle weakness associated with MD, all of the test protocols were developed to ensure that completion was possible by the most severe participants. The seven tests measured isometric force during hip flexion, hip adduction, hip abduction, ankle dorsi-flexion, ankle plantar-flexion, hip extension and elbow flexion, using an S Beam strain-gauge (SGA/A; Load Cell Shop, Richmond Industries Ltd., Reading, UK) that collected force-time data in newtons (N). The load cell was calibrated using known loads ranging from 5 g -5 kg, at 500 g increments.

The strength tests were completed on the dominant limb with participants in one of three positions: lay prone, lay supine or seated on a physiotherapy treatment bed. Assessment of hip flexion, hip adduction and hip abduction was measured in a

supine position with the leg horizontal. Ankle dorsi-flexion was measured whilst participants lay supine with the long axis of the foot vertical. Elbow flexion and ankle plantar flexion were measured whilst participants were seated with the forearm and long axis of the foot horizontal. Hip extension was measured whilst participants lay prone with the leg horizontal. Straps were secured to both ends of the load-cell, with one strap secured to a stable base to ensure that an isometric contraction occurred. The opposite end, the cuff, was secured around the participant's ankle during hip flexion, hip adduction, hip abduction and hip extension, around the participant's forefoot during ankle plantar-flexion and ankle dorsi-flexion or within the participant's hand during elbow flexion. The strap was tightened until it was taught, without altering the position of the limb. A detailed description of the testing protocol for each MVC is provided in Table 3.3.

Participants completed practise trials followed by two MVCs. Participants were instructed to contract maximally for approximately 4 seconds until verbally cued to relax and encouragement was given throughout each MVC. Force (N) was accessible instantaneously using MyLabView software on a HP computer (Elite Book 850 G3) via an A/D converter (National Instruments Berkshire, UK). The moment arm of the MVC force was measured from the joint axis of rotation (anterior superior iliac spine, lateral malleolus or lateral epicondyle of the elbow) to the line of action of the force (the distance from the axis of rotation to the centre of the cuff) with a tape measure, to enable the calculation of torque (N.m) during data analysis.

Force traces were processed and analysed using Microsoft Excel. The baseline force, due to the initial tension on the load-cell, was removed by subtracting the average

force over the first 3 seconds from the entire force trace. Subsequently, the highest force produced during MVC was taken as peak force with the higher of both trials used for further analysis.

Torque, presented as MVC, was calculated using the following calculation:

$$\text{Torque (N.m)} = \text{force (N)} \times \text{External Moment Arm (m)}$$

3.2.3.4.1 Reliability

This method of strength assessment is similar to those previously utilised within clinical research to assess muscle strength, including hand-held dynamometry and quantitative strength testing, which have been reported as reliable in healthy populations (Hogrel et al., 2007; Mentiplay et al., 2015), weaker populations with muscle myopathy (Baschung Pfister et al., 2018) and MD (Brussock et al., 1991).

Test-retest reliability of the strength tests was determined in five healthy individuals (Mean \pm SD: age: 29.4 \pm 9.5 years, mass: 84.7 \pm 17.5 kg, height: 175.5 \pm 13.3 cm). Between day reliability was assessed by measuring MVC (as described above) on two different days, separated by an average of 48 hours. The data were checked for a normal distribution via the Shapiro-Wilk test, and then paired sample t-tests were conducted to detect any significant change in MVC between the two measures and Intraclass correlation coefficients were calculated to provide a complete assessment of reliability (Hopkins, 2000).

Reliability tests indicated that all strength tests were reliable. There was no significant change in MVC between the two days in any of the seven MVC tests and Intraclass correlation coefficients showed good test-retest reliability across all



seven MVCs, ranging from .86 to .99 (Table 3.4). The absolute and relative change in MVC between the two days ranged from -9.7 ± 24.5 to 1.8 ± 11.5 N and -4 ± 6.6 to 1.1 ± 7.4 %, respectively.

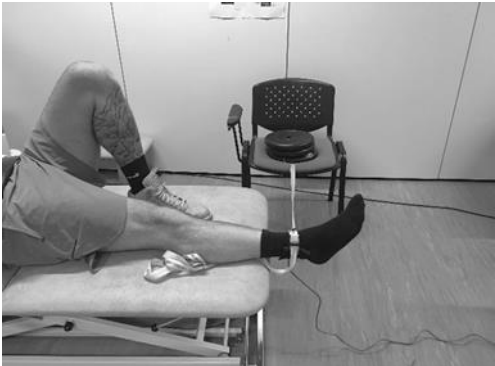

Table 3.4: Reliability of muscle strength tests using the S Beam load cell in healthy individuals.


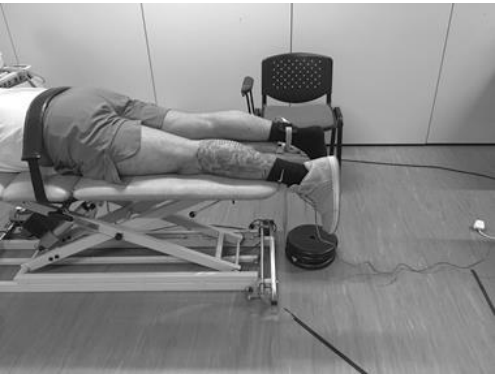
	Day 1 Mean \pm SD (N)	Day 2 Mean \pm SD (N)	Δ D2-D1 Mean \pm SD (N)	Δ D2-D1 Mean \pm SD (%)	ICC (95% CI)
Plantar Flexion	294.7 \pm 150.1	288.4 \pm 139.5	-6.3 \pm 12.2	-1.3 \pm 2.9	.96 (.95 -.99)
Dorsi Flexion	246.8 \pm 86.4	237.1 \pm 65.8	-9.7 \pm 24.5	- 4.0 \pm 6.6	.94 (.60 -.99)
Hip Flexion	192.3 \pm 63.6	186.8 \pm 69.1	-5.6 \pm 29.7	- 2.9 \pm 12.0	.90 (.33 -.99)
Hip Extension	195.8 \pm 72.2	195.7 \pm 72.9	- 0.2 \pm 3.9	< 0.1 \pm 2.0	.99 (.98 -1.00)
Hip Abduction	141.7 \pm 32.0	143.5 \pm 34.7	1.8 \pm 11.5	1.1 \pm 7.4	.94 (.55 - .99)
Hip Adduction	145.7 \pm 46.3	142.8 \pm 41.1	-3.0 \pm 23.4	- 0.8 \pm 14.3	.86 (.17 -.98)
Elbow Flexion	155.7 \pm 61.2	155.9 \pm 61.3	0.2 \pm 2.4	< 0.1 \pm 1.7	.99 (.99 -1.00)


ICC = Intraclass correlation coefficient, CI = confidence interval.

Table 3.3: Description of protocol for the measurement of MVC at the hip, ankle and elbow joint.

MVC	Position	Instruction	
Hip Flexion	<p>The participant lay supine with the hip and knee extended at 0° (straight), 0° of hip abduction and neutral hip rotation with the foot hanging freely over the plinth. The cuff was secured around the ankle, 2 cm proximal to the medial malleolus. The load cell was parallel to line of gravity and secured by sufficient weight so that it was taut when the hip and knee of the leg were horizontal.</p>	<p>Maximally lift the leg upwards, by flexing at the hip without bending the knee.</p>	
Hip Adduction	<p>The participant lay supine with the hip and knee extended at 0° (straight), 10° of hip abduction and neutral hip rotation, with the foot hanging freely over the plinth. The cuff was secured around the ankle, 2cm proximal to the medial malleolus. The load cell was at the same height as the plinth, perpendicular to the leg and to the line of gravity, in the opposite direction to the pending force and secured by sufficient weight so that it was taut.</p>	<p>Maximally pull the leg inwards, towards the opposite leg. Do not bend at the knee or rotate the foot.</p>	

MVC	Position	Instruction	
Hip Abduction	<p>The participant lay supine with the hip and knee extended at 0°, 0° of hip abduction and neutral hip rotation, with the foot hanging freely over the plinth. The cuff was secured around the ankle, 2cm proximal to the medial malleolus. The load cell was at the same height as the plinth, perpendicular to the leg and to the line of gravity, in the opposite direction to the pending force and secured by sufficient weight so that it was taut.</p>	<p>Maximally push the leg outwards away from the body. Do not bend at the knee or rotate the foot.</p>	
Plantar Flexion	<p>Participants sat upright on the edge of the plinth with their hands resting on the bed at either side. The knee was flexed at 90°, with the ankle dorsi-flexed at 90° to the shank. The cuff was secured around the dorsal surface of the foot with the load cell directly above, perpendicular to the foot and parallel to the line of gravity, so that the strap was taut when the ankle was at 90° to the shank.</p>	<p>Maximally pull your heel upwards, without lifting your knees from the surface of the bed.</p> <p>Note: If 90° of ankle dorsi-flexion could not be achieved due to limited range of motion, the closest possible angle to 90° was used</p>	

MVC	Position	Instruction	
Dorsi-Flexion	<p>Participants lay supine with the hip and knee extended at 0°, 0° of hip abduction and neutral hip rotation, with the foot hanging freely over the plinth and the ankle flexed at 90° to the shank. The cuff was secured around the forefoot with the load cell positioned perpendicular to the foot and to the line of gravity, in the opposing direction to the pending force and secured by sufficient weight so that the strap was taut when the ankle was at 90° to the shank.</p>	<p>Maximally pull your foot towards your lower leg, without bending at the knee or moving the pelvis.</p> <p>Note: If 90° ankle dorsi-flexion could not be achieved due to limited range of motion, the closest possible angle to 0° was used.</p>	
Hip Extension	<p>Participants lay prone with the hip and knee extended at 0° (straight), 0° of hip abduction and neutral hip rotation with the foot hanging freely over the plinth. The cuff was secured around the ankle, 2cm proximal to the medial malleolus. The load cell was parallel to line of gravity and secured by sufficient weight so that it was taut when the hip and knee of the leg were horizontal.</p>	<p>Maximally lift the leg upwards, without bending the knee.</p>	

MVC	Position	Instruction	
Elbow Flexion	The participant sat upright on the edge of the plinth, with their feet firmly on the ground. The elbow was flexed at 90° with the hand in supination and the shoulder adducted by 10°. The cuff was held in the hand with the load cell positioned below, parallel to the line of gravity and secured by sufficient weight so that the straps were taut when the elbow was at 90° flexion.	Maximally pull the lower arm upwards, with no movement of the torso.	

MVC = maximum voluntary contraction.

3.2.3.5 Adapted Six-Minute Walk Test

A six-minute walk test was conducted with participants who self-reported confidence in their ability to walk for 6 minutes. An adapted version of the protocol set out by the American Thoracic Society (2002) was utilised. Participants were instructed to walk at their self-selected walking pace, instead of as far as possible as prescribed by the American Thoracic Society (2002), due to safety concerns in the current population.

The test took place along a flat, straight corridor that was rarely used. Each end of the 25 m course was marked with tape on the ground. Participants were instructed to turn clockwise at each end and walk in a straight path of movement. One investigator timed the walk with a stopwatch and kept count of the laps completed on each minute and overall. A second investigator walked behind the participant, keeping at least a 2 m distance, to provide encouragement (in accordance with The American Thoracic Society guidelines), to assess fall risk and to place markers on the course at each minute to enable the calculation of minute-distance splits. Participants were instructed to use their walking aids during the six-minute walk test if they would typically use them to walk for a time period of six-minutes. If walking aids were used, this remained constant throughout the study.

A five-minute seated rest period was provided before completion of the walking test. To start the test, participants were readied at the start line and the timer was started once they began to walk. Participants were instructed to stop walking at six minutes and were subsequently seated until fully recovered.

3.2.3.6 Functional Tests

Four timed functional tests were completed at the NMC: a sit-to-stand, a stair ascent, a stair descent and a 30 s maximum balance test. The sit-to-stand movement required participants to rise from a seated position to a standing position, from a standardised chair that measured approximately 45 cm from the floor to the seat. The stair ascent test required participants to climb four steps with an approximate rise of 15 cm between the steps. The stair descent test required participants to climb down the same set of four steps. The balance test required participants to stand on one leg with the other leg raised from the floor, for as long as possible up to a maximum of 30 s.

Participants were instructed to complete all tasks as fast but as safely as possible and were initially given a practise trial before PRE1. Participants were encouraged not to use the arms of the chair during the sit to stand test or the handrails during the stair ascend/descent test, unless it was not possible to complete the test without using them, in which case this remained consistent throughout the study. Each test was timed using a stopwatch and recorded using a video camera.

3.2.4 Resistance Exercise Training Programme

The RT programme consisted of two supervised gym sessions at the NMC gym each week, for a total of 12 weeks. Collectively, previous research highlights that a frequency of 2 training days per week is sufficient to induce muscular adaptations in novice resistance trainers (Bird et al., 2005) whilst also requiring minimal time commitments and therefore promoting adherence. The 12-week duration was extended where necessary so that everyone performed 24 gym sessions in total.

Participants received a personalised training plan that was progressive and designed specifically to their individual needs and capabilities. To do this the research team, using muscle strength and 3D gait analysis data collected at PRE1, conducted an individual needs analysis. The muscles that were most weak, along with the most pronounced gait pattern abnormalities (e.g. excessive knee extension/hyper-extension or limited plantar flexion during the late stance phase of a gait cycle) were identified. Subsequently, a training programme was designed that included two warm-up and four consistent exercises across all participants, in addition to six individualised resistance exercises. Training sessions ranged between 45 minutes to 90 minutes depending on the functional ability of the participant.

3.2.4.1 Exercise Selection

All exercises consisted of dynamic repetitions of concentric and eccentric muscle actions. Single-joint exercises formed the majority of the exercise programme, to ensure isolation of specific muscle groups and to ensure ease of learning a safe technique in novice lifters. Multi-joint exercises are more neurally and coordination demanding than single-joint exercises (Bird et al., 2005; Kraemer and Ratamess, 2004) and therefore two multi-joint exercises were included within every programme; squat and step-up. These specific exercises were chosen due to the simplicity of their technique for a group of novice exercisers with muscle weakness.

The two warm-up and 4 consistent exercises across all exercise programmes are described as follows. All training sessions commenced with a 5-minute warm up, which was completed on a cycle ergometer, rowing machine or seated cross trainer, followed by 5-10 minutes of balance training on a Wii Fit video game balance board

(Nintendo of America Inc, Redmond, WA). Specific balance games on the Wii Fit video game system, that required participants to transfer their centre of pressure in an anterior-posterior and a medial-lateral direction, were chosen. Subsequently, all participants then completed two multi-joint exercises: freestanding squats or assisted squats (further details on assisted squats are provided in *3.2.4.2 Load and Volume*) and a step-up exercise onto a box of various and progressive heights. The final two exercises included within all programmes were two seated resistance exercises (knee flexion and knee extension) completed on a seated leg curl and extension machine (Pro Heavy Duty, XS Sports). Descriptions and examples of these exercises are provided in *Appendix 2.2*. Participants then completed 6 additional single-joint resistance exercises, based on the needs analysis completed at PRE1.

The potential muscle groups targeted within the individual exercises included 8 muscle groups of the lower body (dorsi-flexors, plantar-flexors, hip flexors, hip extensors, hip adductors, hip abductors, hip internal rotators and hip external rotators), along with the abdominals and/or lower back muscles. The research team, who have expertise in resistance exercise, movement analysis and muscle physiology, selected the target muscle groups using an impairment-based approach. Where required, the physiotherapists at the NMC were also involved in this process. The impairment-based approach utilised firstly, gait data to highlight the most pronounced gait deviations (compared to the control data) and then secondly, combined this information with muscle strength data to decipher which gait deviations were primary (due to a muscle weakness) or secondary (a compensatory mechanism for a weakness/gait deviation elsewhere). Thus, 6 resistance exercises were selected, to specifically target those muscle groups that

were deemed responsible for the primary gait deviations. Gait deviations within the sagittal plane held the highest priority, given that walking occurs primarily in this sagittal plane.

Once the target muscle groups had been identified, the selection of exercises to train each muscle group was completed by the research team, with the help of the NMC physiotherapists where required. Several variations of exercises to train the same muscle group were developed, to enable exercises to be completed in various positions (standing, seated and/or lying), depending on the functional ability and initial strength of the participant. Descriptions and examples of exercises for each muscle group are presented in *Appendix 2.3*.

3.2.4.2 Load and Volume

Initially, two sets of 10 repetition maximums (RM) per exercise were performed. Participants lifted enough weight so that they could only lift it ten times before experiencing fatigue. The initial starting weight for each exercise was ascertained in the first week of the exercise programme. The number of sets increased to three after 3 weeks. The training weight of 10RM was reviewed and adjusted (if the current load could be lifted for two repetitions over the desired amount) every three weeks. This training load and volume are in line with those recommended by the American College of Sport Medicine to increase muscle strength in previously untrained adults (Tawil et al., 1994; Kraemer et al., 2002). In addition, this training load and volume are similar to those previously shown to be achievable in adults with MD. For example, adults with Myotonic MD lifted 3 sets of 8-10 repetitions at 80% of their 1RM (Tollback et al., 1999; Lindeman et al., 1995), adults with FSHD

and LGMD lifted a 12RM load and a second group lifted 3 sets at 85% of 1RM, with no change in plasma creatine kinase levels (Sveen et al., 2013).

Training load was provided through various pieces of equipment, which was dependent upon the initial strength of the participant and, as a consequence of that, the position that the movement was completed in (standing, seated or lay). Load was provided through the use of resistive rubber bands, ankle weights and dumbbells and once a certain degree of strength was attained, load was provided through a cable machine (Bodymax CF820 Functional Trainer), plate weights or weighted barbells. In circumstances where participants were unable to complete an exercise with resistance, their body or limb weight was used as the initial resistance. In circumstances where participants could not complete an exercise through a complete range of motion, due to the weight of their body or limb, the investigator provided assistance manually or with rubber bands or the movement was completed in a gravity neutral/assisted position (e.g. bent knee hip flexion in a side lying position). The degree of assistance provided was reviewed and adjusted (if appropriate) every three weeks.

In order to provide assistance during the squat exercise, in circumstances where participants could not safely lower or lift their body weight in a freestanding position, two alternative options were developed. Option one comprised of a squat exercise with a Swiss ball placed between the participant's lower back and the wall, to aid balance in the posterior direction. The second alternative involved a physiotherapy treatment bed that was modified into a piece of equipment, named a squat bed. This enabled a movement similar to that of a squat (simultaneous

flexion and extension of the ankle, knee and hip joint) to be completed with a reduced amount of body weight involved in the movement. Details of this modification are provided in *3.2.4.4 Squat Bed Modification*. The angle of the plinth, and therefore the proportion of body weight involved in the movement, was reviewed and increased (if appropriate) every three weeks.

Descriptions and examples of the squat modifications are provided in *Appendix 2.2*. In addition, descriptions of training load variations for both the consistent exercises and each muscle group are provided in *Appendix 2.2* and *Appendix 2.3*, respectively.

3.2.4.3 Rest and Velocity

One-minute rest was given between exercise sets, but in cases where participants felt heavily fatigued, due to the nature of MD, they were offered a further rest period up to a total of three-minutes between exercise sets. Participants were instructed to complete exercises at a moderate repetition velocity (2 second concentric: 4 second eccentric), a protocol previously shown to induce greater 1RM strength gains (39% versus 15%) than slower repetition velocity protocols (Keeler et al., 2011).

3.2.4.4 Squat Bed Modification

The aim of the physiotherapy treatment bed modification was to create a piece of equipment that enabled participants with significant muscle deterioration and weakness to complete supported squat like movements, at progressive proportions of their bodyweight. This was achieved by modifying a physiotherapy treatment bed (Huntleigh Healthcare, Akron Products Division, model: A9622/2/THS), which

already had the function to move up and down mechanically and incline between a horizontal and vertical position. Whilst participants lay on the bed, the gradient of the plinth could be increased from a horizontal position to a full, but supported, standing position or any gradient in-between. This function is visually demonstrated in Figure 3.5



Figure 3.5: Representation of the physiotherapy treatment bed demonstrating the pre-existing incline function.

The modification involved raising the plinth onto two metal bars with runners; this allowed the plinth of the bed to slide forwards and backwards with external force. Additionally, the existing footplate was enlarged to enable participants to push with their feet during the squat movement. Furthermore, a mechanism to disable this sliding function was installed to ensure participant safety whilst getting onto and off the equipment. The sliding function is visually demonstrated in Figure 3.6.



Figure 3.6: Representation of the physiotherapy treatment bed demonstrating the sliding function modification.

The squat bed enabled participants to complete a movement that replicates a freestanding squat (triple flexion and extension at the ankle, knee and hip joints) whilst lying supine on the plinth or at any gradient in-between supine and vertical. As the plinth inclined from a horizontal to a vertical position, the proportion of body weight involved in the movement increased with the angle of the plinth. The proportion of body weight involved in the movement can be calculated using vector components for an object on a slope, via the following equation:

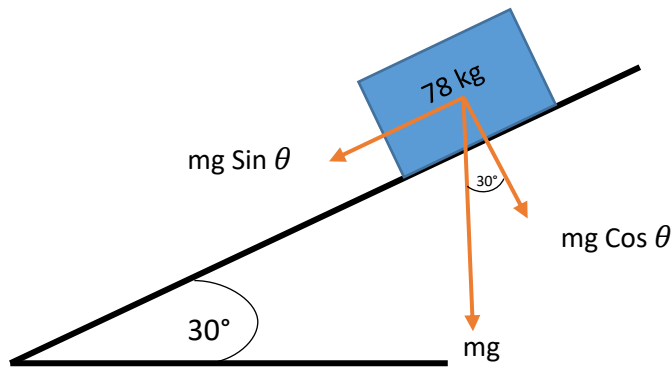
$$W = mg \times \sin \theta$$

Where W is the component of weight acting parallel to the plinth angle, m is body mass (kg), g is gravity and θ is plinth angle to the horizontal.

To convert W to a percentage of body mass, the following equation was used:

$$(W \div g) / m \times 100 = \%$$

For example, an object with a mass of 78 kg sliding down a slope of 30° to the horizontal has 39 kg of mass acting parallel to the slope (Figure 3.7).



$$78 \times 9.81 \times \sin 30^\circ = 383.3 \text{ N}$$

$$383.3 \div 9.8 = 39 \text{ kg}$$

$$39 \div 78 \times 100 = 50\%$$

Figure 3.7: Example of the vector components of weight for an object sliding at an incline to the horizontal.

3.2.5 Data Analysis

All data were stored and analysed in Microsoft Excel. Data are presented as means and standard deviations for the control group, FSHD, BMD and LGMD group, for part A. For part B, data are presented as means and standard deviations for the overall MD group, at each time point. In addition, all MVC torque measures are presented relative to the matched control group, but statistical analysis was not completed on these data, they were instead described.

3.2.6 Statistical Analysis

All statistical analysis were completed using IBM SPSS Statistics 25 software. The critical level of significance was set at $p \leq .05$.

3.2.6.1 Part A – MD versus Controls

All data was checked against the parametric assumptions. For parametric data, differences between the groups (control, FSHD, BMD and LGMD) were assessed

using a one-way ANOVA with Tukey post-hoc tests where appropriate. The following data did not satisfy one or more of the parametric assumptions: knee extension and knee flexion MVC torque, lean body mass, six-minute walk distance, dorsi flexion MVC torque, hip abduction MVC torque, hip adduction MVC torque, plantar flexion MVC torque, hip flexion MVC torque and hip extension MVC torque. In these cases, Kruskal Wallis tests were conducted with Mann-Whitney U post-hoc comparisons (least significant difference) where necessary. Statistical analysis of hip extension MVC torque was not undertaken in the LGMD group, as data was limited to one participant in this group due to issues with the testing position (lay prone). For analysis of the six-minute walk data a subgroup of MD participants was utilised. This comprised of eighteen MD participants (7 FSHD, 5 BMD and 6 LGMD).

3.2.6.2 Part B – Effects of RT

All data were checked against the parametric assumptions and the following data were parametric: six-minute walk test, sit to stand time, stair ascend time, elbow flexion and hip abduction MVC torque. For parametric data, differences between the time points (PRE1, PRE2 and POST or PRE1, PRE2, Mid-Train and POST) were assessed using a one-way repeated measures ANOVA. If the data did not pass Mauchly's test of sphericity ($P < .05$), a Greenhouse-Geisser correction was applied. From the ANOVA, both the retrospective observed power and the effect size, calculated as partial eta squared (η^2), were reported. Post hoc analysis was completed using the least significant difference pairwise comparisons, where appropriate. Non-parametric data were analysed using a Friedman's ANOVA, followed by post-hoc analysis using Wilcoxon-signed rank tests (least significant

difference), where required. For analysis of the six-minute walk test data, a subgroup of 15 MD participants was utilised (5 FSHD, 4 BMD and 6 LGMD). For analysis of the hip extension MVC torque, a subgroup of 9 MD participants was assessed, which included 3 FSHD, 5 BMD and 1 LGMD participant.

3.3 Results

3.3.1 Part A – MD versus Controls

3.3.1.1 Participant Characteristics

There were no differences between any of the participant groups for age, body mass, stature or lean body mass ($p > .05$; Table 3.5).

Table 3.5: Mean \pm standard deviation of participant characteristics in the control (CTRL), FSHD, BMD and LGMD groups.

	CTRL	FSHD	BMD	LGMD
n	10	9	7	6
Age (years)	46.8 \pm 10.1	46.7 \pm 11.2	42.1 \pm 7.6	47.3 \pm 11.3
Body mass (kg)	79.4 \pm 12.3	88.2 \pm 18.4	93.0 \pm 16.7	82.0 \pm 19.4
Stature (cm)	174.4 \pm 7.5	181.4 \pm 6.3	179.9 \pm 9.4	170.9 \pm 9.0
Lean body mass (kg)	56.1 \pm 11.7	60.8 \pm 13.9	62.0 \pm 6.9	54.0 \pm 15.4

3.3.1.2 Knee Flexion MVC Torque

There was an overall main effect of group on knee flexion MVC torque ($p \leq .01$; Figure 3.7). Knee flexion MVC torque was lower in each MD group compared to the control group, by 47.1% in the FSHD ($p = .022$), by 72.9% in the BMD ($p \leq .001$) and by 74.8% in the LGMD group ($p \leq .001$), with no differences evident between the MD groups ($p > .05$).

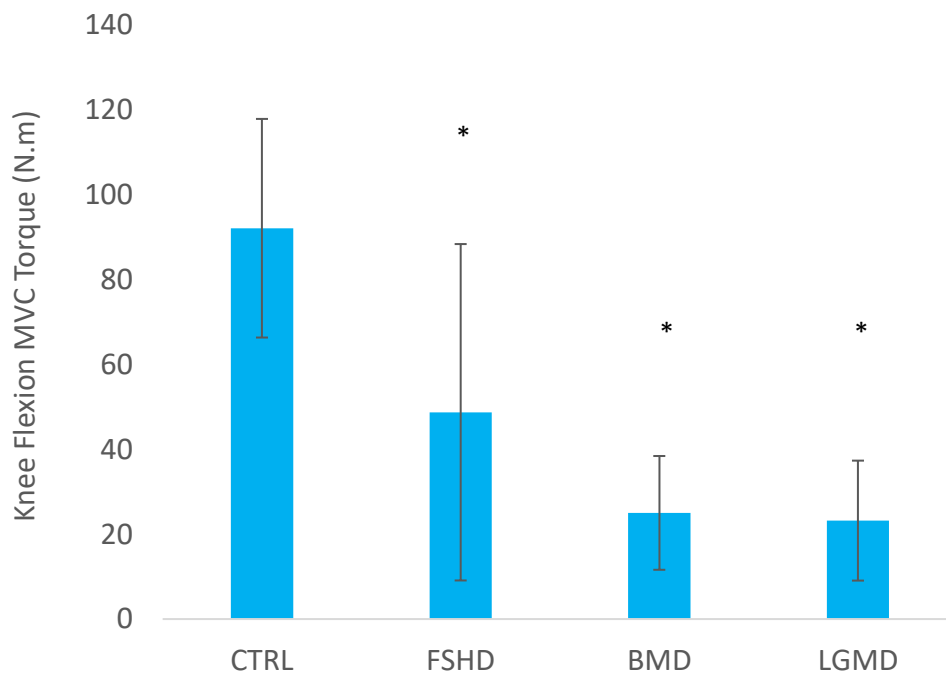


Figure 3.7: Knee flexion MVC torque for the control (CTRL), FSHD, BMD and LGMD group. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from the control group.

3.3.1.3 Knee Extension MVC Torque

There was an overall main effect of group on knee extension MVC torque ($p \leq .001$; Figure 3.8). Knee extension MVC torque was lower in each MD group compared to the control group, by 41.0% in the FSHD ($p = .039$), by 89.4% in the BMD ($p \leq .001$) and 78.7% in the LGMD group ($p \leq .001$). Furthermore, knee extension MVC torque was 82% less in the BMD than the FSHD group ($p \leq .01$) with no other differences between the MD groups ($p > .05$).

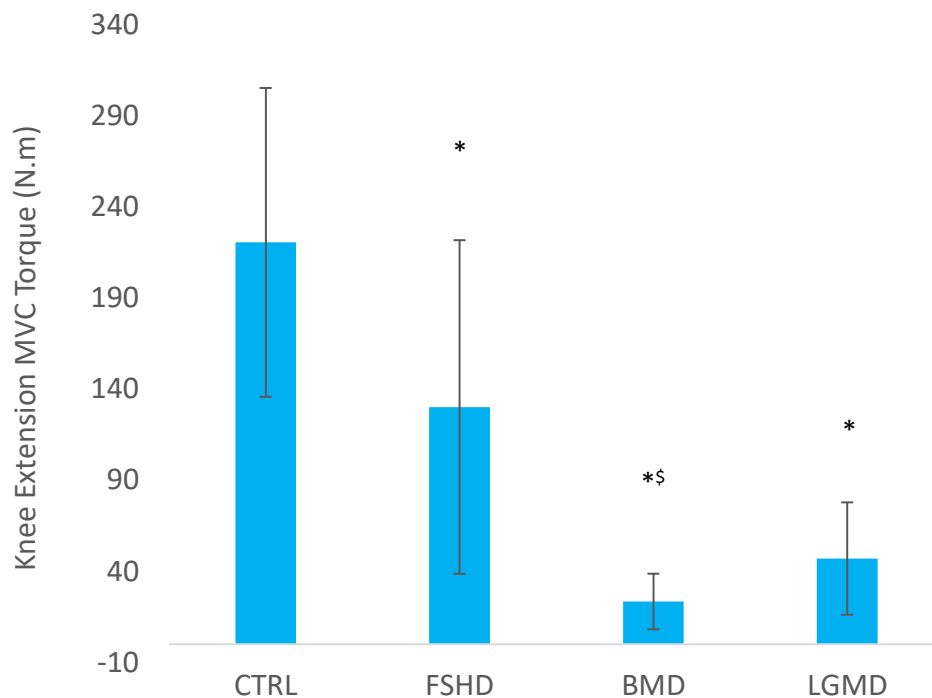


Figure 3.8: Knee extension MVC torque for the control (CTRL), FSHD, BMD and LGMD group. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from the control group and \$ represents a significant difference from the FSHD group.

3.3.1.4 Strength Tests

The absolute MVC torque values for each strength test are presented in Table 3.6 and described below. In Figure 3.9, the MVC torque for each strength test are presented visually and quantitatively, relative to the control group values.

There was an overall main effect of group on MVC torque during dorsi flexion ($p \leq .01$). Post hoc tests showed that dorsi flexion MVC torque was reduced by 66.7% in the FSHD ($p \leq .001$), by 65.7% in the BMD ($p \leq .001$) and by 75.3% in the LGMD group ($p \leq .001$), compared to the control group. There were no differences between the three MD groups ($p > .05$).

There was an overall main effect of group on MVC torque during plantar flexion ($p < .05$). Post hoc tests showed plantar flexion MVC torque did not differ between then BMD and the control group ($p > .05$) but was reduced by 60.5% in the FSHD ($p = .022$) and by 70.4% in the LGMD ($p \leq .01$) group, compared to the control group. There were no differences between the three MD groups ($p > .05$).

There was an overall main effect of group on MVC torque during hip abduction ($p \leq .001$). Post hoc tests showed that hip abduction MVC torque was not significantly different between the FSHD and control group ($p = .056$) but was reduced by 66.5% in the BMD ($p \leq .01$) and by 80.3% in the LGMD group ($p \leq .001$), compared to the control group. In addition, there was 65.9% less hip abduction MVC torque in the LGMD than the FSHD group ($p \leq .01$). There were no other differences between the MD groups ($p > .05$).

There was an overall main effect of group on MVC torque during hip adduction ($p \leq .001$). Post hoc tests showed that hip adduction MVC torque was 52.5% smaller in the FSHD ($p \leq .01$), 70.5% smaller in the BMD ($p \leq .001$) and 77.6% smaller in the LGMD ($p \leq .001$) group, compared to the control group. In addition, hip adduction MVC torque was smaller in the BMD and LGMD groups compared to the FSHD group by 38% ($p = .038$) and 52.8% ($p = .025$), respectively.

There was an overall main effect of group on MVC torque during hip flexion ($p \leq .001$). Post hoc tests showed that hip flexion MVC torque was reduced by 53.0% in the FSHD ($p \leq .01$), by 72.3% in the BMD ($p \leq .001$) and by 76.9% in the LGMD group ($p \leq .001$), compared to the control group. There were no differences between the three MD groups ($p > .05$).

There was an overall main effect of group on MVC torque during elbow flexion ($p \leq .01$). Post hoc tests showed that elbow flexion MVC torque did not differ between the control and FSHD group ($p = .89$) but was 52.8% smaller in the BMD ($p = .037$) and 61.9% smaller in the LGMD group ($p = .017$) compared to the control group. There were no differences between the three MD groups ($p > .05$).

There was an overall main effect of group on MVC torque during hip extension ($p \leq .001$). Post hoc tests showed that hip extension MVC torque was reduced by 51.7% in the FSHD ($p \leq .01$) and by 84.2% in the BMD ($p \leq .001$), compared to the control group. In addition, hip extension MVC torque was 16.2% less in the BMD than the FSHD group ($p = .026$).

Table 3.6: Mean \pm standard deviation of MVC torque during seven strength tests, in the control (CTRL), FSHD, BMD and LGMD groups. * represents a significant difference from the control (CTRL) group and § represents a significant difference from the FSHD group.

	Dorsi Flexion (N.m)	Plantar Flexion (N.m)	Hip Abduction (N.m)	Hip Adduction (N.m)	Hip Flexion (N.m)	Hip Extension (N.m)	Elbow Flexion (N.m)
CTRL	41.7 \pm 13.2	31.1 \pm 23.8	132.8 \pm 92.8	116.8 \pm 48.5	146.1 \pm 55.3	153.5 \pm 56.2	51.5 \pm 24.5
FSHD	13.9 \pm 13.2*	12.3 \pm 6.6*	76.9 \pm 26.6	55.5 \pm 29.9*	68.6 \pm 38.2*	74.2 \pm 38.6*	29.0 \pm 12.8
BMD	14.3 \pm 10.4*	15.8 \pm 8.7	44.5 \pm 31.7*	34.4 \pm 26.4* §	40.4 \pm 23.3*	24.3 \pm 21.1* §	24.3 \pm 21.1*
LGMD	10.3 \pm 8.2*	9.2 \pm 3.0*	26.2 \pm 16.7* §	26.2 \pm 17.2* §	33.7 \pm 14.7*	~30.7	19.6 \pm 12.5*

Note: Hip Extension MVC torque in the LGMD group was not completed in enough participants to enable statistical analysis. The value presented represents data from one LGMD participant.

Hip Flexion
 Hip Extension
 Hip Abduction
 Hip Adduction
 Knee Extension
 Knee Flexion
 Plantar Flexion
 Dorsi Flexion

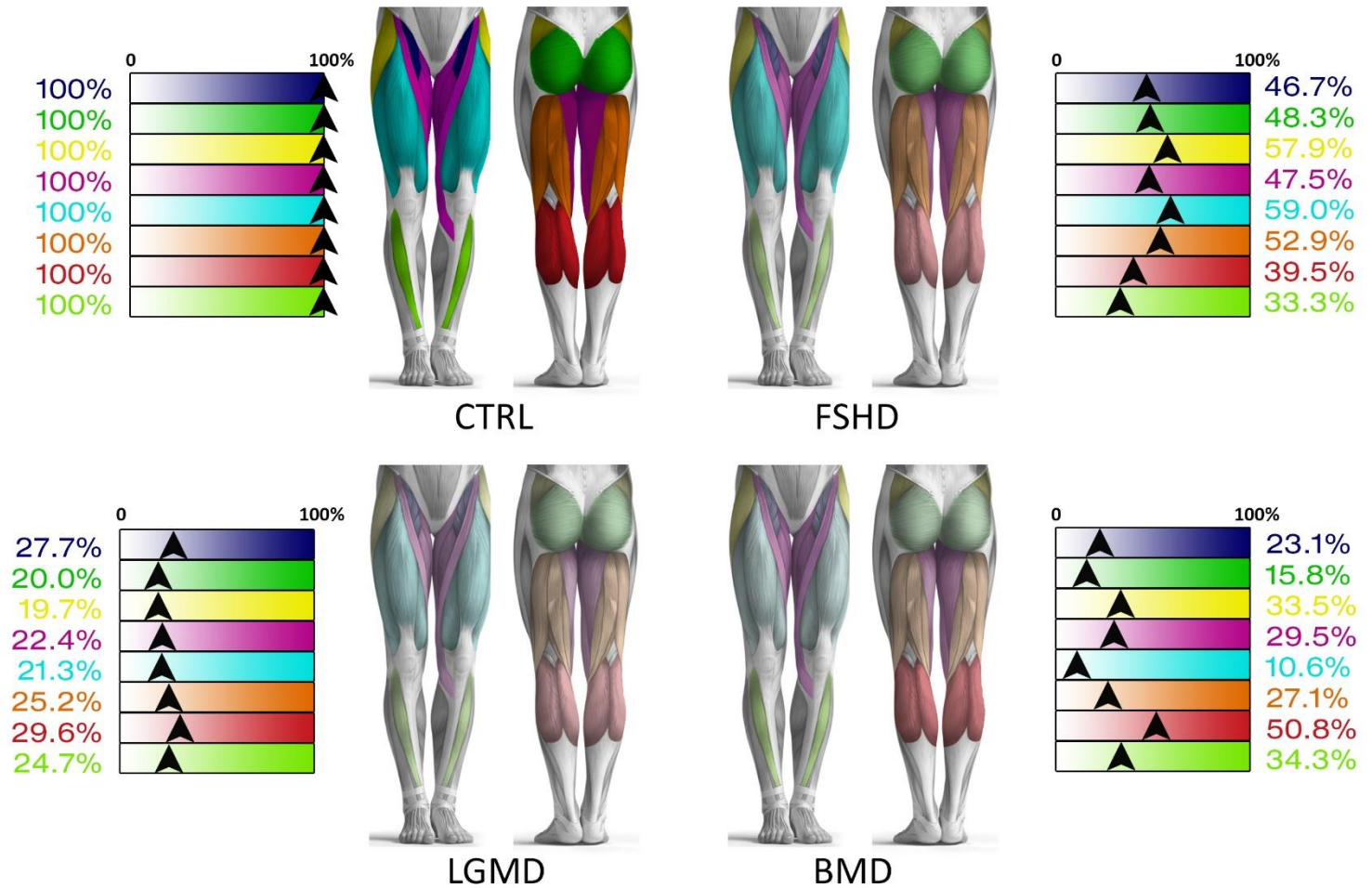


Figure 3.9: Visual representation of MVC torque in the FSHD, LGMD and BMD groups as a percentage of the control (CTRL) MVC torque, represented by the change in colour gradient, (decreasing colour gradient with decreasing percentage of MVC torque). Numerical percentages are presented beside each key.

3.3.1.4 Six-minute Walk Distance

There was an overall main effect of group on six-minute walk distance ($p \leq .01$; Figure 3.10). Six-minute walk distance was reduced in each MD group compared to the control group, by 21.3% in the FSHD ($p = .017$), by 35.3% in the BMD ($p \leq .001$) and by 45.6% in the LGMD group ($p \leq .01$). In addition, six-minute walk distance was 27% less in the LGMD than the FSHD group ($p \leq .051$). No further differences between the MD groups were found ($p > .05$).

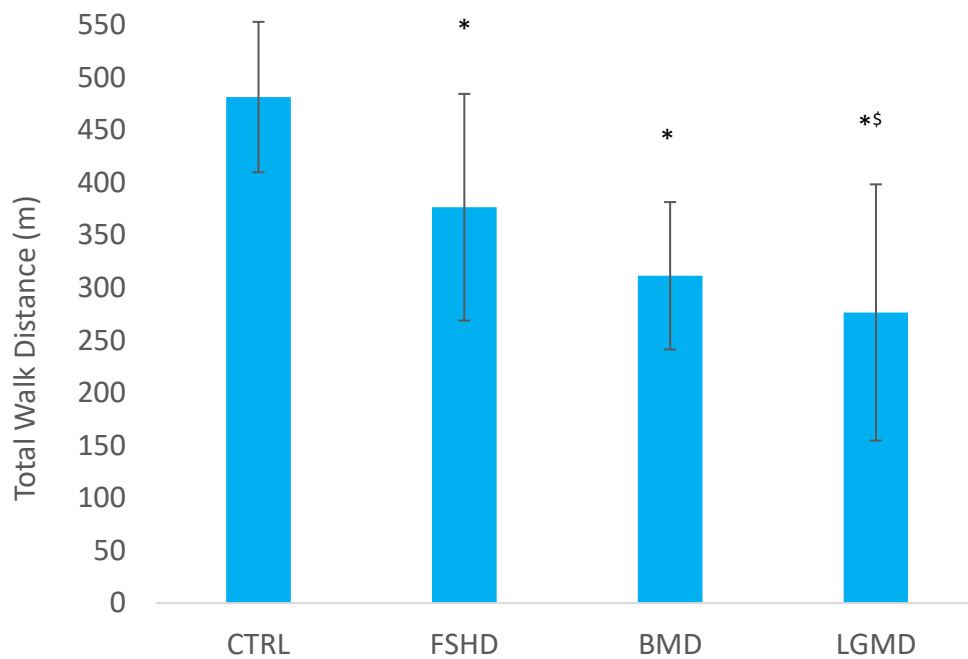


Figure 3.10: Six-minute walk distance for the control (CTRL), FSHD, BMD and LGMD groups. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from the control group and \$ represents a significant difference from the FSHD group.

3.3.2 Part B – Effects of RT

Two participants dropped out of the RT programme (2 out of 19). One after completion of the second exercise session and the second after the fifth exercise session. The reasons stated for dropping out were 1) a lack of time and 2) flare up of an injury that was sustained before the RT programme. On average, 23 ± 1.5 of 24 exercise sessions were completed, totalling a mean adherence rate of 96%. Other than the flare up of a pre-existing injury, no other adverse events were reported to investigators, but one participant fell during a training session. However, the participant sustained no lasting injuries and continued with the programme the following week. All data presented represent the 17 participants who completed all elements of the training study.

3.3.2.1 Knee Flexion MVC Torque

There was an overall main effect of time on knee flexion MVC torque ($p \leq .01$; Figure 3.11). Post hoc tests showed no difference between PRE1 and PRE2 ($p > .05$), a 15.4% increase from PRE1 to POST ($p \leq .01$) and a 12.6% increase from PRE2 to POST ($p \leq .001$).

3.3.2.2 Knee Extension MVC Torque

There was no overall main effect of time on knee extension MVC torque ($p = .084$; Figure 3.12).

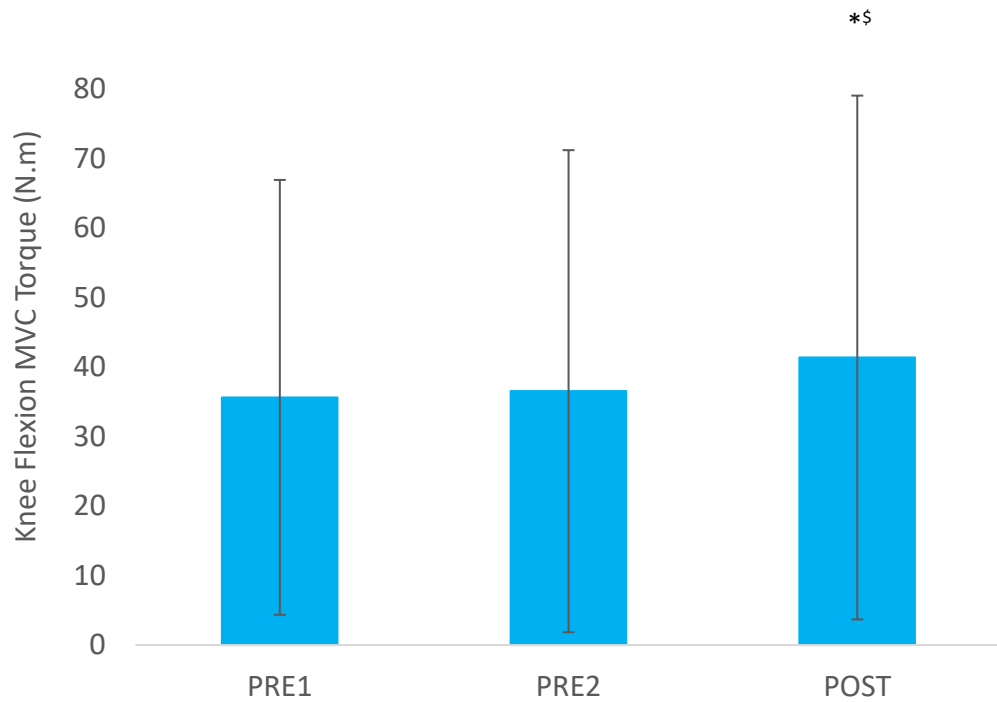


Figure 3.11: Knee flexion MVC torque at PRE1, PRE2 and POST the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

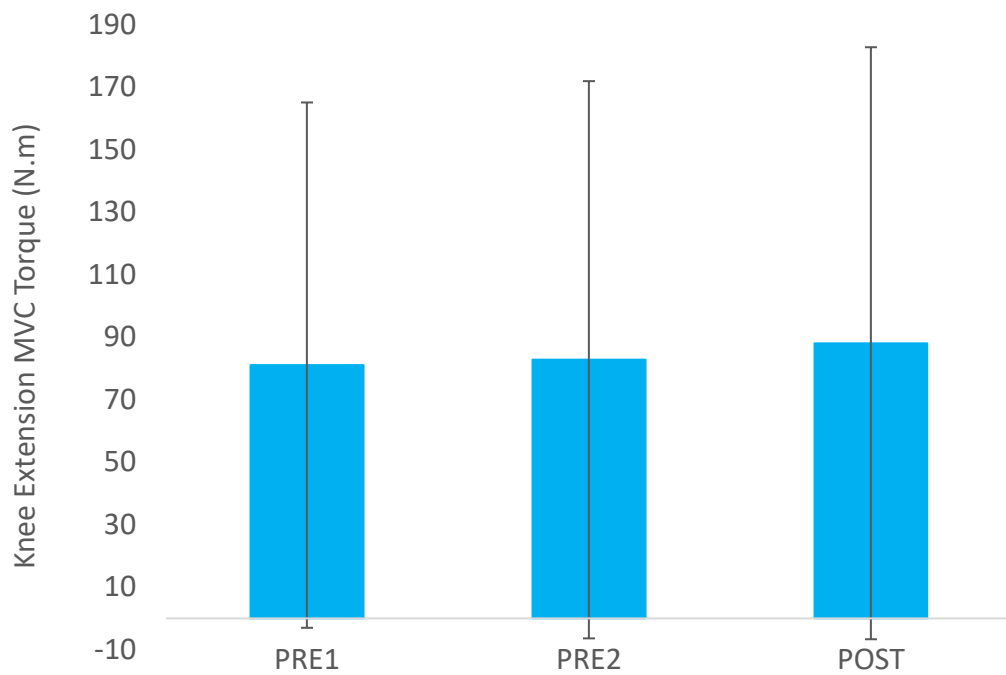


Figure 3.12: Knee extension MVC torque at PRE1, PRE2 and POST the RT programme. Bars represent the mean and error bars represent the standard deviation.

3.3.2.3 Strength Tests

The absolute values for MVC torque during each strength tests are presented in Figure 3.13 and described below.

There was no overall main effect of time on MVC torque during elbow flexion ($p > .05$) or hip adduction ($p = .059$).

There was an overall main effect of time on MVC torque during hip flexion ($p \leq .001$).

There was no difference in MVC torque between PRE1 and PRE2 ($p > .05$) but a 33.8% increase from PRE1 to POST ($p \leq .001$) and a 27.3% increase from PRE2 to POST ($p \leq .01$).

There was an overall main effect of time on MVC torque during hip abduction ($p \leq .01$, $\eta p^2 = .25$), with an observed power of .80. There was no difference in MVC torque between PRE1 and PRE2 or between PRE1 and POST ($p > .05$), but a 20.1% increase in MVC torque between PRE2 and POST ($p = .02$).

There was an overall main effect of time on MVC torque during plantar flexion ($p \leq .001$). There was an 11.4% reduction in MVC torque between PRE1 and PRE2 ($p = .045$), a 46.2% increase from PRE1 to POST ($p \leq .001$), and a 65.0% increase from PRE2 to POST ($p \leq .001$)

There was an overall main effect of time on MVC torque during dorsi flexion ($p < .05$). There was no difference in MVC torque between PRE1 and PRE2 ($p > .05$) but a 47.2% increase from PRE1 to POST ($p \leq .01$) and a 27.9% increase from PRE2 to POST ($p \leq .01$).

There was an overall main effect of time on MVC torque during hip extension ($p \leq .01$). There was no difference in MVC torque between PRE1 and PRE2 ($p > .05$), but a 62.5% increase from PRE1 to POST ($p \leq .01$) and a 22.8% increase from PRE2 to POST ($p \leq .01$).

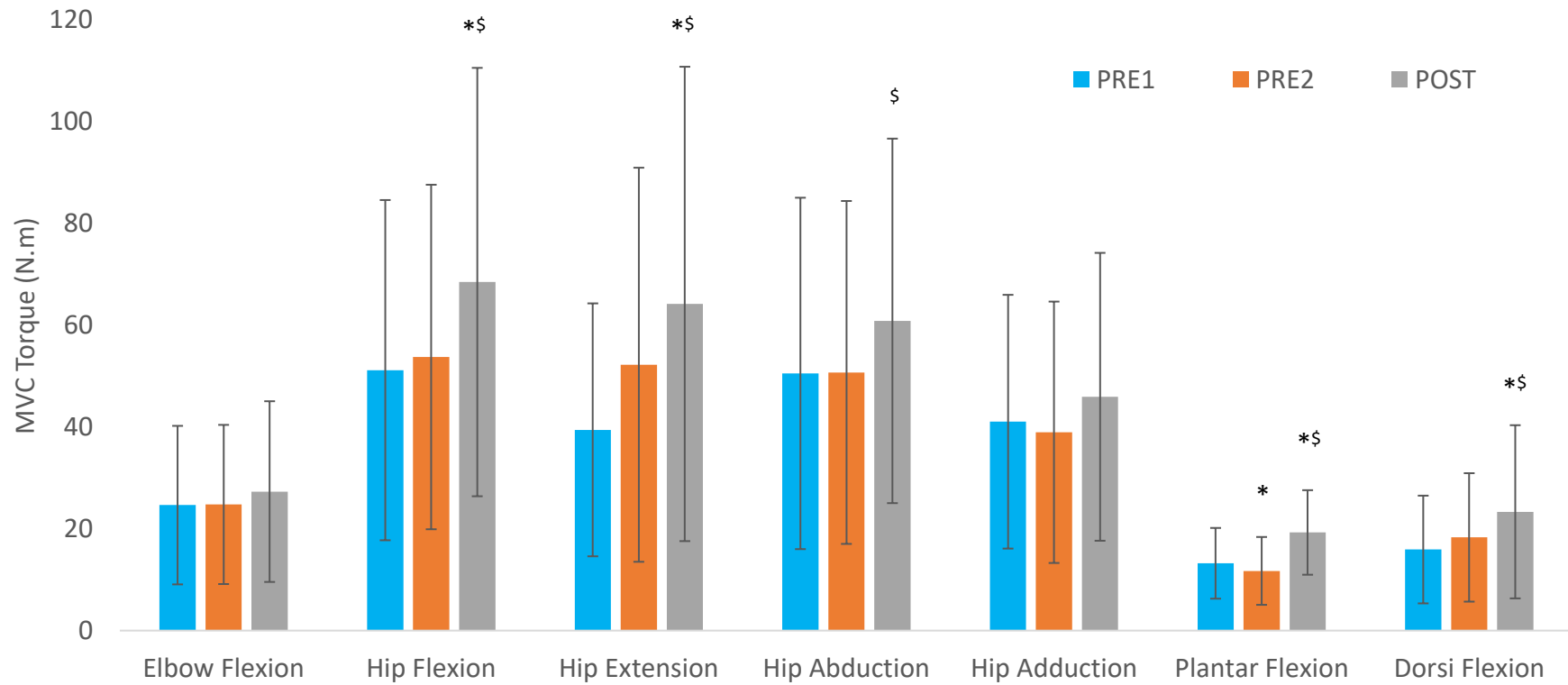


Figure 3.13: MVC torque during seven strength tests at PRE1, PRE2 and POST the RT programme. Bars represent means and error bars represent the standard deviation. * represents a significant difference to PRE1 and [§] represents a significant difference to PRE2.

3.3.2.4 Six-minute Walk Distance

There was an overall main effect of time on six-minute walk distance ($p \leq .01$, $\eta^2 = .38$; Figure 3.14), with an observed power of .88. Post hoc tests showed no difference in walk distance between PRE1 and PRE2 ($p > .05$), a 9.3% increase from PRE1 to POST ($p = .016$) and a 4.0% increase from PRE2 to POST ($p = .028$).

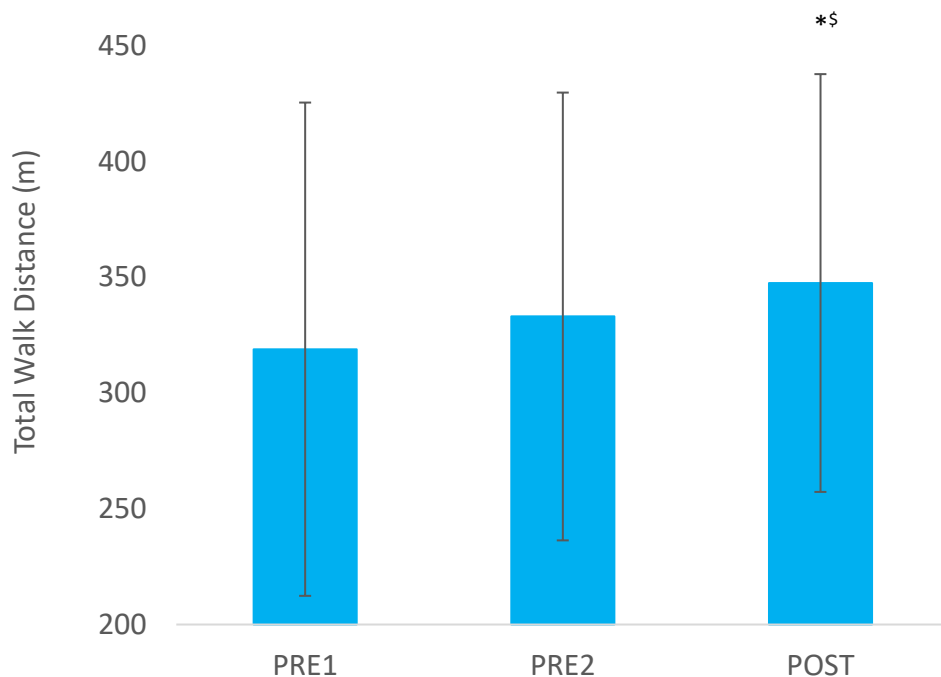


Figure 3.14: Six-minute walk distance at PRE1, PRE2 and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and [§] represents a significant difference from PRE2.

3.3.2.5 Functional Tests

Time to complete each functional test between PRE1, PRE2 and POST the RT programme are presented in Table 3.7 and described below.

There was an overall main effect of time on balance time ($p \leq .01$). Post hoc tests showed that balance time was increased by 4.2% between PRE1 and PRE2 ($p = .031$)

and by 29.1% between PRE1 and POST ($p = .016$). In addition, balance time was increased by 24% between PRE2 and POST ($p = .016$). There were no differences between PRE1 or PRE2 and Mid-Train or between Mid-Train and POST ($p > .05$).

There was an overall main effect of time on sit to stand time ($p < .001$, $\eta^2 = .35$), with an observed power of .96. Post hoc tests showed that sit to stand time did not differ between PRE1 and PRE2 or between PRE1 and Mid-Train ($p > .05$) but was 30.1% quicker at POST compared to PRE1 ($p \leq .001$). In addition, sit to stand time did not differ between PRE2 and Mid-Train ($p > .05$) but was 35.9% quicker at POST than PRE2 ($p \leq .01$) and did not differ between Mid-Train and POST ($p > .05$).

There was an overall main effect of time on stair ascend time ($p < .05$, $\eta^2 = .22$), with an observed power of .60. Post hoc tests showed that stair ascend time did not differ between PRE1 and PRE2 or between PRE1 and Mid-Train ($p > .05$), but that it was 20.1% quicker at POST than PRE1 ($p \leq .05$). In addition, stair ascend time did not differ between PRE2 and Mid-Train ($p > .05$) but was 18.1% quicker at PRE2 than POST ($p = .035$), with no difference between Mid-Train and POST ($p > .05$).

There was an overall main effect of time on stair descend time ($p \leq .001$). Post hoc tests showed that stair descend time increased by 9.8% between PRE1 and PRE2 ($p = .012$), did not differ between PRE1 and Mid-Train ($p > .05$) but was reduced by 15.7% between PRE1 and POST ($p \leq .01$). In addition, stair descend time was reduced by 16.1% between PRE2 and Mid-Train ($p \leq .01$), by 23.2% between PRE2 and POST ($p \leq .001$) and by 8.5% from Mid-Train to POST ($p \leq .01$).

Table 3.7: Mean \pm standard deviation of time to complete functional tests at PRE1, PRE2 and POST the RT programme. * represents a significant difference from PRE1, § represents a significant difference from PRE2 and # represents a significant difference

	Balance (s)	Sit-Stand (s)	Stair Ascend (s)	Stair Descend (s)
PRE1	19.1 \pm 13.5	3.6 \pm 1.6	7.4 \pm 3.3	5.1 \pm 2.0
PRE2	19.9 \pm 12.9*	3.9 \pm 2.0	7.2 \pm 3.4	5.6 \pm 2.3*
Mid-Train	23.9 \pm 10.5	3.3 \pm 2.1	6.6 \pm 3.1	4.7 \pm 1.5 §
POST	24.7 \pm 10.6* §	2.5 \pm 1.4* §	5.9 \pm 2.5* §	4.3 \pm 1.5* § #

3.4 Discussion

3.4.1 Part A – MD versus Controls

Part A of this study aimed to quantify the MVC torque of 8 lower-limb muscle groups and the physical function, via a 6-minute walk test, of adults with FSHD, BMD and LGMD, compared to an age-matched control group. Overall, significant muscle weakness was identified in a variety of muscle groups, along with reduced physical function across all 3 types of MD, compared to the control group.

There are few previous quantitative measures of MVC torque in FSHD, BMD and LGMD, compared to non-dystrophic control groups. This study is novel in the assessment of MVC torque in four previously unquantified lower-limb muscle groups in these populations; the hip flexors, hip extensors, hip abductors and hip adductors. Interestingly, significant muscle weakness was established in the majority of muscles for all MD groups compared to the control group, except for the hip abductors which were spared in the FSHD group and the plantar flexors, which did not differ between the BMD and the control group. These findings concur with previous research showing significant muscle weakness in the knee extensors of individuals with FSHD (Jacques et al., 2018; Marra et al., 2018; Skalsky et al., 2008; Bachasson et al., 2014), BMD (Jacques et al., 2018) and LGMD (Jacques et al., 2018), in the knee flexors of individuals with FSHD (Skalsky et al., 2008), in the dorsi flexors of individuals with LGMD (Lokken et al., 2016) and BMD (Lokken et al., 2016), and in the plantar flexors of individuals with LGMD (Jacques et al., 2018; Lokken et al., 2016) and FSHD (Jacques et al., 2018). However, the current study findings disagree with those of two previous studies that have shown significant weakness in the

plantar flexor muscles of 52% (Lokken et al., 2016) and 51% (Jacques et al., 2018), in adults with BMD compared to age-matched control groups. It is possible that the reason for this discrepancy is due to differences in condition severity, as 44% of BMD participants were non-ambulatory in the latter study (Jacques et al., 2018) whereas all participants were ambulant in the current study. However, this is not the case for the former study (Lokken et al., 2016), as all participants were also ambulatory and younger than in the present study.

Of the muscle groups measured in the previous literature (knee flexors, knee extensors, plantar flexors and dorsi flexors), there is fairly little agreement between the current study and previous ones regarding relative severity of muscle weakness. The likely reasons for these differences in weakness severity may be attributed to the heterogeneity of the conditions, differences in measurement technique, differences in joint angle, differences in participant ages, participant sex differences and/or differences in the matching of control groups to experimental groups, but each muscle group will be discussed individually.

Knee flexion MVC torque was 47% weaker in the FSHD group, 72% weaker in the BMD group and 75% weaker in the LGMD group, compared to the control group within the current study. This is the first study to quantify knee flexion MVC torque in adults with BMD and LGMD, but one study has previously measured knee flexion MVC torque in adults and children with FSHD (Skalsky et al., 2008), reporting a 56% reduction compared to a sex, height and mass-matched control group. The small difference in weakness severity between the current study and Skalsky et al. (2008) is likely due to the heterogeneity of FSHD, participant ages (adults only were

included within the present study) or differences in knee joint angle (tested at 45° knee flexion previously, versus 70° knee flexion in the present study).

This study established that knee extension MVC torque was 40% weaker in the FSHD, 79% weaker in the LGMD and 89% weaker in the BMD group, compared to the control group. These strength deficits are higher than those reported previously for BMD and LGMD (Jacques et al., 2018) of 41% and 43%, respectively, compared to controls. The almost two-fold increase in knee extension weakness severity in the LGMD and BMD group compared to Jacques et al. (2018) could be due to the heterogenous nature of these conditions, or sex differences in the LGMD groups (both male and female in the current study versus an all-male population). In FSHD, the 40% lower MVC torque from the current study sits centrally within deficit values previously reported for this population of 25% (Jacques et al., 2018), 42% (Skalsky et al., 2008), 45% (Bachasson et al., 2014) and 66% (Marra et al., 2018). The more severe weakness of 66% (Marra et al., 2018) is likely a result of the 20.5-year age difference between the control group and the experimental group within that study. At the other end of the scale, the less severe knee extensor weakness of 25% reported in Jacques et al. (2018) likely differs to the current study due to sex differences (a mixed sex population was utilised in the current study compared to an all-male population). population).

Dorsi flexion MVC torque was 67% lower in the FSHD group, 66% lower in the BMD and 75% lower in the LGMD group, compared to the control group within this study. Dorsi flexion MVC torque has not previously been reported in FSHD but was shown to be reduced by 41% in BMD (Lokken et al., 2016) and 39% in LGMD (Lokken et al.,

2016). The severity of dorsi flexion weakness in the current study is much higher than previously reported by Lokken et al. (2016). This could be attributed to differences in measurement technique and joint angles, as an isokinetic dynamometer was used with a knee flexion angle of 140°, compared to a strain-gauge and an extended knee angle of 0° within the current study.

Plantar flexion MVC torque did not differ between the BMD and control group but was reduced by 61% in the FSHD and 70% in the LGMD group. These reductions in strength are almost double the severity of those reported previously in FSHD of 35% (Jacques et al., 2018), and in LGMD of 38% (Lokken et al., 2016) and 58% (Jacques et al., 2018). The disparity in findings regarding plantar flexion strength in BMD were discussed earlier. The greater severity of plantar-flexor muscle weakness for LGMD and FSHD in the current study compared to previous data could be attributed to heterogeneity within the conditions, participant sex differences compared to Jacques et al. (2018) and differences in measurement technique with Lokken et al. (2016) (isokinetic dynamometer with 140° knee flexion versus a strain-gauge with 90° knee flexion).

An important consideration of this study is the comparison of quantitative data to the pre-existing clinical classifications of weakness distribution in FSHD, BMD and LGMD (Emery, 2002; Mercuri and Muntoni, 2013). Using the MVC torque data relative to the MVC torque in the age-matched control group, it is possible to establish which muscle groups exhibited the most pronounced weakness within each MD group. This was visually presented in Figure 3.9. Accordingly, in the FSHD group, the distal dorsi flexor and plantar flexor muscle groups, followed by the

proximal hip flexor and hip adductor muscle groups experienced the highest relative weakness severity. This agrees somewhat with the clinical classifications of weakness distribution in FSHD, although the current data provide detail regarding important proximal muscle weakness in this population. In the BMD group, the proximal knee extensor, hip extensor, hip flexor and knee flexor muscle groups demonstrated the most pronounced weakness severity, respectively. This echoes the pre-existing clinical classifications of descending weakness distribution from proximal to distal regions in BMD (Emery, 2002). However, this was closely followed by a severe weakness in the dorsi flexor muscle group which was 65% lower than the control group strength. Finally, in the LGMD group, the hip abductor, hip extensor, knee extensor and hip adductor muscle groups presented the most pronounced weaknesses. This was closely followed by a severe weakness in the dorsi flexor muscle group of 25% of the control group strength. Again, this finding parallels the clinical classification of predominantly proximal muscle weakness in this MD population, but it provides a more detailed insight into which proximal muscles are most affected.

Previous studies quantifying MVC torque in MD have demonstrated discrepancies with the clinical descriptions of weakness in MD, such as a more severe distal muscle weakness than proximal muscle weakness in both LGMD and BMD (Jacques et al., 2018). The current study does not replicate those findings. Although it is extremely important to note that whilst certain muscle groups did not exhibit the highest strength deficits, they were often almost as weak as the weakest muscles. For example, the plantar flexors were not one of the four weakest muscle groups in the LGMD group, but their strength was still significantly reduced by 75% compared to

the control group. Therefore, it is important that the pre-existing clinical classifications of weakness distribution are taken as areas of principal muscle weakness only. The additional information provided by the measures of MVC torque during hip flexion, hip extension, hip abduction and hip adduction provide additional detail to the pre-existing descriptions of weakness distribution in FSHD, BMD and LGMD. In particular, it is clear that the hip abductors and hip extensors are the most limited of the proximal muscle groups in the LGMD population.

Concerning physical function, the distance walked during the 6-minute walk test was significantly reduced in all MD groups compared to the control group, by 22% in the FSHD group, by 35% in the BMD group and by 43% in the LGMD group. Hence, the LGMD group were the most limited of the MDs with regards to physical function, which is unsurprising given that they were the weakest of all 3 MD groups in 5 of the 8 lower-limb muscle groups measured, and the second weakest in the remaining 3 lower-limb muscle groups.

Part A of this chapter quantified muscle strength in 8 lower limb muscle groups and 6-minute walk distance across three MD groups. The data contribute to the currently under-reported, but clinically described, physiological and functional understanding of FSHD, BMD and LGMD, and provide support for the pre-existing clinical classifications of weakness distribution in these populations.

3.4.2 Part B – Effects of RT

Part B of this study demonstrated that a 12-week, twice a week, programme of RT was both feasible and beneficial in ambulatory adults with FSHD, BMD and LGMD. The average adherence rate of 96% is more than satisfactory. The single adverse

event that occurred throughout the study caused no lasting injury and the two cases of participant drop out were both due to circumstances external to the RT programme. Overall, positive changes in both muscle strength and physical function as a result of the RT programme were evident.

In our study, knee flexion MVC torque increased by 12.6% from immediately before to post completion of the RT programme, with stable values during the initial 12-week control period. However, no change in knee extension MVC torque was evident, although the direction of change was positive it did not reach significance. The latter finding is in contrast to Sveen et al. (2013), who reported an approximate 35% increase in knee extension strength with RT in adults with BMD and LGMD. However, muscle strength was quantified via 1-repetition maximum strength compared to isometric MVC torque in the current study and the RT programme lasted for 24-weeks compared to 12-weeks within the current study. Of particular note is the large standard deviation in the knee extension MVC torque in the present study, due to the heterogeneity of these MD conditions. This likely contributed towards the lack of a significant difference found in this variable. In addition, there was a potential ceiling effect with this muscle group for some individuals who had greater strength before the training programme. As seen in part A of this study, the knee extension MVC torque was higher within the FSHD group than the BMD and LGMD group. Hence, the inclusion of FSHD in the current study compared to only BMD and LGMD in Sveen et al. (2013) may have constrained the overall change in knee extension MVC torque through a ceiling effect.

MVC torque was increased by variable amounts in all other muscle groups, except for the hip adductors and elbow flexors (ranging from 27% in the hip flexors, 20% in the hip abductors, 28% in the dorsi flexors, 65% in the plantar flexors and 23% in the hip extensors), with stable values in the control period for each muscle group. The only study to have previously assessed the effect of a RT programme on any of these muscle groups in either FSHD, BMD or LGMD was Van der Kooi et al. (2004), who examined the effect of 52-weeks of RT on dorsi flexor muscle strength in adults with FSHD, but reported no change to dorsi flexion MVC torque post RT. However, it is important to note that the RT programme was unsupervised and the frequency of the RT programme was three times per week, compared to two supervised training sessions per week in current study. It is possible that the lack of supervision hindered the RT or that the higher frequency was excessive in the MD population.

It is unsurprising that the elbow flexor MVC torque was unchanged in the current study, as this muscle was not trained as part of the RT programme. However, it is unclear why the hip adductor muscle group was unchanged post completion of the RT programme. It is possible that this muscle group is resistant to the effects of RT in at least one or all of the types of MD studied, although this seems unlikely given the response to RT across the other muscle groups. Alternatively, it may be due to the difficulty that was experienced by the investigators in training this muscle group, both in a gravity neutral position and through its full range of movement. In other words, if participants were either too unstable or weak to train this muscle group in a single leg stance position (by adducting their leg across the front of their body), the exercise was completed whilst laying supine. The first exercise option in this lying position was often intolerable for participants as it required them to first lift

their leg higher than their body by flexing at the hip joint for the entirety of the exercise, which was often not possible. The alternative exercise involved squeezing a ball of progressive rigidities between the knees whilst lying supine, although this was possible it was limited in the range of movement it required. This limitation did not apply to any other muscle group.

Functionally, the RT programme within this study was extremely positive in this population of adults with FSHD, BMD and LGMD. The distance walked during the 6-minute walk test remained stable between PRE1 and PRE2, with a 4% increase from immediately before to after completion of the RT programme. This improvement in walking capacity is fairly small relative to the increases in muscle strength presented, but never the less, such an increase demonstrates an improved walking capacity. In the additional functional tests, much larger improvements were found between the PRE2 time point and completion of the RT programme, ranging from 24% increase in balance time, a 36% reduction in sit to stand time, an 18% reduction in the time taken to climb stairs and a 23% reduction in the time taken to descend stairs. Hence, the increase in muscle strength in these individuals was successfully translated into improvements in physical function. With this in mind, it is highly possible that the benefits of RT may spread further than muscle strength and functional ability in these populations. Walking speed over the 6-minute walk test was improved, which suggests that the more detailed parameters of gait may also be influenced by RT in this population. Future research should seek to quantify the gait alterations that may occur with RT in MD.

Overall, the RT programme positively influenced the muscle strength and physical function of this MD group. Almost all variables of muscle strength and physical function were improved, and importantly, the few that were not improved remained unchanged. This is important to consider as maintenance of muscle strength or function in this progressive condition is a positive outcome in itself. These findings dispute the historical perspective that RT should be avoided in individuals with MD. The clinical implications of this research are that ambulatory adults with these forms of MD can safely undertake RT programmes similar to the one described in this study, and effectively improve lower-limb muscle strength and physical function as a result.

This study has a noteworthy limitation; although the three types of MD examined in this study are functionally similar, the combination of the different types of MD may have concealed differences in the response to RT between the conditions. Future investigations with a larger sample size would benefit from examining whether the individual forms of MD differ in their responses to RT. In addition, future research should examine the influence of RT programme frequency and intensity in these populations. It would be advantageous to determine if a higher or lower frequency and intensity of RT are also beneficial in these populations. This study showed that a RT programme can feasibly be undertaken in adults with FSHD, BMD and LGMD, but an important question remains regarding how much RT is too much in these conditions. In order to provide detailed advice to patients with these forms of MD regarding the appropriate frequency and intensity of RT, future research should seek to examine these factors in more detail.

In conclusion, this study provides quantitative data on the strength of eight lower-limb muscle groups in ambulatory adults with FSHD, BMD and LGMD. A comprehensive comparison between the current data and the pre-existing clinical classifications of weakness distribution in MD highlights agreement between the two. This is the first study to demonstrate the feasibility and beneficial effects of a programme of RT compared to a control period, across a wide range of lower-limb muscles and functional tests in ambulatory adults with FSHD, BMD and LGMD. Despite previous medical concerns, these findings provide support for RT in these forms of MD and highlight that RT is a viable option within the management and treatment programmes of adults with these MDs. RT is an innovative approach to maintaining or improving muscle strength and physical independence in adults with these forms of MD.

Chapter 4

**Influence of resistance training on the
kinematics of gait in adults with
Facioscapulohumeral, Limb-girdle and
Becker muscular dystrophy**

4.1 Introduction

Muscular dystrophy (MD) is a group of over thirty neuromuscular conditions caused by a variety of genetic mutations (Huml, 2015). Each genetic mutation ultimately results in an altered expression of proteins that are typically located within muscle cells, which leads to progressive weakening and deterioration of the muscles (Mercuri and Muntoni, 2013). Subsequently, individuals with MD experience increasing levels of disability and reduced physical function (Huml, 2015).

Duchenne MD is the most severe form of MD characterised by early childhood onset, rapid progression, loss of ambulation in childhood and premature death (Bushby et al., 2010). Other types of MD vary between childhood and adult onset, progress more slowly and typically the ability to walk is not compromised at least until adulthood (Emery, 2002; Mercuri and Muntoni, 2013). Three common types of MD that fit the latter description are Facioscapulohumeral MD (FSHD), Limb-girdle MD (LGMD) and Becker MD (BMD), which are described clinically to remain ambulant until at least the second decade of life (Huml, 2015), although precise measures of age at loss of ambulation are not available.

4.1.1 Part A

In Chapter 3 of this thesis, varying severities of lower-limb muscle weakness in adults with FSHD, BMD and LGMD were reported, in conjunction with a lower physical function through slower self-selected walking speed compared to a matched control group. Accordingly, these findings indicate that lower-limb muscle weakness likely influences gait in MD. Clinically it is well recognised that functional tasks, such as a person's ability to walk, are diminished in adults with FSHD, BMD

and LGMD (Emery, 2002; Huml, 2015) and quantitative descriptions of gait consistently report slower self-selected walking speeds and reduced stride lengths in FSHD (Aprile et al., 2012; Iosa et al., 2007; Iosa et al., 2010; Rijken, van Engelen, de Rooy, et al., 2015; Rijken, van Engelen, Geurts, et al., 2015) compared to control participants or normative reference data. In addition, some of those studies also reported an increased stance duration (Iosa et al., 2007) and reduced cadence (Iosa et al., 2010) in FSHD compared to control groups. Although clinical knowledge of impaired gait in FSHD, BMD and LGMD exists, no spatial-temporal analysis of gait in humans with BMD and LGMD exists. In addition, very few quantitative studies of the lower-limb joint kinematics during gait have been conducted in BMD, LGMD or FSHD, with the majority of kinematic analysis occurring in adults with Myotonic MD or children with Duchenne MD.

Three studies have described gait and lower-limb joint kinematics in adults with Myotonic MD and four for children with Duchenne MD. Numerous sagittal plane kinematic abnormalities have been reported in both of these MDs, including excessive anterior pelvic tilt (Galli et al., 2012; Doglio et al., 2011; D'Angelo et al., 2009), inadequate hip extension in stance (Galli et al., 2012; Gaudreault et al., 2010; Sutherland et al., 1981), a lack of knee flexion or hyper-extension in stance (Galli et al., 2012; D'Angelo et al., 2009) and additional knee flexion in the swing phase (Galli et al., 2012; D'Angelo et al., 2009; Doglio et al., 2011). In addition, limited plantar flexion in the stance phase (Galli et al., 2012) was also reported in adults with Myotonic MD. In children with Duchenne MD, excessive hip flexion in the swing phase (D'Angelo et al., 2009; Gaudreault et al., 2010; Sutherland et al., 1981) and reduced dorsiflexion at initial contact have also been found (D'Angelo et al., 2009;

Doglio et al., 2011). In the frontal and transverse plane, excessive external pelvic rotation, increased pelvic obliquity and early abduction of the hip joint during the stance phase of gait have been reported in children with Duchenne MD (Doglio et al., 2011). These kinematic abnormalities however cannot be directly applied to ambulatory adults with FSHD, BMD and LGMD. This is because Myotonic MD differs widely from the other eight types of MD as nearly all systems in the body are affected, and Duchenne MD has a severe childhood onset that renders children wheelchair bound by adolescence (Emery, 2002). Furthermore, the differences in lower-limb weakness distribution between the MDs presented in Chapter 3 of this thesis likely predispose adults with FSHD, BMD and LGMD to employ different compensatory mechanisms during ambulation.

One study has measured lower-limb joint kinematics during gait in adults with FSHD (Iosa et al., 2007). To date there appear to be no published studies that have measured the kinematics of gait in humans with LGMD or BMD. Iosa et al. (2007) assessed sagittal plane joint kinematics during self-selected walking in the hip, knee and ankle joint of adults with FSHD. They found reduced ankle dorsi flexion at initial contact, insufficient knee flexion during the stance phase and reduced hip extension at toe-off, compared to non-dystrophic controls. In addition, dorsi flexion angle at initial contact and hip extension angle at toe-off were negatively associated with an MRI score of fat infiltration in the tibialis anterior and hip extensor muscles, respectively, indirectly alluding to a relationship between these gait abnormalities and muscle strength. A more complete description of joint kinematics, including the pelvis joint and variables within the frontal and/or transverse plane would provide a more detailed insight into FSHD gait.

The kinematic gait deviations previously presented in MD populations may have implications for physiological variables in MD, such as the metabolic cost of walking. Given the importance of maintaining physical independence in adults with MD, quantifying the metabolic cost of walking is of particular importance. However, this is yet to be done in FSHD, BMD or LGMD.

The first aim of this study is to describe the spatial-temporal variables, the lower-body angular kinematics and the metabolic cost of gait in adults with FSHD, LGMD and BMD, compared to a matched control group.

4.1.2 Part B

Alongside descriptions of gait in adults with FSHD, BMD and LGMD, of particular interest to this study is the suitability of resistance training (RT) as an intervention for kinematic abnormalities in these populations. RT is a form of exercise that has previously been shown to alter spatial-temporal variables of gait and joint kinematics in a range of clinical populations that commonly exhibit gait abnormalities. In individuals with multiple sclerosis, RT resulted in increased walking speeds and step lengths, along with reductions in double support time (Manca et al., 2017; Kierkegaard et al., 2016; Gutierrez et al., 2005). In children with cerebral palsy, programmes of RT have increased stride length and reduced cadence (Eek et al., 2008), along with reducing the severity of crouch gait (knee flexion angle) during the stance phase (Engsberg et al., 2006). Furthermore, Cao et al. (2007) reported an increase in total ankle range of motion during gait, plantar flexion angle at toe-off and maximum dorsi flexion angle in the swing phase following an exercise programme that included RT in elderly women. Alongside these experimental

studies, positive associations between lower-limb muscle strength and walking speed have been demonstrated in older adults (Buchner et al., 1996), a population that also experiences muscle weakness, and adults with Myotonic MD (Lindeman et al., 1998). We have presented evidence in Chapter 4 that RT increases lower-limb muscle strength in adults with FSHD, BMD and LGMD and therefore, RT may also influence gait and joint kinematics in these individuals.

The influence of RT is relatively un-reported in MD due to historical concerns that it should be avoided in adults living with MD. These concerns were based on indirect evidence that RT was detrimental to dystrophic muscle cells (Ansved, 2001; Petrof, 1998). To the contrary, Sveen et al. (2013) presented the first evidence of a beneficial effect of RT in MD; a 35% increase in knee extensor muscle strength post 24-weeks' RT in adults with BMD and LGMD. Furthermore, Chapter 3 of this thesis presents increased maximum voluntary contraction (MVC) torque in six lower-limb muscle groups post 12-weeks' RT in adults with FSHD, BMD and LGMD. In addition to these strength gains, RT may also influence gait in individuals with MD but only one study has previously investigated this notion.

Missaoui et al. (2010) investigated the effect of 6-weeks' rehabilitation training on adults with Myotonic MD. The program consisted of stretching and balance exercises, resistance exercises and aerobic treadmill training. Knee extension and knee flexion MVC torque increased by 18% and 32%, respectively, together with improvements in the functional reach test, timed up and go test, and a 6% increase in fast walking speed. Unfortunately, the more detailed parameters of gait, such as the spatial-temporal parameters of the gait cycle, joint angular displacements and

oxygen cost were not measured. Hence it remains unknown if a programme of lower-body RT influences key gait parameters in adults with MD.

The second aim of this study is to investigate the influence of a 12-week, twice a week, lower-body RT programme on spatial-temporal parameters, joint kinematics and the metabolic cost of gait in a group of ambulatory adults with MD (FSHD, BMD and LGMD).

4.2 Method

4.2.1 Participants & Study Design

The experimental design for this study is presented in two parts. Part A presents group comparisons between adults with FSHD (9), BMD (7), LGMD (6) and a group of 10 control adults matched in age, stature and body mass.

Part B is a within-participant design, involving a group of 17 adults with MD, inclusive of FSHD (6), BMD (5) and LGMD (6). Data were collected at three time points: PRE1 (before a 12-week control period), PRE2 (immediately after the 12-week control period) and POST (immediately after a 12-week RT programme). All 17 MD participants completed a 12-week, twice a week, RT programme.

Detailed descriptions of the study design, participants and RT programme are provided *in Chapter 3.2 Method*.

Manchester Metropolitan University Ethics Committee granted ethical approval and all participants provided written informed consent after which data collection took place at Manchester Metropolitan University on all occasions.

4.2.2 Procedures

Testing procedures and data collection for anthropometric and body composition measures are provided in *Chapter 3.2 Method*.

4.2.2.1 Gait Analysis

4.2.2.1.1 Equipment

A Vicon motion capture system (Oxford Metrics Ltd., Oxford, UK) was used to collect data during gait. The system consisted of 14 infrared Vicon cameras (MX-T Series) and two Bonita video cameras, with two floor mounted AMTI force platforms (AMTI, Watertown, MA, USA), a Dell computer (Precision T1650) and Vicon Nexus software (Version 1.7) to capture and process data (Figure 4.1).

The 14 infrared cameras were positioned on a metal frame around the edge of the capture volume, at a height of ~2.4 m above the ground. The Bonita video cameras were mounted on tripods within the capture volume, which measured ~ 170 m³ (length x width x height: 10 x 7 x 2.4 m). One video camera was positioned perpendicular to the walking direction and the second was positioned parallel to the walking direction, offering a sagittal and coronal view of the participants. The Vicon and Bonita cameras were connected via Ethernet cables to one of two Vicon connectivity units (MX-Giganet), which contained a 64-channel analogue-digital converter. The primary connectivity unit was connected via Ethernet cable to a Dell computer (Precision T1650) that used Vicon Nexus software to obtain kinematic and video data at 100 Hz. The secondary connectivity unit was connected to the primary unit via an MX Giganet cable, to carry synchronisation signals to the secondary unit.

The two AMTI force platforms were located side by side in the centre of the capture volume. Each platform measured 46.7 x 51.0 cm and was mounted flush to the laboratory floor. Each force platform was connected via a 26-pin connector cable to an amplifier, which was connected via the amplifier output cable to a Vicon connectivity unit (MX-Giganet). All force data were sampled at 1000 Hz through a 64-

channel analogue-digital converter, which was connected to a Dell computer (Precision T1650) that used Vicon Nexus software to obtain kinetic data.

Muscle activity of four muscles in the dominant limb: tibialis anterior (TA), medial gastrocnemius (GM), vastus lateralis (VL) and bicep femoris (BF) was measured. Data were captured using wireless surface electrodes (Trigno™ Wireless System, Delsys, Inc, Boston, USA). The electrodes measured 27.6 x 24.1 x 12.7 mm and consisted of a four-bar formation with a 10 mm distance between the bars. Raw signals were detected via a Bluetooth receiver in the Delsys unit and collected by Delsys EMGworks® Acquisition software on a HP computer (ProBook 4320), at a sampling frequency of 1000 Hz.

Force data were collected simultaneously with motion data using Vicon Nexus software. To enable time synchronisation of data collection between the motion capture and EMG data acquisition systems, a Delsys Trigger Module (SP-U02) was used. This acted as an independent push button device that was connected to the Vicon connectivity unit and the Delsys unit, to start both EMGworks acquisition and Vicon Nexus simultaneously.

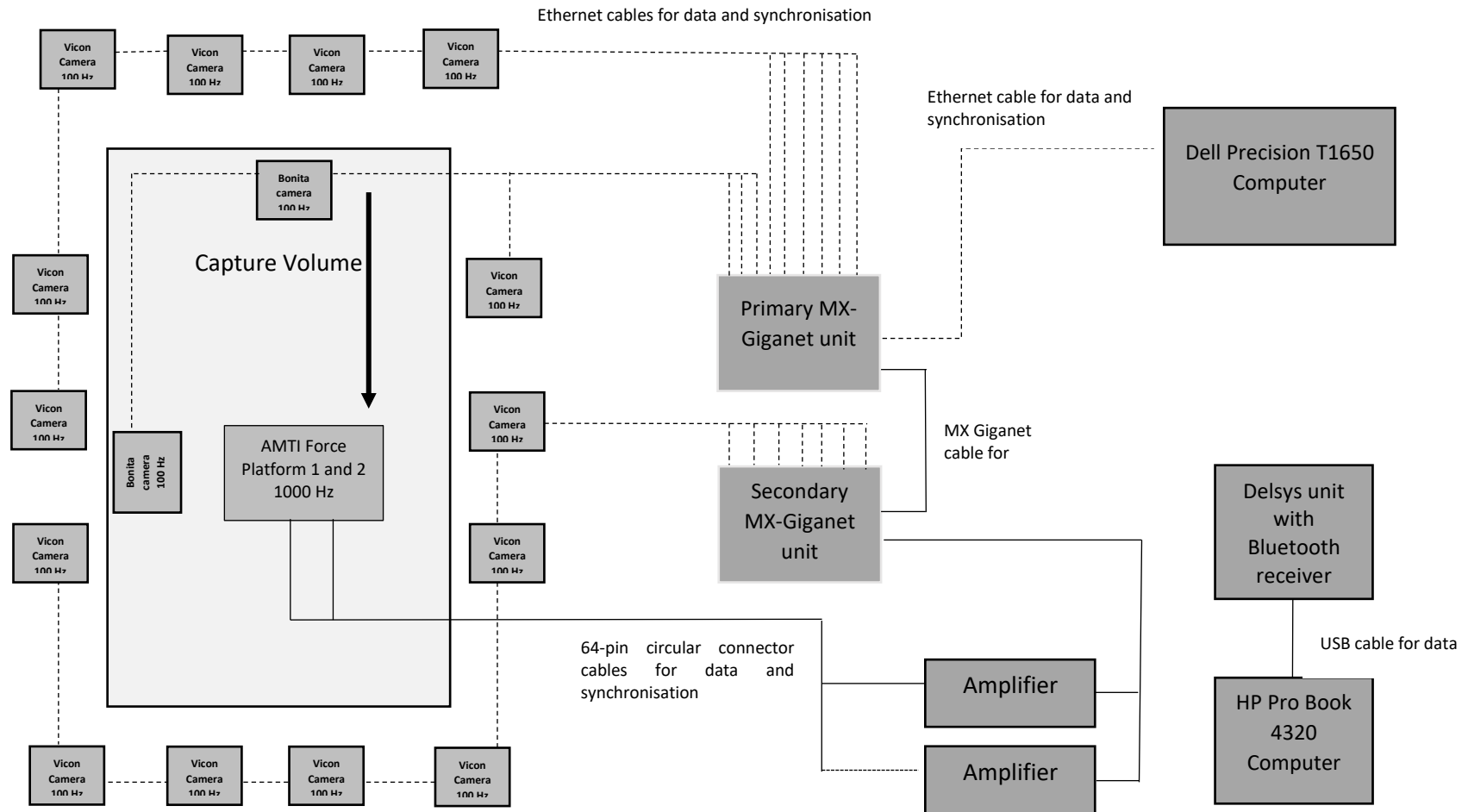


Figure 4.1: Schematic showing the Vicon, AMTI force platforms and Delsys equipment set-up in the gait laboratory.

4.2.2.1.2 System Calibration

Before the collection of data, the Vicon system was calibrated and a residual of equal to or less than .2 mm for each camera was accepted. An L frame Vicon active wand with five LEDs was used according to the manufacturer's guidelines. Firstly, a dynamic calibration was undertaken, in which the investigator waved the L frame within the estimated capture volume in a variety of positions and orientations, until each camera had viewed a variety of wand positions. Next, the origin of the global coordinate system was defined. The L frame was placed flat in the top corner of the right AMTI force plate, to define the laboratory origin. The lab coordinate system was defined as Y-axis: anterior-posterior, X-axis: medial-lateral and Z-axis: superior-inferior. Force platform signals were zeroed using the automatic zero function in Vicon Nexus.

4.2.2.1.3 Marker and Electrode Placement

Vicon infrared camera lenses contain a set of diodes that emit light; this light is reflected back by retro-reflective markers on the participant's body to track their motion. Thirty-nine markers were positioned on specific landmarks on the participant's body, according to the standard Vicon plug in gait model marker set (Vicon, 2010), which is demonstrated in *Appendix 2.1*. The plug in gait model is the Vicon's variation of the conventional gait model, which was designed by Davis et al. (1991) and describes the calculations that are used to define each body segment and subsequently to define each joint centre location. Mainly, the markers were secured to the participant's skin, to avoid movement artefacts from moveable clothing. A single investigator located markers by palpating the skin to identify specific bony landmarks.

An example of one participant with all 39 markers located on the body is presented in Figure 4.2

Upper body markers were placed whilst participants were seated to avoid fatigue in participants with limited mobility. Markers were secured onto a headband so that they were positioned over the left and right temple at the front of the head and on the left and right side of the back of the head. Markers were also placed on the spinous process of the 7th cervical and the 10th thoracic vertebra, on the jugular notch where the clavicles meet the sternum, on the xiphoid process of the sternum and anywhere on the right scapula. Bilateral upper body markers were positioned on the acromioclavicular joints, on the upper lateral third of the arms, on the lateral epicondyle of the elbows, on the lower lateral third of the forearms, on either side of the wrist at the xiphoid process of the radius and ulna and on the hands proximal to the middle knuckle.

Lower body markers were placed whilst participants were stood, holding onto a walking aid or support where required. Markers were placed bilaterally over anterior superior iliac spines, posterior superior iliac spines, lateral distal third of the thigh (in line with the hip and knee joint centres), on the lateral epicondyle of the femur, lateral distal third of the shank (in line with the ankle and knee joint centres), lateral malleolus, and at the point of the calcaneus and head of the second metatarsal on the participant's shoe. Due to MD participants reporting feelings of reduced stability and walking confidence when walking barefoot, gait analysis was completed shod. Participants were instructed to wear comfortable shoes that they would typically wear to walk outside of their home. Of note is that the sole of most footwear typically

introduces a vertical difference between the toe and the heel marker, despite participants achieving a flat foot with respect to the footwear. Thus, a measure of sole delta was recorded (described in Chapter 3.2 *Anthropometry*) and the height of the heel marker in comparison to the toe marker was adjusted accordingly within the Vicon Nexus software.



Figure 4.2: Example of marker placement on participants from an anterior (left) and posterior (right) view.

EMG sensors were attached onto the skin at the belly of each muscle, according to the SENIAM guidelines (Hermens et al., 2000). Before application, the surrounding skin was shaved and cleaned with an alcohol wipe to ensure optimal electrical conductance. For the TA muscle, the sensor was placed at one third of the distance between the tip of the fibula and the tip of the medial malleolus and it was orientated in the direction of this line. For the GM muscle, the sensor was positioned on the most protruding part of the muscle, in the direction of the limb. For the VL muscle, the sensor was placed at two thirds of the distance between the anterior spina iliaca

superior to the lateral side of the patella and it was orientated in the direction of the muscle fibres. For the BF, the sensor was placed mid-way between the ischial tuberosity and the lateral epicondyle of the tibia and it was orientated along this line.

4.2.2.1.4 Protocol

Throughout the gait analysis assessment, participants wore their own shoes and minimal non-reflective clothing, inclusive of shorts for men and shorts and a sports bra or tight fitted vest top for women. In instances where a top was worn, it was rolled up so that markers could be attached directly onto the skin. The instructions given to participants regarding their shoes was that they should be comfortable to walk in and reflect typical shoes that they wear regularly, for example shoes that would be worn to go shopping. Shoes were deemed appropriate if they were non-slip, suitable to be worn outside and flat without a significant sole wedge (for example trainers). Trials were completed with or without personal walking aids (if applicable; crutch or walking stick), dependant on whether these were typically used to walk short distances (e.g. to walk around their home).

Initially, a static calibration was completed. Participants stood with one foot on each force platform within the capture volume, facing forward with their arms raised away from their body. Static marker data were collected and together with anatomical measurements were utilised to define each body segment and establish the location of each joint centre, relative to the coordinate system. Details of the calculations used to estimate lower body joint centre locations are described by Davis et al. (1991).

Participants completed a minimum of five practise trials. This enabled them to become familiar with their surroundings and to establish a starting position that rendered a

clean foot strike on the force platform with their dominant leg. Subsequently, participants completed four successful walking trials. Participants were instructed to walk at their self-selected walking pace; for example, the speed that they would typically use to walk to the shop. They walked along a 10 m level walkway but starting position was modified to make sure that the foot strike on the force platform was clean. Participants were offered as much rest as they required between walking trials, particularly those with severely reduced mobility and functional ability.

4.2.2.2 Oxygen Consumption

Expired gases were collected during a six-minute walk test, which was conducted in the control group and a subgroup of MD participants who self-reported confidence in their ability to walk for 6 minutes. A portable breath by breath gas analyser (Metmax 3B, Cortex, Leipzig Germany) was used to collect VO_2 ($\text{mL}\cdot\text{min}^{-1}$), via indirect calorimetry. Before use, the system was calibrated to the manufacturer's guidelines, using known concentrations of gas. The system comprised of a fitted face mask with a gas sensor and turbine, a Polar Bluetooth heart rate monitor and a portable unit that was carried in a material harness around the participant's chest and back. The unit weighed ~ 1 kg and was secured with Velcro straps. Data were collected using MetaSoft Studio software on an HP computer that used a Bluetooth receiver.

An adapted version of the 6-minute walk test protocol set out by the American Thoracic Society (2002) was utilised. Participants were instructed to walk at a steady self-selected pace instead of as far as possible as specified in the protocol devised by the American Thoracic Society (2002). This was due to safety concerns in the current population and to ensure steady state was achieved. The test took place along a flat

straight corridor. Each end of the 25 m course was marked with tape on the ground. Participants were instructed to turn clockwise at each end and walk in a straight line. One investigator walked behind the participant keeping at least a 1.5 m distance to provide encouragement (in accordance with The American Thoracic Society guidelines), to assess fall risk and to place markers on the course at each minute for the calculation of minute-distance splits. Participants were instructed to use their walking aids during the test if they did so during 3D gait analysis.

Before the test, participants rested for 5 minutes in a seated position. To start the test, participants were readied at the start line and the timer was started once they began to walk. Participants were instructed to stop walking at six minutes and were subsequently seated until fully recovered. Expired gases were measured for the entirety of the rest period and the 6-minute walk test.

4.2.3 Data Processing and Analysis

Unless otherwise stated, data are presented as means and standard deviations for the control group, FSHD, BMD and LGMD group in part A, and means and standard deviations for the MD group at each time point (PRE1, PRE2 and POST) in part B.

4.2.3.1 Joint Kinematics

Processing of each walking trial was completed using Vicon Nexus software. The markers were reconstructed and then their trajectories labelled. Gait events (initial contact and toe-off) were determined via vertical ground reaction forces on the dominant side with force plate contact, using a force threshold of 20 N. On the non-dominant side or without force platform contact, gait events were determined manually via frame by frame visual inspection. For each trial, the stride that

occurred in the centre of the capture volume over the force platform was selected for analysis. Gaps (≤ 10 frames) in the marker trajectories were filled using a cubic spline interpolation. The dynamic plug-in gait model (Vicon, 2010) was then applied to each walking trial to calculate marker trajectories and joint kinematics. Data were smoothed using a low-pass 4th order Butterworth filter, with a cut off frequency of 6 Hz.

Spatial and temporal data and lower-limb angular displacements in the dominant leg were averaged across four trials and used for further analysis. Kinematic data for a full gait cycle were time normalised to 100 data points using a cubic spline interpolation method in Microsoft Excel, representing initial contact at 0% and the following foot contact on the same side at 100%.

The selection of discrete dependant variables was guided by Beneditti et al. (1998). Ensemble average graphs for angular displacement of the pelvis, hip, knee and ankle were produced in Microsoft Excel and are presented in the results section, along with the mean \pm standard deviation for each discrete variable. Statistical analysis was completed on all discrete variables. The spatial and temporal variables chosen for analysis are presented in Table 4.1 and the discrete kinematic variables chosen for analysis are presented in Table 4.2.

The root mean square difference in joint angle between each MD group and the control group and between the time points of PRE1 compared to PRE2 and PRE2 compared to POST were calculated at the pelvis, hip, knee and ankle in the sagittal plane. This was calculated during the stance phase, the swing phase and the over

the entire gait cycle as a descriptive measure of the global difference in joint angle during gait.

4.2.3.2 Additional Kinematic Analysis

In part B, additional analysis was completed on a sub-group of MD participants that exhibited excessive hyper-extension of the knee joint during the stance phase (defined as an angle that was $\leq -3^\circ$ in the stance phase) and another subgroup of participants who exhibited limited dorsi flexion of the ankle joint during the swing phase (defined as a mean ankle angle that was $\leq -1^\circ$ during the swing phase). This was done to establish the effect of RT on these specific kinematic abnormalities during gait. Eight participants were involved in the former sub-group and eleven in the latter sub-group.

Table 4.1: Definition of spatial and temporal gait variables.

Variable	Definition
Gait speed (m/s)	Stride length divided by the total time over one stride
Stride length (m)	Anterior distance from toe marker position at initial ground contact and at the second ipsilateral ground contact
Step width (m)	Lateral distance between the toe marker position and the contralateral toe marker position at initial ground contact
Cadence (strides/minute)	Number of strides per minute
Stance time (% of gait cycle)	Time between initial ground contact and toe-off, expressed as a percentage of total gait cycle time
Double support time (% of gait cycle)	Total duration during one gait cycle that both feet are in contact with the floor simultaneously

Table 4.2: Numerical system for discrete kinematic variables.

Pelvis (°)		Hip (°)	
P1	Mean pelvic tilt	H1	Hip flexion at initial contact
P2	Max anterior tilt in stance	H2	Max hip extension
P3	Max anterior tilt in swing	H3	Hip extension at toe-off
P4	Max pelvic rise in stance	H4	Max flexion in swing
P5	Max pelvic drop in swing	H5	Mean adduction in stance
P6	Max internal rotation	H6	Max abduction in swing
P7	External rotation at toe-off	H7	Internal rotation at initial contact
		H8	External rotation at toe-off
Knee (°)		Ankle (°)	
K1	Flexion at initial contact	A1	Angle at initial contact
K2	Max flexion in early stance	A2	Max dorsiflexion in stance
K3	Max extension in stance	A3	Max plantar flexion in stance
K4	Max flexion in swing	A4	Plantar flexion at toe-off
K5	Max extension in swing	A5	Max dorsi-flexion in swing
K6	Mean varus in stance	A6	Mean dorsi flexion in late swing
K7	Varus angle at toe-off	A7	Inversion at initial contact
		A8	Eversion at toe-off
		A9	Abduction at initial contact

4.2.3.3 Oxygen Cost

Oxygen consumption (VO_2) and heart rate data were averaged over the final minute of seated rest and the 4th minute of the walk test. Steady state was confirmed by a respiratory exchange ratio less than 1, and a visual plateau of heart rate and VO_2 (Reeves et al., 2004). Data were recorded as a rolling average of six measurements every 10 seconds. Net VO_2 (ml/kg/min) was calculated by subtracting the average VO_2 collected during the final minute of rest from the average VO_2 collected during the 4th minute of the 6-minute walk test. This was then normalised to walking speed by calculating the oxygen cost; net VO_2 was divided by the distance covered during the 4th minute of the test (ml/kg/m). Net VO_2 and oxygen cost were subsequently normalised to lean body mass (net VO_2 ; ml/kg^{LBM}/min, oxygen cost: ml/kg^{LBM}/m).

4.2.4 Statistical Analysis

All statistical analyses were completed using IBM SPSS Statistics 25 software. The critical level of significance was set at $p \leq .05$.

4.2.4.1 Part A – MD versus Controls

Data were compared between the FSHD, BMD, LGMD and control group. All data were checked against the parametric assumptions and data that satisfied the assumptions were assessed using a one-way ANOVA with least significant difference post hoc pairwise comparisons where required. The following variables were non-parametric: stride length, stride width, cadence, P1, P2, P3, P5, P7, H2, H3, H5, K2, A3 and A7. In these cases, Kruskal Wallis tests were conducted with Mann-Whitney U post-hoc comparisons (least significant difference) where necessary. Analysis of

oxygen cost data were conducted in sub-groups of MD participants (7 FSHD, 5 BMD and 5 LGMD).

4.2.4.2 Part B – Effects of RT

Data were compared between the time points (PRE1, PRE2 and POST) in the MD group. All data were checked against the parametric assumptions and data that satisfied these assumptions were assessed using a one-way repeated measures ANOVA. If the data did not pass Mauchly's test of sphericity ($P < .05$), a Greenhouse-Geisser correction was applied. From the ANOVA, both the retrospective observed power and the effect size, calculated as partial eta squared (η^2), were reported. Post hoc analysis was completed using least significant difference pairwise comparisons where appropriate. Data that were non-parametric (stride width, K7, H4, H8, A8 and A9) were analysed using a Friedman's ANOVA, followed by post-hoc analysis using Wilcoxon-signed rank tests (least significant difference) where required. Analysis of net VO_2 and oxygen cost were conducted in a sub-group of 14 MD participants (5 FSHD, 4 BMD and 5 LGMD). Data from the sub-group of participants that demonstrated hyper-extension of the knee joint and excessive plantar flexion of the ankle joint were checked for parametricity and subsequently analysed as described above.

4.3 Results

4.3.1 Part A – MD versus Controls

4.3.1.1 Participant Characteristics

There were no differences between the groups for age, body mass, stature or lean body mass ($p > .05$; Table 4.3). Individual participant characteristics, including use of walking aids and completion of the 6-minute walk test, are provided in Table 4.4.

Table 4.3: Mean \pm standard deviation of participant characteristics in the control (CTRL), FSHD, BMD and LGMD group.

	CTRL	FSHD	BMD	LGMD
n	10	9	7	6
Age (years)	46.8 \pm 10.1	46.7 \pm 11.2	42.1 \pm 7.6	47.3 \pm 11.3
Body mass (kg)	79.4 \pm 12.3	88.2 \pm 18.4	93.0 \pm 16.7	82.0 \pm 19.4
Stature (cm)	174.4 \pm 7.5	181.4 \pm 6.3	179.9 \pm 9.4	170.9 \pm 9.0
Lean body mass (kg)	56.1 \pm 11.7	60.8 \pm 13.9	62.0 \pm 6.9	54.0 \pm 15.4

Table 4.4: Individual MD participant characteristics, use of walking aids during gait analysis and completion of the 6-minute walk test (6MWT). Y = yes, N = no.

	Sex	MD	Walking Aid	6MWT
MD1	F	FSHD	Stick (1)	Y
MD2	M	FSHD	None	Y
MD3	M	FSHD	None	Y
MD4	F	FSHD	None	Y
MD5	M	FSHD	Stick (1)	N
MD6	M	FSHD	Stick (1)	Y
MD7	F	FSHD	None	Y
MD8	M	FSHD	None	Y
MD9	M	FSHD	Stick (1)	N
MD10	M	BMD	None	Y
MD11	M	BMD	None	N
MD12	M	BMD	None	N
MD13	M	BMD	None	Y
MD14	M	BMD	Stick (2)	Y
MD15	M	BMD	None	Y
MD16	M	BMD	None	Y
MD17	M	LGMD	Crutches (2)	Y
MD18	M	LGMD	None	Y
MD19	F	LGMD	None	N
MD20	F	LGMD	Stick (1)	Y
MD21	F	LGMD	Crutches (2)	Y
MD22	M	LGMD	None	Y

4.3.1.2 Spatial and Temporal Variables

There was an overall main effect of group on gait speed ($p \leq .001$), stride length ($p \leq .01$), stride width ($p < .05$), cadence ($p \leq .001$), double support time ($p \leq .01$) and stance time ($p < .05$). All spatial and temporal values are presented in Table 4.5.

Post hoc tests revealed that gait speed was slower in the FSHD, BMD and LGMD group compared to the control group by 26.4% ($p \leq .05$), 33.3% ($p \leq .01$) and 44.4% ($p \leq .001$), respectively. No differences in gait speed were found between the MD groups ($p > .05$).

Post hoc tests revealed that stride length was shorter in the FSHD, BMD and LGMD groups compared to the control group by 12.9% ($p \leq .05$), 16.7% ($p \leq .01$) and 36.1% ($p \leq .001$), respectively. Stride length was 26.6% shorter in the LGMD group than the FSHD group ($p < .05$). No other differences in stride length were found between the MD groups ($p > .05$).

Post hoc tests revealed that stride width was greater in the BMD group compared to the control group by 80.0% ($p \leq .01$). No differences in stride width were evident between any other groups ($p > .05$).

Post hoc tests revealed that cadence was lower in the FSHD, BMD and LGMD group by 16.0% ($p \leq .01$), 19.6% ($p \leq .001$) and 27.7% ($p \leq .001$) compared to the control group. No differences in cadence were found between the MD groups ($p > .05$).

Post hoc tests revealed that double support time lasted 12% longer in the LGMD group than the control group ($p \leq .001$) and 39.1% longer in the LGMD than the BMD group ($p < .05$). No other differences in double support time were found between the groups ($p > .05$).

Post hoc tests revealed that stance time was 4% longer in the LGMD group than the control group ($p \leq .05$) and the FSHD group ($p < .05$). No other differences in stance time were found between the groups ($p > .05$).

Table 4.5: Mean \pm standard deviation of spatial and temporal gait variables of self-selected walking in the FSHD, BMD, LGMD and control (CTRL) group. * represents a significant difference from the control group. $\text{\$}$ represents a significant difference from FSHD. # represents a significant difference from BMD.

	CTRL	FSHD	BMD	LGMD
Gait speed (m/s)	1.44 \pm 0.23	1.06 \pm 0.34*	0.96 \pm 0.23*	0.80 \pm 0.20*
Stride length (m)	1.55 \pm 0.21	1.35 \pm 0.22*	1.29 \pm 0.22*	1.20 \pm 0.14* $\text{\$}$
Cadence (steps/minute)	112 \pm 9	94 \pm 15*	90 \pm 9*	81 \pm 15*
Step width (m)	0.10 \pm 0.02	0.15 \pm 0.07	0.18 \pm 0.04*	0.14 \pm 0.04
Stance time (%)	62 \pm 2	62 \pm 3	63 \pm 4	66 \pm 3* $\text{\$}$
Double support (%)	20 \pm 5	24 \pm 6	23 \pm 6	32 \pm 6*#

4.3.1.3 Joint kinematics

Angular displacement of the pelvis, hip, knee and ankle joint during the gait cycle are presented as ensemble averages in the sagittal, frontal and transverse planes for the FSHD, BMD and LGMD group in Figures 4.3, 4.4 and 4.5.

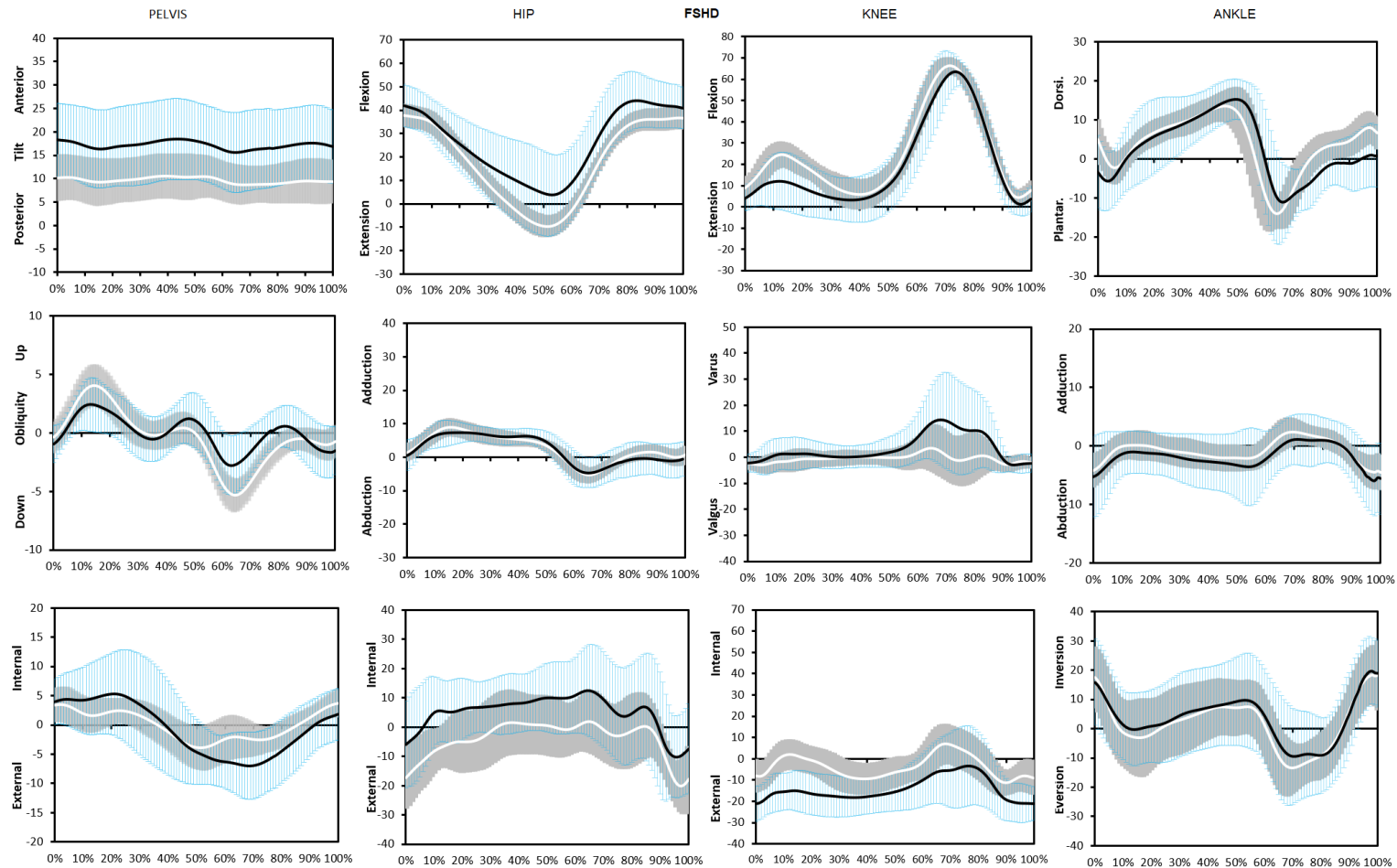


Figure 4.3: Pelvis, hip, knee and ankle angle during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents the control group mean \pm 1 standard deviation, and the black line and the blue band represents the FSHD group mean \pm 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

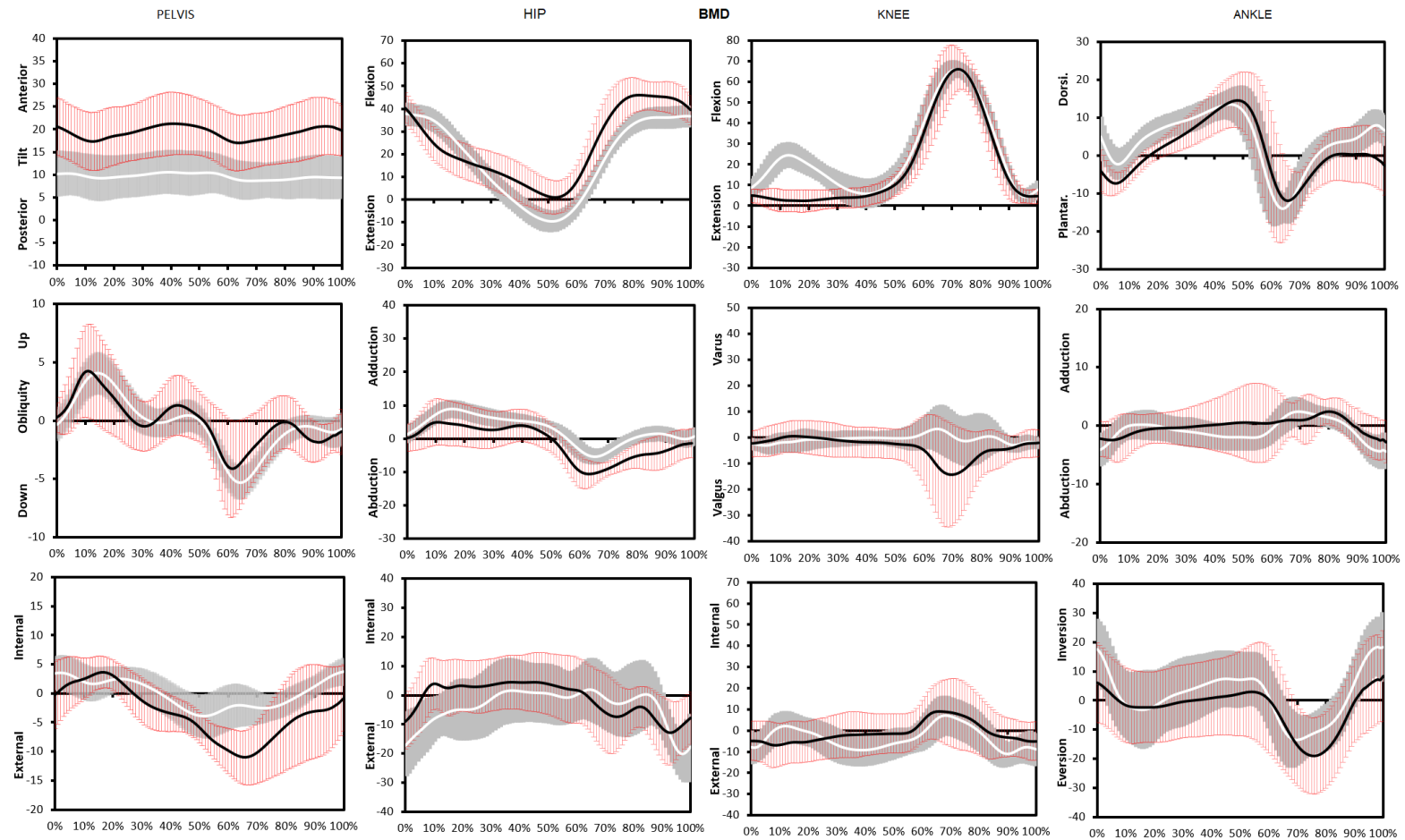


Figure 4.4: Pelvis, hip, knee and ankle angle during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents the control group mean \pm 1 standard deviation, and the black line and the blue band represents the BMD group mean \pm 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

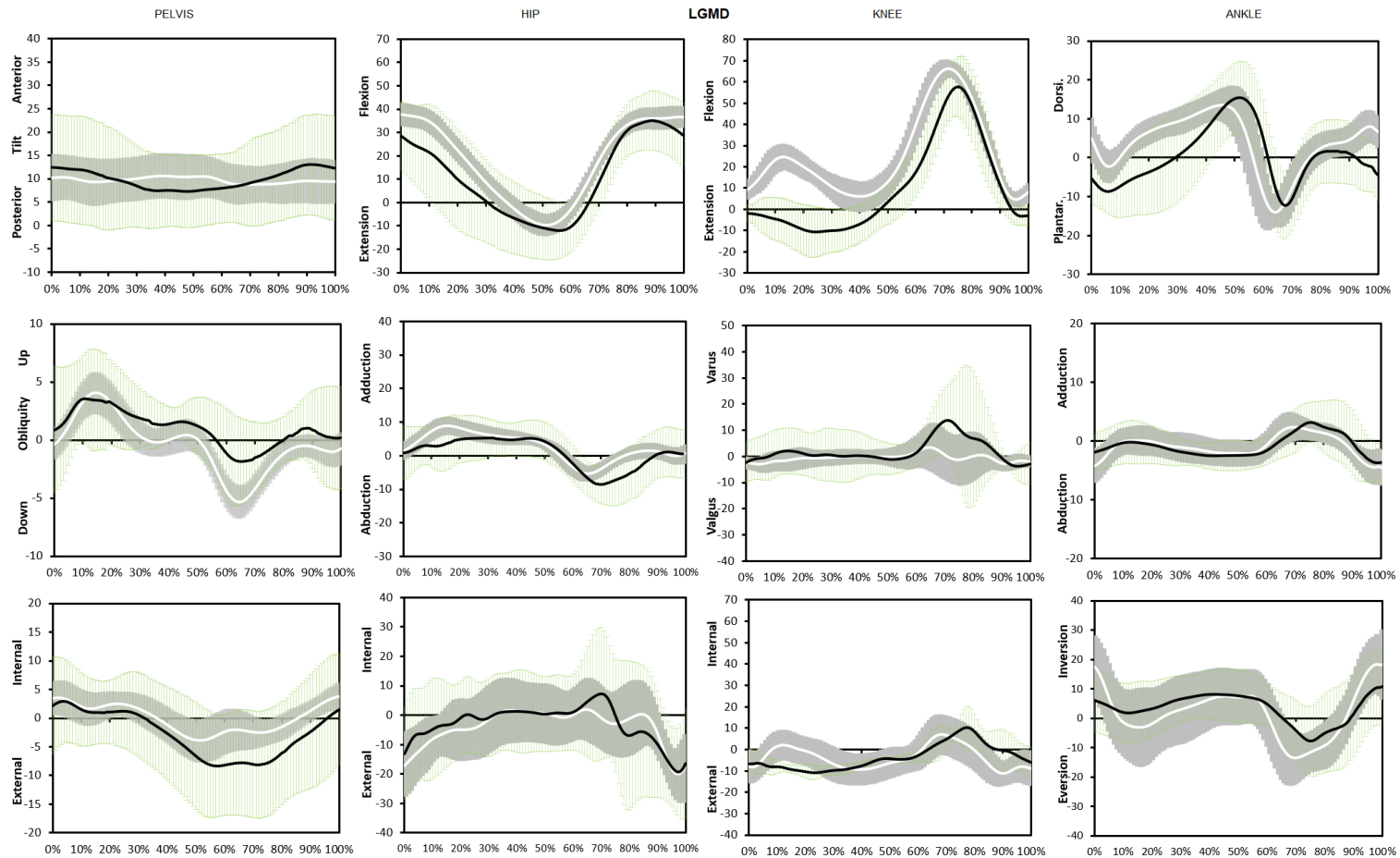


Figure 4.5: Pelvis, hip, knee and ankle angle during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents the control group mean \pm 1 standard deviation, and the black line and the blue band represents the LGMD group mean \pm 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

The root mean square difference in joint angle over the entire gait cycle and in the stance and swing phase compared to the control group are presented in Table 4.6.

Table 4.6: Root mean square difference in joint angle over the entire gait cycle, in the stance phase and in the swing phase, compared to the control group.

	FSHD	BMD	LGMD
Pelvic Tilt (°)			
Gait cycle	7.5	9.5	2.0
Stance phase	7.4	9.4	2.0
Swing phase	7.5	9.8	2.0
Hip Flexion (°)			
Gait cycle	8.2	8.9	6.8
Stance phase	7.9	7.6	8.0
Swing phase	8.8	11.2	4.6
Knee Flexion (°)			
Gait cycle	5.1	6.3	15.6
Stance phase	6.4	8.9	19.7
Swing phase	3.1	2.0	8.0
Ankle Flexion (°)			
Gait cycle	3.5	4.1	6.2
Stance phase	2.5	4.0	7.7
Swing phase	5.0	4.0	3.4

Discrete variables at the pelvis, hip, knee and ankle joint for each group are presented in Table 4.7, 4.8, 4.9 and 4.10, respectively.

Pelvis

Table 4.7: Mean \pm standard deviation of discrete kinematic variables ($^{\circ}$) of the pelvis during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
P1 ($^{\circ}$)	9.7 \pm 4.6	17.1 \pm 8.2*	19.2 \pm 6.2*	9.8 \pm 9.2
P2 ($^{\circ}$)	11.6 \pm 4.6	19.2 \pm 8.4*	21.9 \pm 6.4*	13.4 \pm 10.9
P3 ($^{\circ}$)	10.1 \pm 4.6	17.3 \pm 8.0*	21.2 \pm 6.4*	13.5 \pm 10.7
P4 ($^{\circ}$)	4.2 \pm 1.8	3.3 \pm 1.8	5.2 \pm 2.4	5.6 \pm 2.2
P5 ($^{\circ}$)	-5.5 \pm 1.4	-4.0 \pm 2.1	-4.6 \pm 3.1	-3.1 \pm 4.2
P6 ($^{\circ}$)	4.6 \pm 2.9	7.3 \pm 8.0	4.5 \pm 4.2	5.7 \pm 7.8
P7 ($^{\circ}$)	-2.1 \pm 3.8	-6.4 \pm 4.9*	-10.7 \pm 4.3*	-7.8 \pm 9.2*

Note: P1 = mean pelvic tilt, P2 = max. anterior tilt in stance, P3 = max. anterior tilt in swing, P4 = max. pelvic rise in stance, P5 = max. pelvic drop in swing, P6 = max. internal rotation, P7 = external rotation at toe-off.

There was a significant main effect of group on mean pelvic tilt, max. anterior tilt in stance, max. anterior tilt in swing and external rotation at toe-off ($p < .05$). No main effect of group was found for max. pelvic rise in stance, max. pelvic drop in swing or max. internal rotation ($p > .05$).

Post hoc tests showed that mean pelvic tilt did not differ between the LGMD and control group ($p > .05$) but was greater in the FSHD group by 7.4° ($p < .05$) and in the BMD group by 9.5° ($p < .01$) compared to the control group.

Post hoc tests showed that max. anterior tilt in stance did not differ between the LGMD and control group ($p > .05$) but was greater in the FSHD group by 7.6° ($p < .05$) and in the BMD group by 10.3° ($p < .01$) compared to the control group.

Post hoc tests showed that max. anterior tilt in swing did not differ between the LGMD and control group ($p > .05$) but was greater in the FSHD group by 10.2° ($p < .05$) and in the BMD group by 11.1° ($p < .01$) compared to the control group.

Post hoc tests showed that max. external rotation at toe-off was 4.3° greater in the FSHD group ($p < .05$), 8.6° greater in the BMD group ($p < .001$) and 5.7° greater in the LGMD group ($p < .05$) compared to the control group.

Hip

Table 4.8: Mean \pm standard deviation of discrete variables ($^{\circ}$) of the hip joint during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
H1 ($^{\circ}$)	37.7 \pm 8.1	42.0 \pm 9.0	40.3 \pm 6.7	28.6 \pm 14.7
H2 ($^{\circ}$)	-9.9 \pm 8.7	2.9 \pm 16.8*	0.6 \pm 7.2*	-13.8 \pm 12.0
H3 ($^{\circ}$)	0.4 \pm 9.7	11.8 \pm 15.6*	14.6 \pm 8.7*	-1.0 \pm 10.9
H4 ($^{\circ}$)	38.1 \pm 7.2	45.3 \pm 11.0	47.1 \pm 7.2	35.8 \pm 12.6
H5 ($^{\circ}$)	4.7 \pm 2.0	4.8 \pm 2.3	1.4 \pm 4.4	3.0 \pm 4.0
H6 ($^{\circ}$)	-5.7 \pm 2.5	-6.1 \pm 4.1	-11.4 \pm 3.2*	-10.1 \pm 5.2*
H7 ($^{\circ}$)	-17.3 \pm 10.5	-5.9 \pm 14.8	-9.1 \pm 9.4	-13.1 \pm 15.7
H8 ($^{\circ}$)	1.2 \pm 9.4	12.0 \pm 14.1	0.4 \pm 10.9	5.4 \pm 20.2

Note: H1 = flexion at initial contact, H2 = max. extension, H3 = extension at toe-off, H4 = max flexion in swing, H5 = mean adduction in stance, H6 = max. abduction in swing, H7 = internal rotation at initial contact, H8 = external rotation at toe-off.

At the hip, there was a significant main effect of group on max. hip extension, hip extension at toe-off and max. hip abduction in swing ($p < .05$). No main effect of group was found for hip flexion at initial contact, max. hip flexion in swing, mean hip adduction in stance, internal rotation at initial contact or external rotation at toe-off ($p > .05$).

Post hoc tests showed that max. hip extension did not differ between the control and LGMD group ($p > .05$), but that H2 was 7 $^{\circ}$ lower in the FSHD group ($p < .05$) and 10.5 $^{\circ}$ lower in the BMD group ($p < .05$) than the control group.

Post hoc tests showed that hip extension at toe-off did not differ between the control and LGMD group ($p > .05$), but that H3 was 11.4° lower in the FSHD group ($p < .05$) and 14.2° lower in the BMD group ($p < .05$) than the control group.

Post hoc tests showed that max. hip abduction in swing did not differ between the control and FSHD group ($p > .05$), but that H3 was 5.7° greater in the BMD group ($p < .05$) and 4.4° greater in the LGMD group ($p < .05$) than the control group.

Knee

Table 4.9: Mean \pm standard deviation of discrete variables ($^\circ$) of the knee joint during gait. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
K1 ($^\circ$)	8.9 \pm 4.4	4.0 \pm 5.9*	4.8 \pm 3.3	-1.9 \pm 3.8*
K2 ($^\circ$)	23.7 \pm 7.7	14.5 \pm 11.5	5.8 \pm 3.9*	0.5 \pm 5.9*
K3 ($^\circ$)	5.1 \pm 6.1	0.6 \pm 8.1	1.3 \pm 4.7	-11.5 \pm 11.4*
K4 ($^\circ$)	67.2 \pm 3.9	66.1 \pm 6.5	68.5 \pm 8.5	58.6 \pm 14.0
K5 ($^\circ$)	4.3 \pm 3.6	-0.1 \pm 5.4*	3.2 \pm 3.5	-4.0 \pm 3.9*
K6 ($^\circ$)	-0.7 \pm 3.4	1.4 \pm 5.9	-1.7 \pm 5.4	0.7 \pm 6.0
K7 ($^\circ$)	2.8 \pm 7.2	10.4 \pm 11.0*	-1.9 \pm 5.9	9.4 \pm 9.7*

Note: K1 = flexion at initial contact, K2 = max. flexion in early stance, K3 = max. extension in stance, K4 = max. flexion in swing, K5 = max. extension in swing, K6 = mean varus in stance, K7 = varus angle at toe-off.

There was a significant main effect of group on knee flexion at initial contact ($p \leq .001$), max. flexion in early stance ($p \leq .001$), max. extension in stance ($p \leq .001$),

max. extension in swing ($p \leq .01$) and varus angle at toe-off ($p < .05$). No main effect of group was found for max. knee flexion in swing or mean varus in stance ($p > .05$).

Post hoc tests showed that knee flexion at initial contact did not differ between the control and BMD group ($p > .05$), but that it was 4.9° lower in the FSHD group ($p < .05$) and 10.8° lower in the LGMD group ($p \leq .001$) than the control group.

Post hoc tests showed that max. knee flexion in early stance did not differ between the control and FSHD group ($p > .05$), but that K2 was 17.9° lower in the BMD group ($p \leq .01$) and 23.2° lower in the LGMD group ($p \leq .01$) than the control group.

Post hoc tests showed that max. knee extension in stance did not differ between the FSHD and control group or between the BMD and control group ($p > .05$) but was 16.6° lower in the LGMD group ($p \leq .001$) than the control.

Post hoc tests showed that max. knee extension in swing did not differ between the control and BMD group ($p > .05$) but was 4.4° lower in the FSHD group ($p < .05$) and 8.3° lower in the LGMD group ($p \leq .001$) than the control group.

Post hoc tests showed that varus angle at toe-off did not differ between the control and BMD group ($p > .05$), but was 7.6° higher in the FSHD group ($p < .05$) and 6.6° higher in the LGMD group ($p \leq .001$) than the control group.

Ankle

Table 4.10: Mean \pm standard deviation of discrete variables ($^{\circ}$) of the ankle during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
A1 ($^{\circ}$)	5.0 \pm 5.3	-3.3 \pm 9.3*	-4.0 \pm 5.6*	-4.5 \pm 7.4*
A2 ($^{\circ}$)	14.6 \pm 4.5	16.9 \pm 6.1	16.1 \pm 7.2	15.5 \pm 8.8
A3 ($^{\circ}$)	-13.8 \pm 5.1	-13.4 \pm 5.1	-14.5 \pm 7.6	-13.7 \pm 9.3
A4 ($^{\circ}$)	-13.6 \pm 4.5	-10.6 \pm 8.4	-10.0 \pm 13.0	-9.8 \pm 11.6
A5 ($^{\circ}$)	8.8 \pm 4.0	2.7 \pm 8.1	1.9 \pm 7.3	3.2 \pm 8.0
A6 ($^{\circ}$)	6.7 \pm 4.0	0.1 \pm 7.7*	-0.4 \pm 7.5*	-1.5 \pm 6.9*
A7 ($^{\circ}$)	17.6 \pm 10.5	15.9 \pm 14.7	6.2 \pm 13.7	6.0 \pm 10.6
A8 ($^{\circ}$)	-5.7 \pm 11.4	-2.1 \pm 15.7	-3.8 \pm 17.5	-0.7 \pm 8.9
A9 ($^{\circ}$)	-4.2 \pm 2.8	-5.3 \pm 7.0	-2.2 \pm 3.0	-1.9 \pm 3.0

Note: A1 = angle at initial contact, A2 = max. dorsiflexion in stance, A3 = max. plantar flexion in stance, A4 = plantar flexion at toe-off, A5 = max. dorsiflexion in swing, A6 = mean dorsi flexion in late swing, A7 = inversion angle at initial contact, A8 = eversion at toe-off, A9 = abduction at initial contact.

At the ankle there was a significant main effect of group on ankle angle at initial contact and mean dorsi flexion in late swing ($p \leq .05$). No main effect of group was found for max. dorsi flexion in stance, max. plantar flexion in stance, plantar flexion at toe-off, max. dorsi flexion in swing, inversion angle at initial contact, eversion at toe-off or abduction at initial contact ($p > .05$).

Post hoc tests showed that ankle angle at initial contact was 8.3° lower in the FSHD group ($p < .05$), 9.0° lower in the BMD group ($p < .05$) and 9.5° lower in the LGMD group ($p < .05$) than the control group.

Post hoc tests showed that mean dorsi flexion in late swing was 6.6° lower in the FSHD group ($p < .05$), 7.1° lower in the BMD group ($p < .05$) and 8.2° lower in the LGMD group ($p \leq .05$) than the control group.

4.3.1.4 Metabolic Cost of Walking

There was a main effect of group on oxygen cost normalised to body mass ($p \leq .01$; Figure 4.6 A) and lean body mass ($p \leq .01$; Figure 4.6 B). Post hoc tests showed an 83% higher oxygen cost (ml/kg/m) in the LGMD than the control group ($p \leq .01$) and the FSHD group ($p \leq .01$). No other differences in oxygen cost normalised to body mass were found between the groups ($P > .05$). Post hoc tests showed oxygen cost normalised to lean body mass in the LGMG group was double that of the control and FSHD group ($p \leq .01$). No other differences in oxygen cost normalised to lean body mass were found between the groups ($p > .05$).

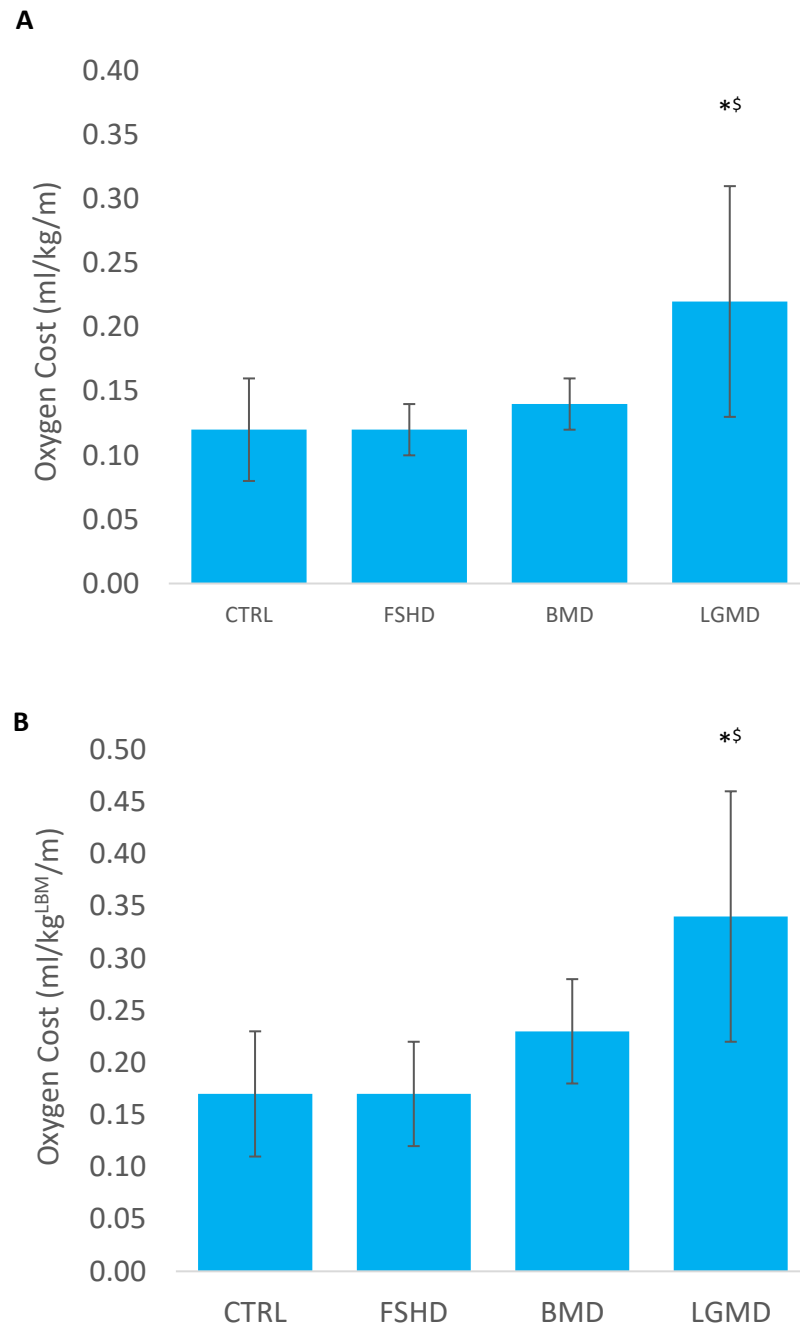


Figure 4.6: Oxygen cost during steady state walking normalised to body mass (A) and lean body mass (B). Bars represent means and error bars represent standard deviation. * represents a significant difference from the control (CTRL) group and [§] represents a significant difference from the FSHD group.

4.3.2 Part B – Effects of RT

4.3.2.1 Participant Characteristics

Individual participant characteristics, including use of walking aids and completion of the 6-minute walk test, are provided in Table 4.11.

Table 4.11: Use of walking aids during gait analysis and completion of the 6-minute walk test (6MWT)

	Sex	MD	Walking Aid	6MWT
MD1	F	FSHD	Stick (1)	Y
MD2	M	FSHD	None	Y
MD3	M	FSHD	None	Y
MD5	M	FSHD	Stick (1)	N
MD7	F	FSHD	None	Y
MD8	M	FSHD	None	Y
MD10	M	BMD	None	Y
MD12	M	BMD	None	N
MD14	M	BMD	Stick (2)	Y
MD15	M	BMD	None	Y
MD16	M	BMD	None	Y
MD17	M	LGMD	Crutches (2)	Y
MD18	M	LGMD	None	Y
MD19	F	LGMD	None	N
MD20	F	LGMD	Stick (1)	Y
MD21	F	LGMD	Crutches (2)	Y
MD22	M	LGMD	None	Y

4.3.2.2. Spatial and Temporal Variables

There was an overall main effect of time on gait speed ($p \leq .001$), stride length ($p \leq .001$), cadence ($p < .05$), and stride width ($p < .05$). No overall effect was found for double support time or stance time ($p > .05$). Data are presented in Table 4.12.

Post hoc tests showed that gait speed did not change between PRE1 and PRE2 ($p > .05$) but that it increased by 8.1% from PRE 1 to POST ($p \leq .001$) and by 7.9% from PRE2 to POST ($p \leq .001$).

Post hoc tests showed that stride length did not change between PRE1 and PRE2 ($p > .05$), but that it increased by 4.3% from PRE 1 to POST ($p \leq .01$) and by 4.0% from PRE2 to POST ($p \leq .001$).

Post hoc tests showed that cadence did not change between PRE1 and PRE2 ($p > .05$) or between PRE1 and POST ($p = .07$), but that it increased by 4.4% from PRE2 to POST ($p \leq .01$).

Post hoc tests showed that stride width increased by 7.1% from PRE1 to PRE2 ($p < .05$) and decreased by 7.1% from PRE2 to POST ($p < .05$) with no difference in-between PRE1 and POST ($p > .05$).

Table 4.12: Mean \pm standard deviation of spatial and temporal variables of self-selected walking at PRE1, PRE2 and POST. * represents a significant difference from PRE1 and § from PRE2.

	PRE1	PRE2	POST
Gait speed (m/s)	0.96 \pm 0.25	0.97 \pm 0.26	1.04 \pm 0.24* §
Stride length (m)	1.30 \pm 0.18	1.31 \pm 0.17	1.36 \pm 0.17* §
Cadence (steps/minute)	88.4 \pm 15.4	87.5 \pm 16.4	91.4 \pm 16.4 §
Step width (m)	0.14 \pm 0.05	0.15 \pm 0.04*	0.14 \pm 0.04*
Stance time (%)	64 \pm 4	64 \pm 3	63 \pm 4
Double support (%)	26 \pm 7	27 \pm 7	26 \pm 7

4.3.2.3 Joint Kinematics

Angular displacement of the pelvis, hip, knee and ankle joint during the gait cycle are presented as ensemble averages in the sagittal, frontal and transverse planes for each time point (PRE1, PRE2 and POST) in Figure 4.7. The root mean square difference in joint angle between PRE1 and PRE2 and between PRE2 and POST over the entire gait cycle and in the stance and swing phase are presented in Table 4.13.

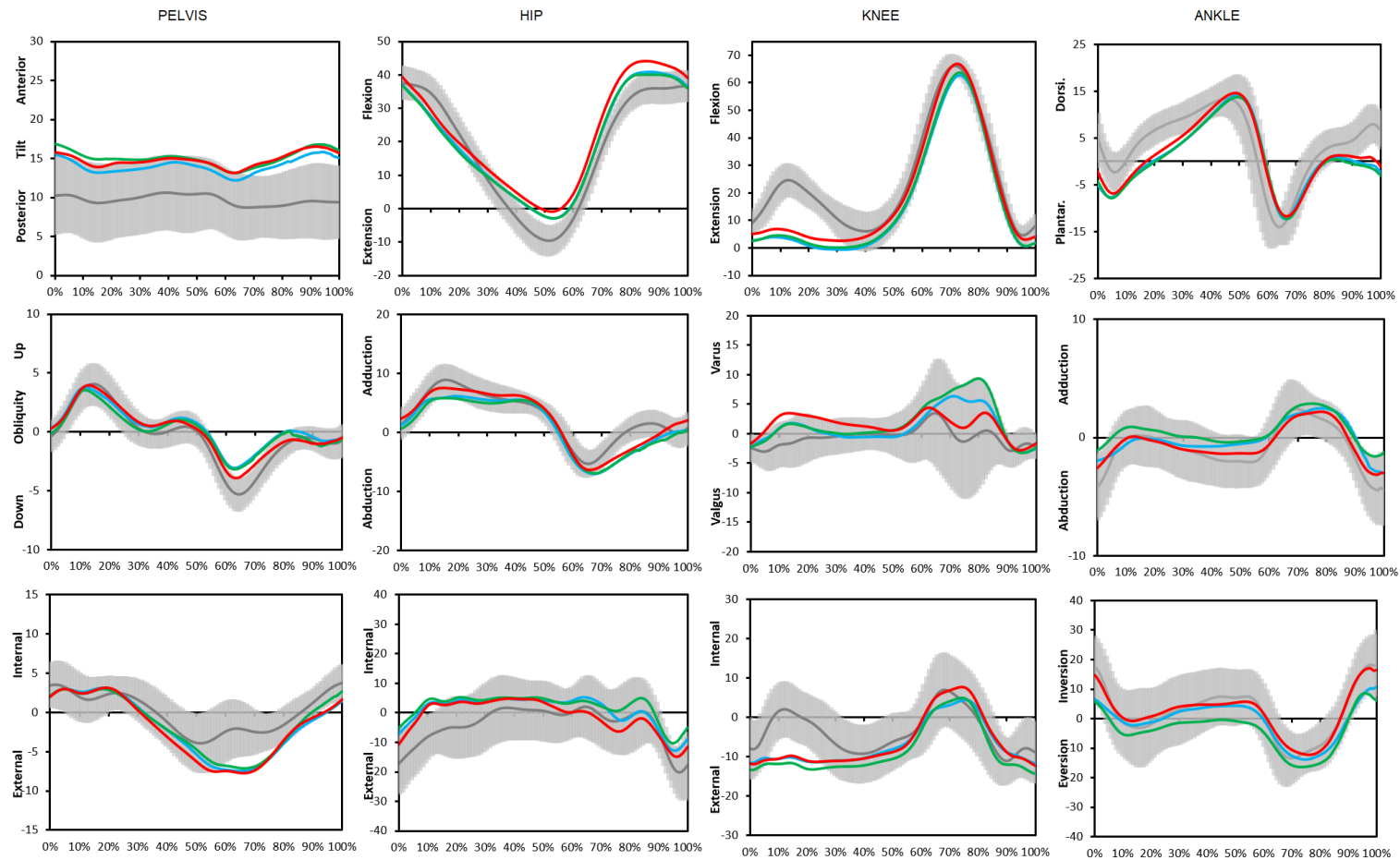


Figure 4.7: Mean pelvis, hip, knee and ankle angle during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents control data mean \pm 1 standard deviation and the blue line represents the mean of the MD group at PRE1, the green line represents the mean at PRE2, and the red line represents the mean at POST. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

Table 4.13: Root mean square difference in joint angle compared to the control group over the entire gait cycle, in the stance phase and in the swing phase at PRE1, PRE2 and POST.

	PRE1-PRE2	PRE2-POST
Pelvic Tilt (°)		
Gait cycle	1.0	0.8
Stance phase	1.2	0.8
Swing phase	0.8	0.9
Hip Flexion (°)		
Gait cycle	0.4	2.7
Stance phase	0.3	2.3
Swing phase	0.4	3.6
Knee Flexion (°)		
Gait cycle	0.5	2.8
Stance phase	0.5	2.9
Swing phase	0.5	2.8
Ankle Flexion (°)		
Gait cycle	0.4	1.0
Stance phase	0.3	1.1
Swing phase	0.5	0.9

Discrete kinematic variables for PRE1, PRE2 and POST are presented in Table 4.14, 4.15, 4.16 and 4.17 for the pelvis, hip, knee and ankle joint, respectively.

Pelvis

Table 4.14: Mean \pm standard deviation of discrete kinematic variables ($^{\circ}$) of the pelvis during the gait cycle. * represents a significant difference from PRE1 and $^{\$}$ represents a significant difference from PRE2.

	PRE1	PRE2	POST
P1 ($^{\circ}$)	15.1 \pm 8.4	14.0 \pm 10.1	14.8 \pm 8.2
P2 ($^{\circ}$)	17.9 \pm 8.8	16.6 \pm 10.6	17.3 \pm 8.6
P3 ($^{\circ}$)	17.2 \pm 8.3	16.4 \pm 10.0	17.1 \pm 8.2
P4 ($^{\circ}$)	5.0 \pm 2.4	4.4 \pm 3.1	4.4 \pm 2.9
P5 ($^{\circ}$)	-3.8 \pm 3.2	-4.1 \pm 2.5	-4.2 \pm 2.6
P6 ($^{\circ}$)	5.8 \pm 6.6	5.5 \pm 6.3	5.3 \pm 5.6
P7 ($^{\circ}$)	-7.4 \pm 6.8	-7.1 \pm 5.4	-7.6 \pm 5.7

Note: P1 = mean pelvic tilt, P2 = max. anterior tilt in stance, P3 = max. anterior tilt in swing, P4 = max. pelvic rise in stance, P5 = max. pelvic drop in swing, P6 = max. internal rotation, P7 = external rotation at toe-off.

No main effect of time was found in in any of the discrete pelvic variables, with the retrospective observed power for these comparisons ranging between .06 and .16.

Hip

Table 4.15: Mean \pm standard deviation of discrete kinematic variables ($^{\circ}$) of the hip joint during the gait cycle. * represents a significant difference from PRE1 and $^{\$}$ represents a significant difference from PRE2.

	PRE1	PRE2	POST
H1 ($^{\circ}$)	37.0 \pm 11.9	36.9 \pm 13.1	39.4 \pm 11.2
H2 ($^{\circ}$)	-4.0 \pm 13.8	-3.8 \pm 14.6	-2.0 \pm 13.6
H3 ($^{\circ}$)	9.1 \pm 15.9	8.8 \pm 16.9	9.8 \pm 14.2
H4 ($^{\circ}$)	42.4 \pm 10.7	42.2 \pm 11.5	45.9 \pm 10.8
H5 ($^{\circ}$)	3.6 \pm 3.1	3.3 \pm 3.0	4.6 \pm 2.9* $^{\$}$
H6 ($^{\circ}$)	-8.9 \pm 5.1	-8.6 \pm 5.1	-8.0 \pm 4.8
H7 ($^{\circ}$)	-7.3 \pm 14.0	-5.4 \pm 16.5	-10.7 \pm 17.7
H8 ($^{\circ}$)	5.3 \pm 16.2	4.1 \pm 16.1	3.5 \pm 12.4

Note: H1 = flexion at initial contact, H2 = max. extension, H3 = extension at toe-off, H4 = max flexion in swing, H5 = mean adduction in stance, H6 = max. abduction in swing, H7 = internal rotation at initial contact, H8 = external rotation at toe-off.

There was a significant main effect of time on mean hip adduction in stance ($p < .05$, $\eta^2 = .19$) with a retrospective observed power of .65. No main effect of time was found in any other discrete hip variable, with the retrospective observed power for these comparisons ranging between .07 and .27.

Post hoc tests showed that mean hip adduction in stance did not differ between PRE1 and PRE2 ($P > .05$) or between PRE1 and POST ($p = .055$) but was increased by 1.3° from PRE2 to POST ($p < .05$).

Knee

Table 4.16: Mean \pm standard deviation of discrete kinematic variables ($^{\circ}$) of the knee joint during the gait cycle. * represents a significant difference from PRE1 and $^{\$}$ represents a significant difference from PRE2.

	PRE1	PRE2	POST
K1 ($^{\circ}$)	2.6 \pm 5.9	2.5 \pm 7.6	5.0 \pm 6.0* $^{\$}$
K2 ($^{\circ}$)	7.6 \pm 10.0	7.6 \pm 11.7	9.9 \pm 10.6* $^{\$}$
K3 ($^{\circ}$)	-3.1 \pm 10.8	-2.6 \pm 11.7	-0.1 \pm 9.7* $^{\$}$
K4 ($^{\circ}$)	64.9 \pm 11.3	65.9 \pm 10.5	68.9 \pm 10.3* $^{\$}$
K5 ($^{\circ}$)	-0.6 \pm 5.6	-1.0 \pm 6.3	1.6 \pm 5.6* $^{\$}$
K6 ($^{\circ}$)	0.2 \pm 5.4	0.8 \pm 3.9	1.9 \pm 4.9
K7 ($^{\circ}$)	5.4 \pm 17.1	5.6 \pm 13.2	4.4 \pm 13.0

Note: K1 = flexion at initial contact, K2 = max. flexion in early stance, K3 = max. extension in stance, K4 = max. flexion in swing, K5 = max. extension in swing, K6 = mean varus in stance, K7 = varus angle at toe-off.

There was a significant main effect of time on knee flexion at initial contact ($p \leq .001$, $\eta^2 = .38$), max. flexion in early stance ($p \leq .01$, $\eta^2 = .31$), max. extension in stance ($p \leq .001$, $\eta^2 = .35$), max. flexion in swing ($p < .05$, $\eta^2 = .22$) and max. extension in swing ($p \leq .001$, $\eta^2 = .36$), with the retrospective observed powers ranging from .73 to .97. No main effect of time was found for mean varus in stance or varus angle at toe-off (observed power = .27).

Post hoc tests showed that knee flexion at initial contact did not differ between PRE1 and PRE2 ($P > .05$) but that it increased by 2.4 $^{\circ}$ from PRE1 to POST ($p \leq .01$) and 2.5 $^{\circ}$ from PRE2 to POST ($p \leq .01$).

Post hoc tests showed that max. flexion in early stance did not differ between PRE1 and PRE2 ($P > .05$) but that it increased by 2.3° from PRE1 to POST ($p \leq .01$) and 2.3° from PRE2 to POST ($p \leq .01$).

Post hoc tests showed that max. extension in stance did not differ between PRE1 and PRE2 ($P > .05$) but that it decreased by 3° from PRE1 to POST ($p \leq .01$) and decreased by 2.5° from PRE2 to POST ($p \leq .01$).

Post hoc tests showed that max. flexion in swing did not differ between PRE1 and PRE2 ($P > .05$) but that it increased by 4° from PRE1 to POST ($p < .05$) and increased by 3° from PRE2 to POST ($p < .05$).

Post hoc tests showed that max. extension in swing did not differ between PRE1 and PRE2 ($P > .05$) but that it decreased by 2.2° from PRE1 to POST ($p \leq .01$) and decreased by 2.6° from PRE2 to POST ($p \leq .01$).

Ankle

Table 4.17: Mean \pm standard deviation of discrete kinematic variables ($^{\circ}$) of the ankle joint during the gait cycle. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

	PRE1	PRE2	POST
A1 ($^{\circ}$)	-5.0 \pm 6.0	-4.3 \pm 5.5	-2.1 \pm 6.3* §
A2 ($^{\circ}$)	15.0 \pm 7.2	14.8 \pm 6.8	15.8 \pm 6.9
A3 ($^{\circ}$)	-14.7 \pm 7.0	-14.8 \pm 7.0	-14.6 \pm 7.4
A4 ($^{\circ}$)	-11.0 \pm 9.7	-10.4 \pm 9.7	-9.1 \pm 13.2
A5 ($^{\circ}$)	2.1 \pm 5.9	1.8 \pm 5.2	4.1 \pm 6.6* §
A6 ($^{\circ}$)	-0.8 \pm 5.8	-1.4 \pm 4.8	0.5 \pm 5.7* §
A7 ($^{\circ}$)	6.5 \pm 10.8	3.3 \pm 10.3	13.1 \pm 12.3* §
A8 ($^{\circ}$)	-6.6 \pm 12.0	-10.4 \pm 12.2	-1.5 \pm 15.4 §
A9 ($^{\circ}$)	-2.0 \pm 2.6	-1.7 \pm 2.1	-2.5 \pm 2.9

Note: A1 = angle at initial contact, A2 = max. dorsiflexion in stance, A3 = max. plantar flexion in stance, A4 = plantar flexion at toe-off, A5 = max. dorsiflexion in swing, A6 = mean dorsi flexion in late swing, A7 = inversion angle at initial contact, A8 = eversion at toe-off, A9 = abduction at initial contact.

There was a significant main effect of time on ankle angle at initial contact ($p \leq .01$, $\eta^2 = .36$), max. dorsi flexion in swing ($p < .05$, $\eta^2 = .24$), mean dorsi flexion in late swing ($p < .05$, $\eta^2 = .24$), inversion angle at initial contact ($p < .05$, $\eta^2 = .24$) and eversion angle at toe-off ($p < .05$), with the retrospective observed power for these comparisons ranging from .65 to .87. No main effect of time was found for max. dorsi flexion in stance, max. plantar flexion in stance, plantar flexion at toe-off or

abduction at initial contact, with the retrospective observed power for these comparisons ranging between .05 and .13.

Post hoc tests showed that ankle angle at initial contact did not differ between PRE1 and PRE2 ($P > .05$) but that it increased by 2.9° from PRE1 to POST ($p \leq .01$) and increased by 2.2° from PRE2 to POST ($p < .05$).

Post hoc tests showed that max. dorsi flexion in swing did not differ between PRE1 and PRE2 ($P > .05$) but that it increased by 2° from PRE1 to POST ($p < .05$) and increased by 2.3° from PRE2 to POST ($p < .05$).

Post hoc tests showed that mean dorsi flexion in late swing did not differ between PRE1 and PRE2 ($P > .05$) but that it increased by 1.3° from PRE1 to POST ($p < .05$) and increased by 1.9° from PRE2 to POST ($p < .05$).

Post hoc tests showed that inversion angle at initial contact did not differ between PRE1 and PRE2 ($P > .05$) or between PRE1 and POST ($p = .06$) but that it increased by 9.8° from PRE2 to POST ($p \leq .01$).

Post hoc tests showed that eversion angle at toe-off did not differ between PRE1 and PRE2 ($P > .05$) or between PRE1 and POST ($p = .09$) but that it decreased by 8.9° from PRE2 to POST ($p < .05$).

4.3.2.4 Additional Kinematic Analysis - knee hyperextension

Knee angle in the sagittal plane for the sub-group of participants that displayed excessive hyperextension of the knee in the stance phase is presented in Figure 4.8, and discrete data from this analysis are presented in Table 4.18.

There was a significant main effect of time on knee flexion at initial contact ($p \leq .01$, $\eta^2 = .53$, observed power = .89) and max. extension in stance ($p \leq .01$, $\eta^2 = .51$, observed power = .87). No main effect of time on max. extension in swing was found ($p = .087$, power = .48).

Post hoc analysis showed that knee flexion at initial contact did not differ between PRE1 and PRE2 ($p > .05$) but that the angle was increased by 2.7° from PRE1 to POST ($p \leq .01$) and increased by 3.9° from PRE2 to POST ($p < .05$).

Post hoc analysis showed that max. extension in stance did not differ between PRE1 and PRE2 ($p > .05$) but that the angle was increased by 4.3° from PRE1 to POST ($p \leq .05$) and increased by 4.1° from PRE2 to POST ($p < .05$).

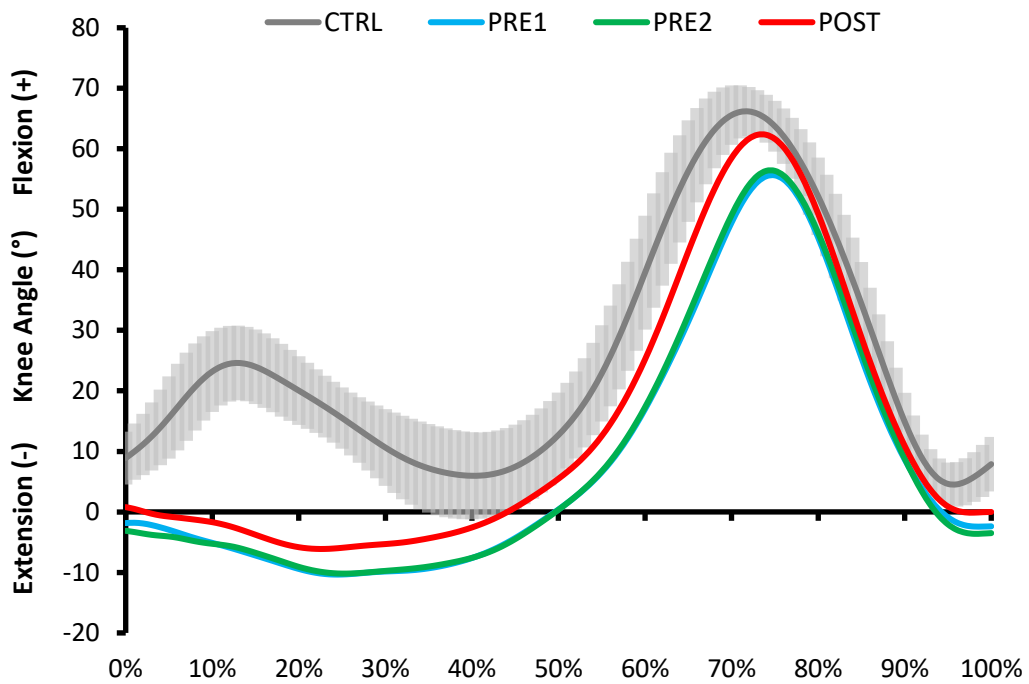


Figure 4.8: Mean knee flexion (+) and extension (-) angle during the gait cycle in individuals with MD who hyper-extend the knee at PRE1 (blue line), PRE2 (green line) and POST (red line) completion of a RT programme. The grey line (\pm grey band) represents control group data mean (\pm 1 standard deviation) for visual comparison. On the x-axis, 0% represents initial ground contact and 100% the following ipsilateral ground contact.

Table 4.18: Mean \pm standard deviation of discrete knee angle data for a sub-group of participants that exhibited excessive hyperextension of the knee during stance. * represents a significant difference from PRE1 and \textasciitilde represents a significant difference from PRE2.

	PRE1	PRE2	POST
K1 (°)	-1.9 \pm 3.4	-3.1 \pm 5.5	0.8 \pm 3.6* \textasciitilde
K3 (°)	-11.2 \pm 9.5	-11.0 \pm 11.1	-6.9 \pm 8.4* \textasciitilde
K5 (°)	-2.9 \pm 4.4	-4.8 \pm 5.2	-1.8 \pm 3.8

Key: K1 = flexion at initial contact, K3 = max. extension in stance, K5 = max. extension in swing.

4.3.2.5 Additional Kinematic Analysis – limited dorsi flexion

Ankle angle in the sagittal plane for the sub-group of participants that displayed excessive plantar flexion of the ankle during the swing phase is presented in Figure 4.9, and discrete kinematic variables from this analysis are presented in Table 4.19.

There was a significant main effect of time on ankle angle at initial contact ($p \leq .05$, $\eta^2 = .39$, observed power = .85) and mean dorsi flexion in late swing ($p \leq .05$, $\eta^2 = .38$, observed power = .78). No main effect of time on max. dorsi flexion in swing was found ($p = .123$, power = .36).

Post hoc analysis showed that ankle angle at initial contact did not differ between PRE1 and PRE2 ($p > .05$) but that the angle was increased by 2.8° from PRE1 to POST ($p \leq .05$) and increased by 1.9° from PRE2 to POST ($p < .05$).

Post hoc analysis showed that mean dorsi flexion in late swing did not differ between PRE1 and PRE2 ($p > .05$) but the angle was increased by 2.3° from PRE1 to POST ($p \leq .05$) and increased by 2.4° from PRE2 to POST ($p < .05$).

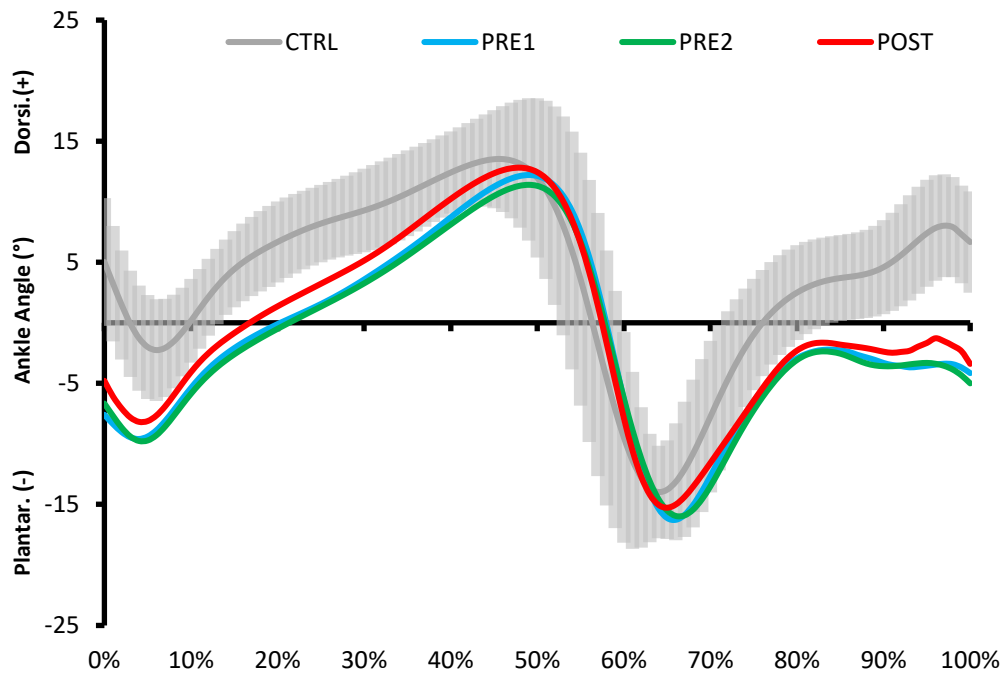


Figure 4.9: Mean ankle dorsiflexion (+) and plantar flexion (-) angle during the gait cycle in individuals with MD who exhibit limited dorsiflexion in the swing phase, at PRE1 (blue line), PRE2 (green line) and POST (red line) completion of a RT programme. The grey line (\pm grey band) represents control group data mean (\pm 1 standard deviation) for visual comparison. On the x-axis, 0% represents initial ground contact and 100% the following ipsilateral ground contact.

Table 4.19: Mean \pm standard deviation of discrete ankle angle data for a sub-group of participants that exhibited limited ankle dorsiflexion during swing. * represents a significant difference from PRE1 and $\text{\$}$ represents a significant difference from PRE2.

	PRE1	PRE2	POST
A1 (°)	-7.6 \pm 5.5	-6.7 \pm 4.8	-4.8 \pm 5.8* $\text{\$}$
A5 (°)	-1.0 \pm 4.8	-1.0 \pm 3.7	1.1 \pm 4.7
A6 (°)	-3.6 \pm 5.0	-3.7 \pm 3.8	-1.3 \pm 4.3* $\text{\$}$

Key: A1 = angle at initial contact, A5 = max. dorsiflexion in swing, A6 = mean dorsiflexion in late swing.

4.3.2.4 Metabolic Cost of Walking

There was a main effect of time on oxygen cost normalised to body mass ($p \leq .05$; Figure 4.10 A). Post hoc tests showed a 9.1% increase from PRE1 to PRE2 ($p = .025$) but no difference between PRE2 and POST or PRE1 and POST ($p > .05$). No effect of time on oxygen cost normalised to lean body mass was found ($p > .05$; Figure 4.10 B).

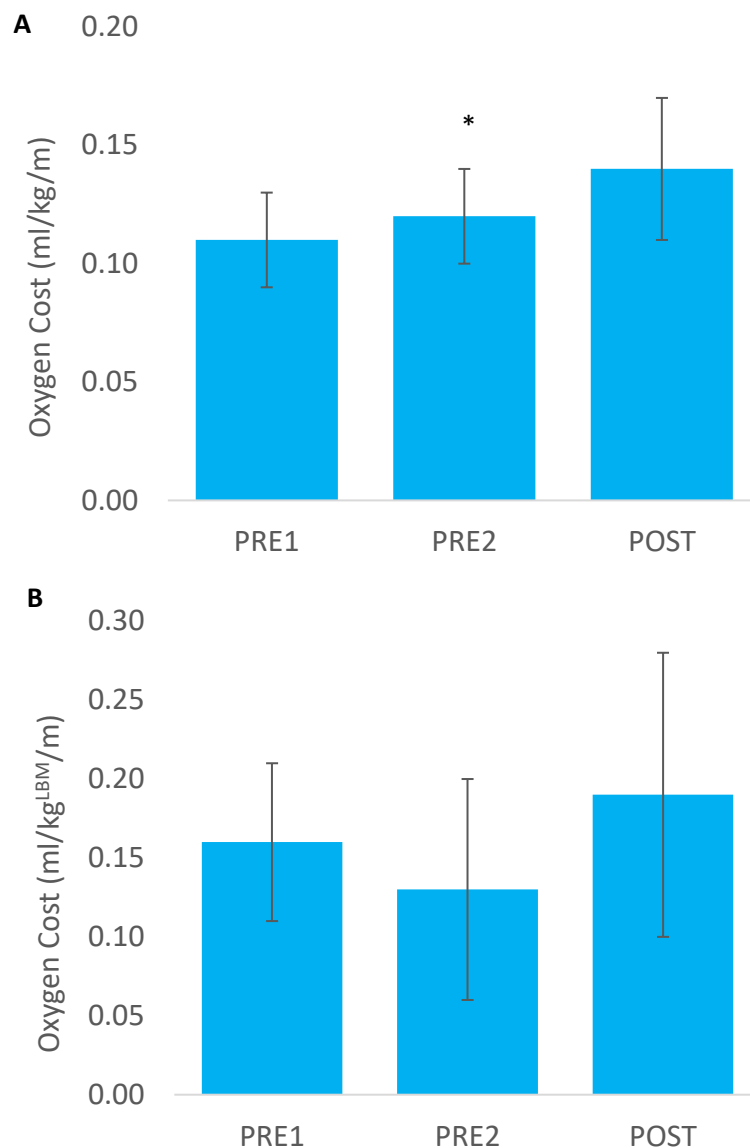


Figure 4.10: Oxygen cost during steady state walking normalised to body mass (A) and lean body mass (B). Bars represent means and error bars represent standard deviation. * represents a significant difference from PRE1.

4.4. Discussion

4.4.1 Part A – MD versus Controls

This study is novel in the description of spatial-temporal variables, lower-body angular kinematics and the metabolic cost of gait in adults with BMD and LGMD. It is also novel in the presentation of angular kinematics at the pelvis and in the transverse and frontal plane as well as the metabolic cost of gait in adults with FSHD. Adults with FSHD, BMD and LGMD walked at a slower self-selected pace, with reduced stride length and reduced cadence compared to the control group. Adults with BMD walked with a greater stride width and adults with LGMD spent a greater proportion of the stride in the stance phase and in double support than controls did. In addition, numerous kinematic gait abnormalities were evident in the MD groups compared to the controls and the oxygen cost of gait was 2 times greater in the LGMD group than the control and FSHD group.

4.4.1.1 Spatial and Temporal Variables

In agreement with most previous research in MD, self-selected gait speed was slower in all MD groups compared to controls, ranging from 26-44% slower. With regards to gait speed, the LGMD group were the most impaired followed by the BMD and subsequently the FSHD group. Slower gait speed resulted from both shorter stride lengths and reduced cadence in all MD groups. The finding of shorter stride length is in accordance with most previous gait studies in MD (Aprile et al., 2012; Iosa et al., 2007; Iosa et al., 2010; Rijken, van Engelen, de Rooy, et al., 2015; Rijken, van Engelen, Geurts, et al., 2015). Reduced cadence on the other hand is not a common finding in MD gait but has previously been reported in one study of adults

with FSHD (Iosa et al., 2010). Gait speed is an important clinical indicator of physical function and independence and offers a functional perspective on the health status of individuals (Fritz and Lusardi, 2009). In our study, gait speeds of 1.1, 1.0 and 0.8 m/s were found for the FSHD, BMD and LGMD groups, respectively, compared to 1.4 m/s in the controls. Thus, it is clear that each MD group was considerably impaired.

Stride width was greater in the BMD group, but not in the FSHD or LGMD group, compared to the controls. Previously, greater stride width has been reported in children with Duchenne MD (Sutherland et al., 1981), whilst several studies in adults with FSHD found no difference in stride width compared to controls (Iosa et al., 2010; Aprile et al., 2012; Rijken, van Engelen, Geurts, et al., 2015). It is interesting to note that as BMD is a less severe variant of Duchenne MD, gait patterns in BMD have previously been presumed to be similar to Duchenne MD. This finding provides evidence of similar gait patterns between these two populations. The greater stride width in adults with BMD may be due to a number of reasons. It may be a functional compensatory mechanism to improve lateral stability by increasing the base of support, but in the absence of an increased double support phase duration it is uncertain whether this is the cause. Alternatively, greater stride width may reflect a mechanical mechanism rather than a functional one. It may be an adaptation that occurs in response to altered trunk mechanics that are described later in this discussion. Essentially, due to an excessive lateral trunk lean towards the stance limb (qualitative observation), a wider stride may be required to ensure that the centre of mass remains within the base of support.

Despite the differences in gait speed, temporal variables were similar between the FSHD and control and BMD and control group. The LGMD group however spent 4% more time in the stance phase and 12% more time in a double support phase than the control group. This gait pattern reflects an avoidance of single support loading during gait, which may be a compensatory mechanism for reduced lateral stability during gait or alternatively it could be a mechanism for pain reduction during single limb stance.

4.4.1.2 Angular Kinematics

Kinematic gait abnormalities at the hip, knee and ankle joint have previously been reported in adults with FSHD in the sagittal plane, but gait patterns have not previously been described for adults with BMD or LGMD. The current study found numerous kinematic abnormalities that were similar between all three MD groups as well as kinematic abnormalities that were specific to the individual types of MD. Although direct associations between these kinematic abnormalities and muscle strength were not conducted as part of this study, some potential reasons behind such abnormalities are proposed.

At the level of the pelvis, greater anterior tilt was found throughout the gait cycle in both the FSHD and BMD group compared to the controls. Excessive anterior pelvic tilt has previously been reported in both adults with Myotonic MD and children with Duchenne MD (Galli et al., 2012; Doglio et al., 2011; D'Angelo et al., 2009). Whilst lower-limb gait kinematics have previously been described in adults with FSHD (Iosa et al., 2007) kinematics at the level of the pelvis have not. With regards to BMD, this finding (greater anterior tilt) supports the previously presumed notion of similar gait

abnormalities between BMD and Duchenne MD. The most likely cause of the excessive pelvic tilt in these groups is a combination of the weak hip extensor and knee flexor muscles presented in Chapter 3 and, potentially, tight hip flexor muscles that cause a forward shift in the position of the pelvis. It makes sense that the BMD group present a more severe anterior pelvic tilt than the FSHD group given the greater strength deficits found in these muscles (Chapter 3). It is interesting that the LGMD group did not present with excessive anterior pelvic tilt despite greater strength deficits in the hip extensor and knee flexor muscle groups than the FSHD group and similar strengths to the BMD group. It is possible that this is due to muscle tightness in the hip extensor and/or knee flexor muscles of individuals with LGMD, which logically would act to pull the pelvis backwards into a more neutral position despite hip extensor and knee flexor muscle weakness. This mechanism is seen in other clinical populations such as cerebral palsy (de Morais Filho et al., 2018), where surgical hamstring lengthening often results in an anterior shift of the pelvis.

An additional abnormality found at the level of the pelvis was greater external rotation of the pelvis at toe-off in all MD groups compared to controls. Pelvic rotation has not previously been measured in FSHD, but increased external pelvic rotation has been reported in children with Duchenne MD (Doglio et al., 2011). This excessive rotation may serve as an attempt to preserve stride length by gaining additional forward advancement through pelvic rotation.

At the hip joint, maximum hip extension and hip extension at toe-off were reduced in the FSHD and BMD group compared to controls. This has previously been reported in Myotonic MD (Galli et al., 2012), Duchenne MD (Sutherland et al., 1981;

Gaudreault et al., 2010) and importantly FSHD (Iosa et al., 2007). It is likely that this insufficient hip motion results from strength deficits in the hip extensor muscles in combination with the excessive anterior pelvic tilt seen in these individuals.

Abnormalities in hip motion were expected in the frontal plane for the BMD and LGMD groups, due to the strength deficits that were found in the hip abductor muscles, as reported in Chapter 3. As such, a Trendelenburg gait pattern was expected to be found in these groups. Trendelenburg gait refers to excessive pelvic drop on the contralateral side during the stance phase, which is due to hip abductor muscle weakness or impairment (Pai, 1996). This typically results in severe adduction of the hip joint throughout the stance phase. However, no difference in mean hip adduction during stance was evident in any of the MD groups compared to controls. Instead, excessive abduction of the hip joint was found during the swing phase in the BMD and LGMD groups and noticeably in Figures 4.4 and 4.5 earlier abduction of the hip joint occurred during stance. This kinematic pattern suggests that a compensated Trendelenburg gait pattern (Vroome et al., 2016) was evident in these MDs (a visual representation of this is provided in *Appendix 3.1*). That is, in order to counteract pelvic drop on the contralateral side to the stance limb, participants abducted the hip joint using a lateral trunk lean towards the stance limb, which was confirmed via video and can be observed in *Appendix 3.2*. This finding agrees with a study in children with Duchenne MD by Gaudreault et al. (2010); the only other study to previously report frontal plane hip kinematics in MD gait. Essentially, excessive adduction of the hip joint during stance is not observed in the data due to the compensatory lateral trunk lean utilised by participants.

Despite this it is still evident that the stability of the pelvis during gait is compromised in these groups.

At the knee joint, numerous gait abnormalities were evident for the MD groups compared to the control. Reduced knee flexion at initial contact and greater knee extension/hyperextension during the late swing phase, was found in both the FSHD and LGMD groups compared to controls. Furthermore, reduced maximum flexion in stance was evident in the BMD and LGMD groups compared to controls. The two former variables have not previously been reported in an FSHD population, but Iosa et al. (2007) did find reduced maximum knee flexion during stance in adults with FSHD compared to controls. Although our study contradicts this finding, as maximum knee flexion in the FSHD group did not significantly differ to controls, qualitatively the magnitude of knee flexion during stance was noticeably smaller in FSHD than controls (Figure 4.3). Importantly, the abnormalities in knee angle during stance in the BMD and LGMD groups were not as simple as a reduced magnitude of knee flexion during the loading response. Instead, there was a complete lack of knee flexion or hyperextension of the knee joint throughout the stance phase in BMD and LGMD, respectively. This kinematic pattern has previously been reported in children with Duchenne MD (D'Angelo et al., 2009). Visual examples of the knee extension/hyperextension that were observed in our study are provided in *Appendix 3.3*.

The lack of knee flexion or hyperextension during stance in the BMD and LGMD groups may be due to the knee extensor strength deficits that were presented in Chapter 3. This likely results in an inability of the knee extensors to eccentrically

control knee flexion whilst weightbearing. An extended knee position likely increases the knee extensor moment during stance through a more anterior direction of the ground reaction force relative to the knee joint, thereby creating a more stable knee position during the loading response (Gaudreault et al., 2010). However, it is unclear why the severity of this abnormality was greater in the LGMD than the BMD group, given the similarities in knee extensor and knee flexor muscle strength deficits between these groups (Chapter 3). This difference may be associated with variances in the direction and/or magnitude of the knee flexion/extension moment between the groups. Alternatively, it is possible that differences in soft tissue properties between the two MDs, such as ligament laxity or tendon stiffness, play a role in this discrepancy.

In agreement with previous studies in children with Duchenne MD (D'Angelo et al., 2009; Doglio et al., 2011; Sutherland et al., 1981), this study found that the ankle was more plantar flexed at initial contact and that dorsi flexion was limited during the swing phase (these abnormalities are defined as drop foot), in all MD groups compared to controls. Whilst reduced dorsi flexion at initial contact has previously been reported in adults with FSHD (Iosa et al., 2007), no comparison of discrete ankle kinematics to a control group in the swing phase has been undertaken. Although significant deficits in dorsi flexor MVC torque were found for each MD group (Chapter 3), the severity of drop foot between the MD groups does not mirror the severity of dorsi flexor muscle weakness (i.e. the BMD group demonstrated the least severe strength deficit in dorsi flexor MVC torque but not the least severe drop foot). Thus, it is likely that both dorsi flexor muscle strength and the presence of

plantar flexor muscle tightness/contractures influence this kinematic abnormality in MD.

4.4.1.3 Oxygen Cost

Oxygen cost during gait was 83% greater in the LGMD group than both the control and the FSHD group and, once it was normalised to lean body mass, oxygen cost was found to be double that of the control and FSHD group. Although not directly assessed in this study there are a plethora of potential reasons for the heightened oxygen cost in the LGMD group. The measure of oxygen cost accounts for gait speed and was further normalised to lean body mass. Therefore, other factors must be associated with the heightened oxygen cost in this group.

Some of the kinematic abnormalities found in this study, either in isolation or in combination, may be associated with the greater oxygen cost of gait in LGMD. Excessive movements that occur during gait may have the potential to increase the oxygen cost of gait through an increased mechanical effort. In this study greater external pelvic rotation, greater hip abduction with a lateral trunk lean and excessive hyperextension of the knee joint were found. It has previously been shown that excessive hip and pelvic motion during gait in children with spina bifida were significantly related to the oxygen cost of gait (Bare et al., 2001). Thus, it is highly likely that the increased hip abduction found within our study contributes towards the greater oxygen cost of gait in the LGMD group. In addition, previous research has demonstrated that ankle range of motion in gait has a strong negative association to energy expenditure during cerebral palsy gait (Ballaz et al., 2010). In our study, limited ankle dorsi flexion was noted in all MD groups and to the greatest

severity in the LGMD group. We proposed that this is due to dorsi flexor muscle weakness in combination with plantar flexor muscle tightness. If the latter is correct, the material properties of the Achilles tendon may also be altered, which has the potential to contribute towards the greater oxygen cost of gait. This is because tendons control the storage and release of elastic energy during movement (Lichtwark and Wilson, 2008).

Alternatively, the greater oxygen cost in LGMD may be associated with physiological mechanisms. Although muscle mass is not a potential factor as it was accounted for, the quality of muscle in LGMD may have influenced oxygen cost during gait. This is because lean muscle mass did not differ between the MD groups but the LGMD were the weakest overall (Chapter 3), signifying a reduced quality of muscle tissue in LGMD. Additionally, it may be related to excessive co-activations of antagonistic muscles in MD. This is considered as increased co-contraction of the knee flexors and knee extensors during gait has previously been shown to be associated with a greater oxygen cost of gait in elderly men (Mian et al., 2006). Although muscle activation patterns during gait have not directly been measured in adults with FSHD, BMD or LGMD, heightened co-contraction between the knee extensor and knee flexor muscles during gait has been demonstrated in children with Duchenne MD (Ropars et al., 2016).

4.4.1.4 Clinical Implications

This study demonstrates numerous kinematic abnormalities in individuals with FSHD, BMD and LGMD compared to controls. These abnormalities have numerous clinical implications including the potential for increased pain, excessive forces at

the joints, increased fall and injury risk, fatigue and psychological implications. For example, excessive anterior pelvic tilt may result in low back pain through greater stresses and loads placed on the intervertebral disks in the spine (Keller et al., 2006), and hyperextension of the knee may result in pain and damage through excessive compressive forces at the structures of the knee joint, including the posterior and anterior cruciate ligaments (Meyer et al., 2011). Furthermore, the presence of drop foot suggests that fall risk is a substantial hazard in these MD groups. In order to minimise these risks, strength training, regular stretching and physiotherapy should be a key element within the management of these conditions. In advanced cases of drop foot, the use of orthotics may be required to enable the continuation of safe ambulation. Finally, it is important to recognise that the greater oxygen cost of walking in MD, particularly in the LGMD group, likely impact levels of fatigue and therefore quality of life.

This study identified the key kinematic gait abnormalities in adults with BMD, LGMD and FSHD and alluded to the potential primary reasons for such abnormalities. Future research should seek to establish direct associations between these kinematic abnormalities and measures of muscle strength.

4.4.1.5 Conclusion

Kinematic abnormalities are evident at all lower-limb joint levels in these MD groups. Some of these abnormalities are similar between the MDs, such as reduced dorsiflexion of the ankle joint at initial contact and during the swing phase, whilst some abnormalities were specific to individual types of MD, such as hyperextension of the knee joint in the LGMD group. It is clear that such gait abnormalities may have

a huge impact on physical function, daily life and independence. Therefore, resistance training that is designed to target these primary gait deviations may be advantageous in these individuals.

4.4.2 Part B -Effects of RT

This is the first study to examine the effect of a RT programme on key gait parameters in individuals with MD. Several changes in spatial and temporal variables of gait were found after completion of the RT programme including increased self-selected gait speed, stride length and cadence. In addition, numerous kinematic parameters were improved at the hip, knee and ankle joint. Despite these changes, no difference in oxygen cost post completion of the RT programme was evident.

4.4.2.1 Spatial and Temporal Variables

Gait speed increased by 8% from immediately before to after completion of the RT programme, with stable values in the control period. Even though this increase is relatively small, the ability to ambulate at a speed closer to control participants may influence daily life considerably, particularly as this may continue to rise with sustained participation in RT. Furthermore, this percentage increase in gait speed is similar to the 9% increase found in adults with multiple sclerosis following completion of a 12-week RT programme (Kierkegaard et al., 2016). The increase in gait speed came from a 4% increase in both stride length and cadence but no change in the temporal parameters of gait were found. However as demonstrated in part A of this study, differences in temporal variables were evident in one of the three types of MD only; stance duration and double support time were increased in

LGMD. As the effect of RT was not measured in each type of MD individually, it is unknown whether differences in temporal parameters of gait may have occurred with separate analysis.

4.4.2.2 Angular Kinematics

Numerous changes in the hip, knee and ankle kinematics were found post completion of the RT programme. The root mean square differences, which provides an insight into the global change in sagittal plane joint angles, were greatest in the hip joint during the swing phase, the knee joint during the stance phase and the ankle joint during the stance phase. In addition, numerous discrete kinematic parameters were improved post completion of the RT programme, compared to stable values in the initial control period. Notably, the discrete variables in which significant differences were found displayed sufficient statistical power, but a few of the variables that did not differ were found to have a low retrospective statistical power (between .05 and .27). Thus, it is viable that a greater sample size would reveal additional differences alongside the ones found in this study.

No change in any of the discrete variables at the pelvis were evident post the RT programme. At the hip however, a 1.3° increase in mean hip adduction angle during the stance phase was found. This brought the hip adduction angle closer to that of the control group and likely occurred in combination with a reduction in the compensatory trunk lean that was discussed in Part A of this study. This finding signifies an improved stability at the hip joint and pelvis and is most likely associated

with the increase in hip abduction muscle strength presented in Chapter 3 of this thesis.

Several improvements in the kinematics of the knee were found post completion of the RT programme. Knee angle at initial contact was unchanged in the control period but increased by 2.5° to a more flexed position post RT. In addition, the maximum knee flexion angle in the stance phase increased by 2.3° post RT. These changes occurred in the opposite direction those previously found in individuals with cerebral palsy post RT (Engsberg et al., 2006) but the adaptations reported in both studies are relative to the initial impairments. These being a reduction in excessive crouch gait in cerebral palsy and an increase in insufficient knee flexion in MD. Importantly, the adaptation in knee angle found in our study shifted the flexion angle time curve closer to that of the control population and demonstrates an improved loading response at the knee joint during stance. Although no significant increase in the knee extensor MVC torque was found in this group post RT (Chapter 3) there was a clear trend for an increase ($p = .08$). Additionally, completion of the RT programme may have improved confidence in gait, such that the increase in knee flexion angle may have occurred as a conscious adaptation due to improved confidence in the knee extensors to eccentrically control this motion. Changes in knee flexion angle were also found in the swing phase of the gait cycle. Maximum knee flexion increased by 3° to an angle comparable to the control group. This is likely a result of the 13% increase in knee flexor MVC torque post completion of the RT programme. Regarding maximum knee extension or hyperextension, significant reductions were found in both the stance and terminal swing phase of 2.5° and 2.6°, respectively, post RT. The latter finding signifies an improved ability of the knee

flexor muscles to control and slow down the advancing lower leg during terminal swing and therefore likely results from the increase in knee flexor MVC torque found in this group (Chapter 3).

At the ankle joint, an increase in dorsiflexion of 2.2° at initial contact was found after completion of the RT programme. This increase demonstrates a movement towards a more dorsi flexed position at ground contact, similar to the control group. In addition, the maximum dorsiflexion angle during swing and the mean angle during the late swing phase increased by 2.3° and 1.9°. respectively. The latter finding agrees with a previous investigation into RT in community dwelling elderly women (Cao et al., 2007), who reported a 4° increase in peak dorsiflexion angle during the swing phase. This adaptation is important as it may reduce the risk of falls in the current population. This is suggested as an increase in dorsiflexion during the swing phase will increase the clearance distance between the ground and the foot and subsequently lower the potential for a trip to occur. In fact, the frequency of falls was reduced by almost half (47%; *Appendix 3.4*) post completion of the RT programme. These gait adaptations parallel the 28% increase in dorsiflexion MVC torque presented in Chapter 3.

Kinematic adaptations in ankle position were also evident in the transverse plane. Inversion at initial contact increased by 9.8° and eversion at toe-off increased by 8.9° post the RT programme, thereby bringing the ankle kinematics closer to that of the control group. The primary dorsiflexor muscles are also involved in these movements and therefore it is likely that the increase in dorsiflexion MVC torque contributed towards these adaptations.

Additional analysis was completed on the knee kinematics in the sagittal plane in those participants who presented with severe hyperextension of the knee joint in stance, and on the sagittal plane ankle kinematics in those participants who presented with severe foot drop in the swing phase. Both of these parameters were primary gait abnormalities rather than compensatory mechanisms. This analysis was undertaken to provide an insight into the effect of RT on those individuals with the most severe gait abnormalities.

The additional analysis completed on those participants categorised as having knee hyperextension, found that knee angle at initial contact increased by 3.9° from immediately before to post completion of the RT programme. This increase shifted the knee angle from a negative angle (knee extension) to a slightly positive angle (knee flexion). Additionally, the maximum hyperextension that occurred during mid-stance was reduced by 4.1° from before to after the RT programme, with no difference between PRE1 and PRE2. Although hyperextension of the knee remained evident in mid-stance, the severity of this abnormality was reduced considerably. A photographic example of this is presented in *Appendix 3.5*. This reduction may be due to changes in the magnitude of the knee flexor/extensor moment. Alternatively, the reduction in knee hyperextension may be caused by adaptations in the material properties of the internal structures at the knee, such as ligament laxity, as a result of RT. This is suggested as previous research has demonstrated adaptations in the material properties of the patella tendon post 14 weeks' RT in elderly individuals (Reeves et al., 2003).

The additional analysis that was completed on participants who demonstrated severe foot drop showed that ankle angle at initial contact increased by 1.9°, and the mean ankle angle during the swing phase increased by 2.4°. These adaptations demonstrate an increased dorsiflexion of the ankle joint as it contacts the ground and moves throughout the terminal swing phase. It is most likely that these adaptations occurred as a result of the increase in dorsiflexor MVC torque presented in Chapter 3. As discussed in part A of this study, limited dorsiflexion at the ankle during swing is likely a combination of weakness in the dorsiflexor muscles and reduced range of motion due to muscle tightness or contractures. Therefore, alongside the increase in MVC torque the exercises completed within the RT programme may have also improved the range of motion at the ankle joint, thereby allowing a greater dorsiflexion angle to be achieved.

It is clear that kinematic gait abnormalities in MD can be improved through the use of RT. In addition, it is important to note that in cases of severe gait impairment the positive effects of RT appear to be even larger, at least for hyperextension of the knee joint and foot drop throughout the swing phase.

4.4.2.3 Oxygen Cost

Despite the changes in gait kinematics with RT found in this study, no change in the oxygen cost of gait was found. Whilst this is surprising there are various potential explanations for this outcome. There is a strong possibility that participants who used walking aids relied less on these aids post completion of the RT programme, and therefore increased weight acceptance on the legs during gait and in turn, oxygen cost. Although this would not reduce the oxygen cost of gait, it would

demonstrate a more independent gait. Additionally, alterations in other biomechanical factors may have occurred post RT which influenced the oxygen cost of gait. Examples include alterations in muscle co-contraction, energy transfer between the segments and energy storage in the tendons. It is also important to consider that the mode of exercise utilised in our study was focused on increasing muscle strength rather than achieving cardiorespiratory adaptations. With this in mind, future exercise interventions aimed at improving the oxygen cost of gait in MD may benefit from the addition of an aerobic element to the training programme. Importantly, the oxygen cost of gait was no worse post RT in our study. Walking is a complex skill, so in order to see improvements in oxygen cost it may be necessary to provide guidance alongside RT. That is, once muscle strength has improved, gait re-training may be a useful technique to assist individuals to walk more economically.

4.4.2.4 Clinical Implication

The implication of these findings is that RT is a practical option to help maintain and improve walking ability in adults living with MD. As an intervention, RT has the potential to improve walking speed and reduce the risk of pain, stress on the joints and fall risk during gait, all of which are important in everyday life and towards the maintenance of physical independence.

4.4.2.5 Limitations

Although this study examined the lower-limb gait impairments in individuals with MD, the plug-in-gait model does not provide detailed data on the kinematics in the foot (Carty et al., 2015). This is because the model assumes the foot to be one rigid

segment (Davis et al., 1991). Therefore, it is unknown whether abnormal motion in the foot during gait is evident in individuals with FSHD, BMD or LGMD. Future research would benefit from applying a multi segment foot model alongside lower-body models in order to assess foot motion in greater detail, such as the Oxford Foot Model (Carsona et al., 2001).

It is clear that RT results in changes to some of the lower-limb kinematics of gait in MD, but the causes behind these changes are unknown. The next chapter will examine the effect of RT on the kinetic parameters of gait in these individuals.

4.4.2.6 Conclusion

In conclusion, this is the first study to demonstrate positive effects of a 12-week RT programme on a number of kinematic impairments in adults with FSHD, BMD and LGMD. Improvements included increased gait speed, stride length and cadence, increased knee flexion at initial contact and during the loading response, increased knee flexion during the swing phase, a reduction in the severity of hyperextension during the stance phase, increased dorsiflexion at initial contact and during the swing phase and increased ankle inversion at initial contact and eversion at toe-off. Overall, RT is an innovative approach to maintaining ambulation in adults with FSHD, BMD and LGMD, particularly for those with more severe gait abnormalities as the improvements observed in these individuals were greater.

Chapter 5

**Influence of resistance training on the
kinetics of gait in adults with
Facioscapulohumeral, Limb-girdle and
Becker muscular dystrophy**

5.1 Introduction

Muscular Dystrophies (MD) are inherited disorders with condition specific manifestations, yet they are all characterised by progressive muscle deterioration and weakness (Mercuri and Muntoni, 2013). This muscle weakness results in progressive disability and impaired physical function and with those, a reduction in physical independence (Huml, 2015).

The severity of MD varies both within and between the different types of the condition. Boys with Duchenne MD become wheelchair bound by adolescence (Bushby et al., 2010), whilst other types of MD may not surface until adulthood and may never require the use of a wheelchair (Mercuri and Muntoni, 2013). FSHD, BMD and LGMD are types of MD that fit the latter description. These types of MD are less severe than Duchenne MD (Emery, 2002) and are considered clinically to remain ambulatory until at least the second or third decade of life (Huml, 2015), although precise measures of age at loss of ambulation are not available.

5.1.1 Part A

In clinical environments it is well recognised that walking is impaired in adults with FSHD, BMD and LGMD, with the potential for individuals to completely lose the ability to walk (Emery, 2002; Huml, 2015). *Chapters 3 and 4* of this thesis present evidence of impaired walking in these populations compared to a matched control group. As such, those adults who remain ambulatory walk slower and experience debilitating kinematic gait abnormalities, such as a lack of knee flexion or even hyper-extension of the knee joint during loading in the stance phase and limited dorsi flexion of the ankle at initial contact and throughout the swing phase, to name

a few. Whilst spatial and temporal variables and joint kinematic profiles describe the nature of movement abnormalities in gait, kinetic variables offer an insight into the causes behind gait abnormalities. However, very few studies of lower-limb joint kinetics of gait have been undertaken in MD, with the majority conducted in children with Duchenne MD (D'Angelo et al., 2009; Gaudreault et al., 2009; Gaudreault et al., 2010).

Three published studies have compared the gait and lower-limb joint kinetics of individuals with Duchenne MD to control groups. Abnormalities in joint powers, joint moments and ground reaction forces have been reported. Concerning joint powers, lower maximum plantar flexion power generation in the stance phase was consistently reported (D'Angelo et al., 2009; Gaudreault et al., 2009; Gaudreault et al., 2010), along with lower hip extensor generation power during the stance phase, lower hip flexor generation power at toe-off (Gaudreault et al., 2010), and lower maximum knee extensor absorption power at toe-off (Gaudreault et al., 2010), in children with Duchenne MD compared to controls.

Joint moments and ground reaction forces have also been found to differ in children with Duchenne MD compared to control groups. D'Angelo et al. (2009) described a knee extensor moment over almost the entire stance phase in children with Duchenne MD, compared to an initial extensor moment followed by a flexor moment in the control group, although statistical analysis of this difference was not undertaken. Similarly, Gaudreault et al. (2010) found greater peak knee extensor moments in the stance phase in Duchenne MD than controls. In addition, Gaudreault et al. (2010) reported a smaller hip flexor moment in the early stance

phase, a smaller hip extension moment at toe-off and a smaller plantar flexor moment in stance, in Duchenne MD compared to controls. Furthermore, peak ground reaction forces were smaller in the vertical, posterior and anterior direction compared to self-selected walking in a control group, but no differences in these variables were evident when controls walked at a slow pace (Gaudreault et al., 2010). On the other hand, medial peak forces were significantly higher in the Duchenne MD group than control group, regardless of walking pace. These reported kinetic gait abnormalities however cannot be presumed to be the same in ambulatory adults with other forms of MD, as Duchenne MD is highly disabling from the very early years of life (Emery, 2002). In addition, differences in lower-limb muscle weakness distribution between adults with FSHD, BMD and LGMD (shown in *Chapter 3*) may result in the use of different compensatory mechanisms during gait between these conditions.

In the MDs specific to this study, two studies have reported lower-limb joint moments and/or powers during gait in adults with FSHD (Rijken, van Engelen, de Rooy, et al., 2015; Iosa et al., 2007) but only one of those compared gait to a control population (Iosa et al., 2007). To date there appear to be no published studies that have measured the kinetics of gait in humans with LGMD or BMD and ground reaction forces remain un-reported in FSHD. Iosa et al. (2007) found no significant differences in the sagittal plane joint moments at the hip, knee or ankle joint during level walking in adults with FSHD compared to a control group. However, the study was limited to mild-moderate presentations of FSHD. This was evidenced as no participants required the use of walking aids and 5 of the 12 participants were categorised as exhibiting no pelvic or lower-limb muscle weakness through a score

of 5 out of a possible 5 on manual muscle tests (5 = movement through a full range of motion against gravity and able to hold against resistance).

Descriptions of ground reaction forces and joint powers during gait in FSHD, BMD and LGMD compared to a control population are un-reported. In addition, descriptions of joint moments in FSHD are limited to the sagittal plane and adults with mild-moderate presentations of the condition. Therefore, the first aim of this study is to describe the ground reaction forces, joint moments and joint powers during gait in adults with FSHD, LGMD and BMD, compared to a control group matched for age, stature and body mass.

5.1.2 Part B

In addition to describing the joint kinetics during gait in adults with FSHD, BMD and LGMD, this study is interested in the effectiveness of RT as an intervention for impaired gait in MD. RT is an exercise modality that has previously altered measures of joint kinematics and joint kinetics during gait in numerous populations that exhibit gait abnormalities. In individuals with multiple sclerosis, RT resulted in increased walking speeds and step lengths, along with reductions in double support time (Manca et al., 2017; Kierkegaard et al., 2016; Gutierrez et al., 2005). In children with cerebral palsy, a programme of RT increased stride length, reduced cadence and increased the maximum ankle power generation during the late stance phase (Eek et al., 2008). In addition, Chapter 4 of this thesis demonstrates that a programme of RT in adults with FSHD, BMD and LGMD resulted in increased self-selected gait speed and adaptations to numerous kinematic abnormalities, such as increased knee flexion during stance, increased knee flexion in swing, increased

dorsi flexion at initial contact and during the swing phase and a reduction in the severity of hyper-extension at the knee joint during stance. Whilst gait speed and kinematic profiles provide information on the nature of gait adaptations with RT, they provide little insight into the kinetics behind these adaptations. As such, in order to fully assess the influence of RT on gait in MD, the kinetics of gait should also be analysed.

Thus, the second aim of this study is to investigate the influence of a 12-week, twice a week, lower-body RT programme on ground reaction forces, joint moments and joint powers during gait in a group of ambulatory adults with MD (FSHD, BMD and LGMD).

5.2 Method

5.2.1 Participants & Study Design

The experimental design for this study is presented in two parts. Part A presents group comparisons between adults with FSHD (9), BMD (7), LGMD (6) and a group of 10 control adults matched in age, stature and body mass.

Part B is a within-participant design, involving a group of 17 adults with MD, inclusive of FSHD (6), BMD (5) and LGMD (6). Data were collected at three time points: PRE1 (before a 12-week control period), PRE2 (immediately after the 12-week control period) and POST (immediately after a 12-week RT programme). All 17 MD participants completed a 12-week, twice a week, RT programme.

Detailed descriptions of the study design, participants and RT programme are provided *in Chapter 3.2 Method*.

Manchester Metropolitan University Ethics Committee granted ethical approval and all participants provided written informed consent after which data collection took place at Manchester Metropolitan University on all occasions.

5.2.2 Procedures

Testing procedures and data collection for anthropometric, body composition and 3D gait analysis measures are provided in *Chapter 3.2 Method*.

5.2.3 Data Processing and Analysis

Unless otherwise stated, all data are presented as means and standard deviations for the control group, FSHD, BMD and LGMD group in part A, and for the combined MD group at each time point (PRE1, PRE2 and POST) in part B.

5.2.3.1 Lower-Limb Joint Kinetics

Processing of each walking trial was completed using Vicon Nexus software. The plug-in gait marker set was used as a kinematic model to obtain lower-limb joint kinematics, centre of mass kinematics using the inertial properties described by Dempster (Dempster, 1995) and lower-limb kinetics. The markers were reconstructed and then the marker trajectories were labelled. Gait events (initial contact and toe-off) were determined via vertical ground reaction forces on the dominant side with force plate contact, using a force threshold of 20 N. On the non-dominant side or without force platform contact, gait events were determined manually via frame by frame visual inspection. For each trial, the stride that occurred in the centre of the capture volume over the force platform was selected for analysis. Gaps (≤ 10 frames) in the marker trajectories were filled using a cubic spline interpolation. The dynamic plug-in gait model (Vicon, 2010) was then applied to each walking trial to calculate marker trajectories, joint kinematics and joint kinetics. Data were smoothed using a low-pass 4th order Butterworth filter, with a cut off frequency of 6 Hz.

Joint moments and joint powers (joint moment x angular velocity) were calculated via inverse dynamics, using the joint kinematic data, ground reaction force data and segment inertial data described by Dempster (Dempster, 1995). Kinetic data were normalised to body mass (kg).

Joint moments are presented as net external joint moments as Vicon calculates joint moments using the local coordinate frame of the distal segment and exports external joint moments (Vicon, 2010). Vicon Plug-in Gait specifies the following

conventions for external joint moments (ankle: dorsiflexor, adduction and internal rotation moment = positive; knee: flexion, varus and internal rotation moment = positive and hip: flexion, adduction and internal rotation moment = positive) (Vicon, 2016). This convention is often used in clinical gait analysis (Baker, 2013; Dicharry, 2010). The net external moment is produced by external forces acting on the joint (Robertson et al., 2013). For example, during the stance phase of gait a net external knee flexion moment acts on the knee joint, which is counteracted by a net internal knee extensor moment produced mainly by the quadriceps muscles. Another example during midstance is when the ankle is in dorsiflexion and an external dorsiflexor moment acts to dorsiflex the ankle, which is counteracted by a net internal plantarflexor moment to maintain the position of the ankle at that time (Dicharry, 2010).

Ground reaction forces and lower-limb joint external moments and powers from the dominant leg were averaged across four trials and used for further analysis. Data were time normalised to 100 data points using a cubic spline interpolation method in Microsoft Excel, representing initial contact at 0% and the following foot contact at 100%.

The selection of discrete dependant variables was guided by Beneditti et al. (1998). Ensemble average graphs for ground reaction forces, joint moments of the hip, knee and ankle and joint powers of the hip knee and ankle were produced in Microsoft Excel and are presented in the results section, along with the mean \pm standard deviation for each discrete variable. Statistical analysis was completed on all discrete variables. The discrete ground reaction force variables and the joint

moment and joint power variables chosen for analysis are presented in Table 5.1 in addition to visual representations of each discrete ground reaction force and joint power variable in Figure 5.1.

The root mean square difference in joint moments between each MD group and the control group and between the time points of PRE1 compared to PRE2 and PRE2 compared to POST were calculated at the hip, knee and ankle in the sagittal plane. This was calculated as a descriptive measure of the global difference in joint moments during gait.

5.2.3.2 Additional Kinetic Analysis

Additional analysis was completed in part B of this study on a sub-group of MD participants who in Chapter 4, exhibited excessive hyper-extension of the knee joint (defined in the Chapter 4). This was done to establish the effect of RT on the knee moment in cases of severe knee hyperextension during the stance phase. Eight participants were included in this sub-group.

Table 5.1: Numerical system for discrete variables of ground reaction forces (GRF), external joint moments and joint powers. Max = maximum, mom = moment, gen = generation, abs = absorption.

GRF		Hip	
Fz1	Max. vertical force in loading	HM1	Max. hip flexor mom. in stance
Fz2	Min. vertical force in mid-stance	HM2	Max. hip extensor mom. in stance
Fz3	Max. vertical force in terminal stance	HM3	1 st Max. hip adductor mom. in stance
Fy1	Max. braking force	HM4	2 nd Max. hip adductor mom. in stance
Fy2	Max. propulsive force	HM5	Max. external hip rotation mom.
Fx1	Max. lateral force in loading	HM6	Max. internal hip rotation mom.
Fx2	Max. medial force in mid-stance	Hp1	Max. hip extensor gen. power
Fx3	Max. medial force in terminal stance	Hp2	Max. hip flexor abs. power
		Hp3	Max. hip flexor gen. power
Knee		Ankle	
KM1	1 st Max. extension mom. in stance	AM1	Max. plantarflexion mom. in stance
KM2	Max. flexor mom. in stance	AM2	Max. dorsiflexor mom. in stance
KM3	2 nd Max. extension mom. in stance	AM3	Max. ankle eversion mom.
KM4	1 st Max. varus mom. in stance	AM4	Max. ankle inversion mom.
KM5	2 nd Max. knee varus mom. in stance	Ap1	Max. plantarflexion abs. power
		Ap2	Max. plantarflexion gen. power
Kp1	Max. knee extension abs. power		
Kp2	Max. knee extension gen. power		
Kp3	Max. knee extension abs. power		
Kp4	Max. knee flexion abs. power		

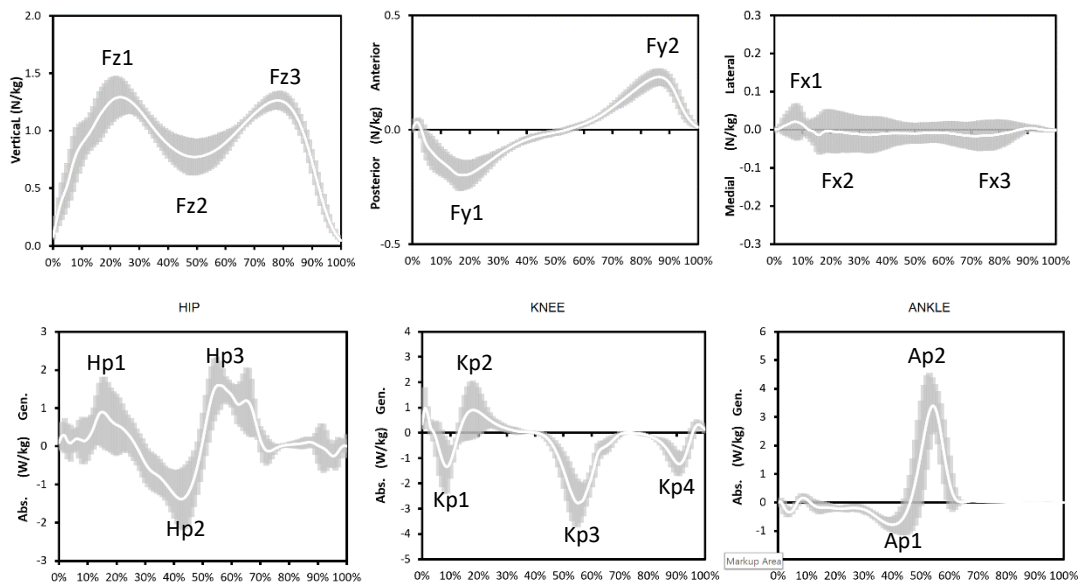


Figure 5.1: Visual example of each discrete ground reaction force and joint power variables as described in Table 5.1.

5.2.4 Statistical Analysis

All statistical analysis were completed using IBM SPSS Statistics 25 software. The critical level of significance was set at $p \leq .05$.

5.2.4.1 Part A -MD versus Controls

Data were compared between the FSHD, BMD, LGMD and control group. All data were checked against the parametric assumptions and data that satisfied these assumptions were assessed using a one-way ANOVA, with least significant difference post hoc pairwise comparisons where required. The following variables were non-parametric: Fz1, Fz2, Fy1, Fx1, HP1, KP1, KP2, KP3, KP4, AP2, HM5, KM5, AM1 and AM3. In these cases, Kruskal Wallis tests were conducted with Mann-Whitney U post-hoc comparisons (least significant difference) where necessary.

5.2.4.2 Part B - Effects of RT

Data were compared between the time points (PRE1, PRE2 and POST) in the MD group. All data were checked against the parametric assumptions and data that satisfied these assumptions were assessed using a repeated measures ANOVA. If the data did not pass Mauchly's test of sphericity ($P < .05$), a Greenhouse-Geisser correction was applied. From the ANOVA, both the retrospective observed power and the effect size, calculated as partial eta squared (η^2), were reported. Post hoc analysis was completed using the least significant difference pairwise comparisons where appropriate. Data that were non-parametric (Fz1, Fz2, Fz3, Fx1, Fx3, Hp1, Hp2, Kp1, Kp2, Kp3, Kp4, Ap1, HM1, HM5, KM2, KM5, AM2 and AM3) were analysed using a Friedman's ANOVA, followed by post-hoc analysis using Wilcoxon-signed rank tests (least significant difference) where required. Data from the sub-group of participants that demonstrated hyper-extension of the knee joint in Chapter 4 were checked for parametricity and subsequently analysed as described above.

5.3 Results

5.3.1 Part A – MD versus Controls

5.3.1.1 Participant Characteristics

There was no differences between the groups for age, body mass, stature or lean body mass ($p > .05$; Table 5.2). Details of walking aid use for each participant is provided in Table 4.4 in *Chapter 4*.

Table 5.2: Mean \pm standard deviation participant characteristics in the control (CTRL), FSHD, BMD and LGMD groups.

	CTRL	FSHD	BMD	LGMD
n	10	9	7	6
Age (years)	46.8 \pm 10.1	46.7 \pm 11.2	42.1 \pm 7.6	47.3 \pm 11.3
Body mass (kg)	79.4 \pm 12.3	88.2 \pm 18.4	93.0 \pm 16.7	82.0 \pm 19.4
Stature (cm)	174.4 \pm 7.5	181.4 \pm 6.3	179.9 \pm 9.4	170.9 \pm 9.0
Lean body mass (kg)	56.1 \pm 11.7	60.8 \pm 13.9	62.0 \pm 6.9	54.0 \pm 15.4

5.3.1.2 Ground Reaction Forces

Ground reaction forces in the vertical, anterior-posterior and medial-lateral direction during the stance phase of the gait cycle are presented as ensemble averages for the FSHD (blue), BMD (red) and LGMD (green) group in Figure 5.2. Discrete variables for the control, FSHD, BMD and LGMD group are presented in Table 5.3.

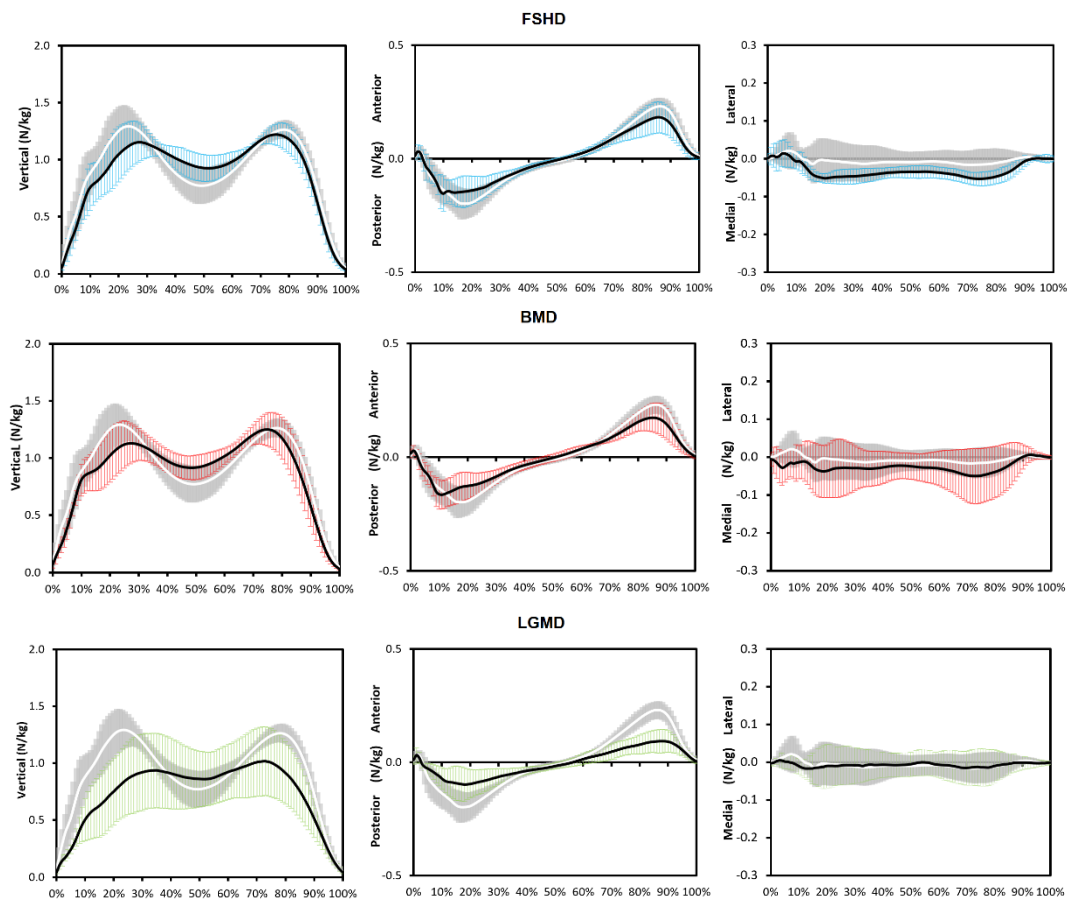


Figure 5.2: Vertical (left), anterior-posterior (middle) and medial-lateral (right) ground reaction force during the stance phase. The white line and grey band represents the control group mean ± 1 standard deviation, and the black line and the coloured band represents the FSHD (blue), BMD (red) or LGMD (green) group mean ± 1 standard deviation. On the x-axis, 0% represents initial contact and 100% represents toe-off.

Table 5.3: Mean \pm standard deviation of discrete ground reaction force variables (N/kg). * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
Fz1 (N/kg)	1.32 \pm 0.16	1.21 \pm 0.14*	1.18 \pm 0.16*	0.97 \pm 0.35*
Fz2 (N/kg)	0.77 \pm 0.16	0.91 \pm 0.10	0.91 \pm 0.10	0.83 \pm 0.29
Fz3 (N/kg)	1.27 \pm 0.09	1.23 \pm 0.09	1.26 \pm 0.15	1.03 \pm 0.30*
Fy1 (N/kg)	-0.20 \pm 0.07	-0.17 \pm 0.08	-0.17 \pm 0.06	-0.11 \pm 0.07
Fy2 (N/kg)	0.23 \pm 0.04	0.19 \pm 0.07	0.18 \pm 0.06	0.10 \pm 0.05*
Fx1 (N/kg)	0.04 \pm 0.03	0.04 \pm 0.06	0.02 \pm 0.04	0.02 \pm 0.01
Fx2 (N/kg)	-0.05 \pm 0.03	-0.06 \pm 0.01	-0.05 \pm 0.05	-0.04 \pm 0.03
Fx3 (N/kg)	-0.03 \pm 0.02	-0.06 \pm 0.02	-0.07 \pm 0.04*	-0.03 \pm 0.02

Key: Fz1= Max. vertical force in loading, Fz2 = Min. vertical force in mid-stance, Fz3 = Max. vertical force in terminal stance, Fy1 = Max. braking force, Fy2 = Max. propulsive force, Fx1 = Max. lateral force in loading, Fx2 = Max. medial force in mid-stance, Fx3 = Max. medial force in terminal stance.

A main effect of group was found in the max. vertical force in loading, max. vertical force in terminal stance, max. propulsive force, and max. medial force in terminal stance ($p < .05$).

No main effect of group was found for min. vertical force in mid-stance, max. braking force, max. lateral force in loading or max medial force in mid-stance ($p > .05$).

Post hoc tests showed that the max. vertical force in loading was 8.3% smaller in FSHD ($p \leq .01$), 10.6% smaller in the BMD ($p < .05$) and 26.5% smaller in the LGMD group ($p \leq .01$) compared to controls.

Post hoc tests showed that max. vertical force in terminal stance did not significantly differ between FSHD and controls or BMD and controls ($p > .05$) but that it was 18.9% smaller in LGMD ($p \leq .01$) compared to controls.

Post hoc tests showed that max. propulsive force did not differ between FSHD and controls or BMD and controls ($p = .07$) but that it was 91.9% smaller in the LGMD group compared to the control group ($p \leq .001$).

Post hoc tests showed that max. medial force in terminal stance did not differ between the controls and FSHD or controls and LGMD ($p > .05$) but that it was 13% greater in the BMD group compared to the controls ($p \leq .01$).

5.3.1.3 External Joint Moments

External joint moments at the hip, knee and ankle joint in the sagittal, frontal and transverse planes during the gait cycle are presented as ensemble averages for the FSHD, BMD and LGMD group in Figures 5.3, 5.4 and 5.5.

FSHD

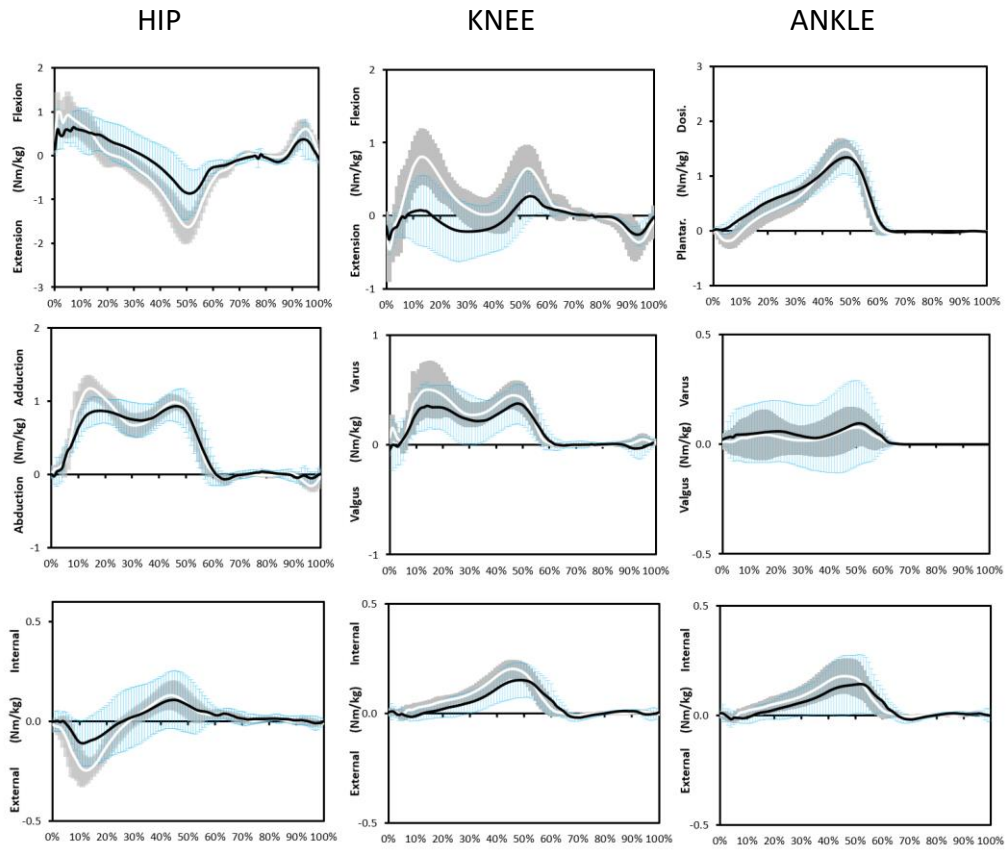


Figure 5.3: Hip, knee and ankle external moment during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents the control group mean ± 1 standard deviation, and the black line and the blue band represents the FSHD group mean ± 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

BMD

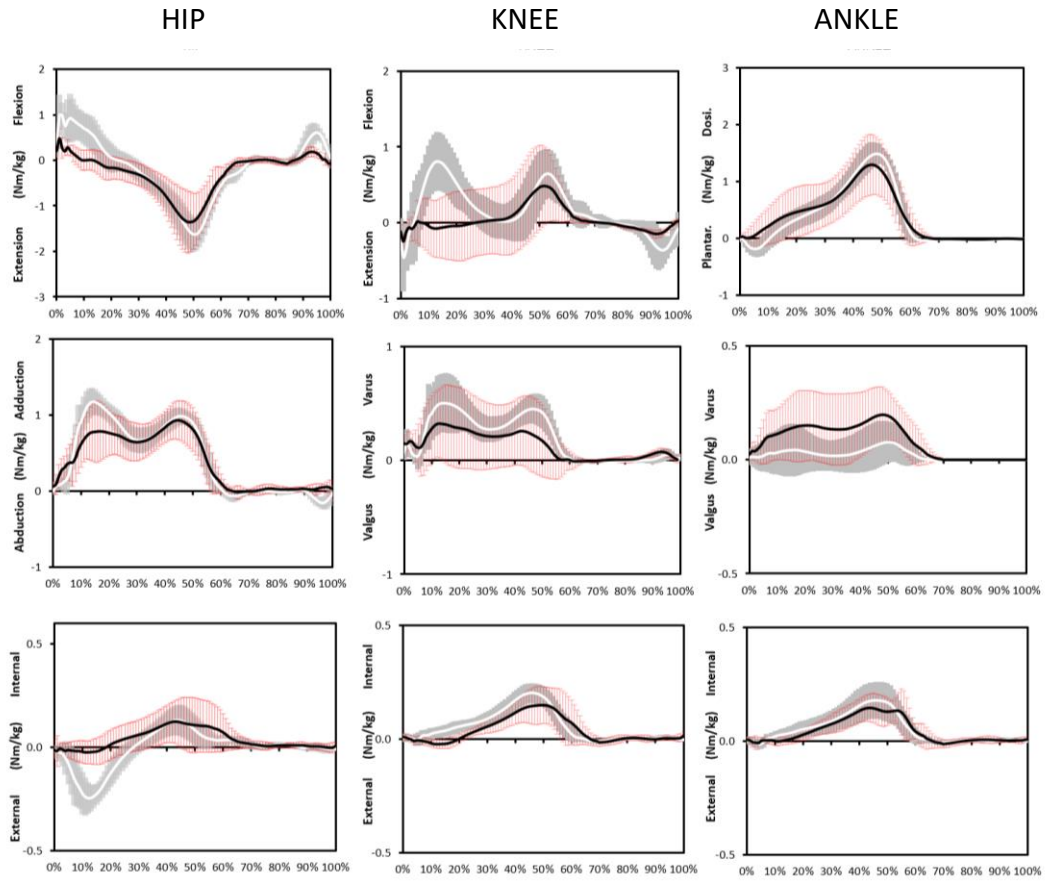


Figure 5.4: Hip, knee and ankle external moment during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents the control group mean \pm 1 standard deviation, and the black line and the red band represents the BMD group mean \pm 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

LGMD

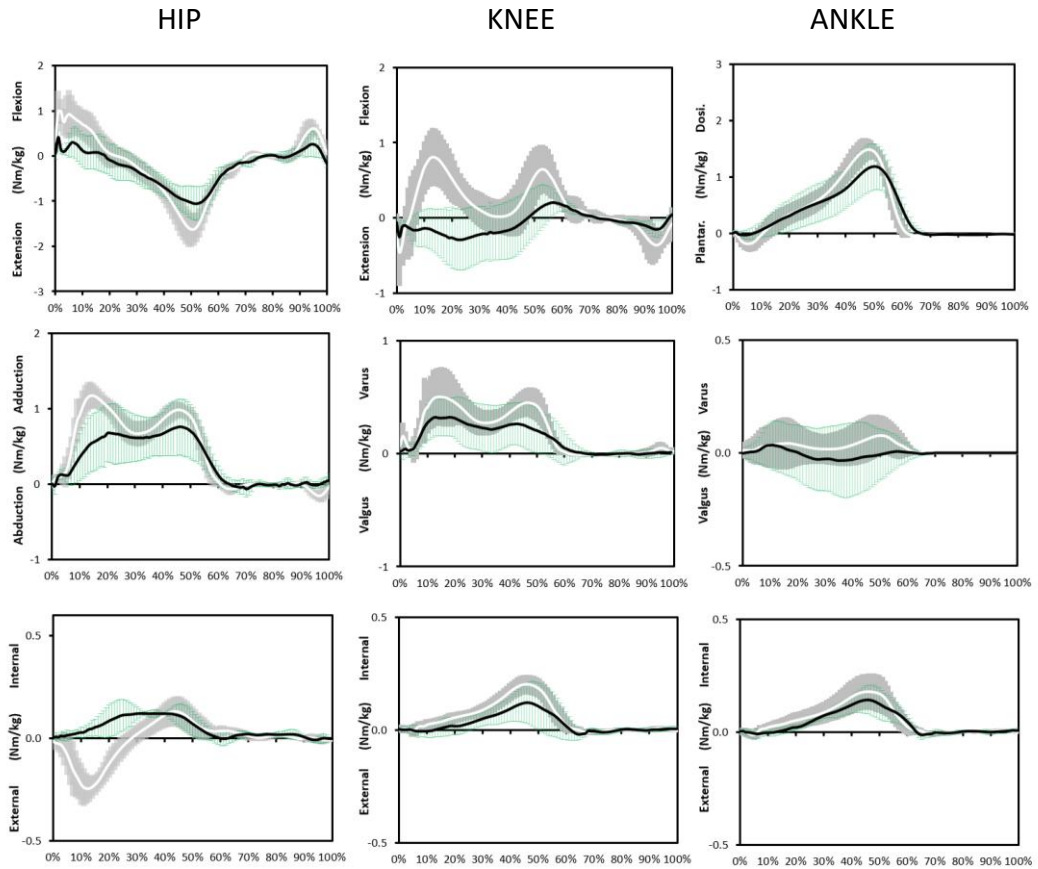


Figure 5.5: Hip, knee and ankle external moment during the gait cycle in the sagittal (top row), frontal (middle row) and transverse (bottom row) planes. The white line and grey band represents the control group mean ± 1 standard deviation, and the black line and the green band represents the LGMD group mean ± 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

The root mean square differences in the sagittal plane hip, knee and ankle joint external moments compared to the control group are presented in Table 5.4.

Table 5.4: Root mean square difference in joint moment over the gait cycle and during the stance phase compared to the control group.

	FSHD	BMD	LGMD
Hip (Nm/kg)			
Gait cycle	0.28	0.22	0.22
Stance phase	0.37	0.26	0.27
Knee (Nm/kg)			
Gait cycle	0.24	0.19	0.29
Stance phase	0.34	0.25	0.41
Ankle (Nm/kg)			
Gait cycle	0.09	0.09	0.10
Stance phase	0.14	0.13	0.15

Discrete variables for the joint moments at the hip, knee and ankle for each group are presented in Table 5.5, 5.6 and 5.7, respectively.

External Hip Moments

Table 5.5: Mean \pm standard deviation of discrete external moments (Nm/kg) at the hip during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
HM1 (Nm/kg)	1.25 \pm 0.40	0.97 \pm 0.39	0.54 \pm 0.16*	0.54 \pm 0.28*
HM2 (Nm/kg)	-1.67 \pm 0.38	-0.98 \pm 0.53*	-1.43 \pm 1.64	-1.12 \pm 0.30*
HM3 (Nm/kg)	1.18 \pm 0.16	0.92 \pm 0.26*	0.96 \pm 0.32	0.73 \pm 0.34*
HM4 (Nm/kg)	0.97 \pm 0.1	0.98 \pm 0.23	0.95 \pm 0.25	0.79 \pm 0.36
HM5 (Nm/kg)	-0.27 \pm 0.08	-0.16 \pm 0.11*	-0.07 \pm 0.07*	-0.02 \pm 0.01*
HM6 (Nm/kg)	0.14 \pm 0.06	0.16 \pm 0.07	0.15 \pm 0.11	0.10 \pm 0.07

Key: HM1 = Max. hip flexor moment in stance, HM2 = Max. hip extensor moment in stance, HM3 = 1st Max. hip adductor moment in stance, HM4 = 2nd Max. hip adductor moment in stance, HM5 = Max. external hip rotation moment, HM6 = Max. internal hip rotation moment.

There was a main effect of group on the max. hip flexor moment in stance, max. hip extensor moment in stance, 1st max. hip adductor moment in stance and max. external hip rotation moment in stance ($p < .05$). No main effect of time was found at any other variables at the hip ($p > .05$).

Post hoc tests showed that the max. hip flexor moment in stance did not differ between the control and FSHD group ($p = .08$) but that it was 41.3% smaller in the BMD ($p \leq .01$) and 32.9% smaller in the LGMD group ($p \leq .05$) compared to the control group, respectively.

Post hoc tests showed that the max. hip extensor moment in stance did not differ between the control and BMD group ($p > .05$) but that it was 41.3% smaller in the FSHD ($p \leq .01$) and 32.9% smaller in the LGMD group ($p \leq .01$) compared to the control group, respectively.

Post hoc tests showed that the 1st max. hip adductor moment in stance did not differ between the BMD and control group ($p > .05$) but was 22.0% smaller in the FSHD group compared to the control ($p < .05$) and 38.1% smaller in the LGMD group than the control ($p < .05$).

Post hoc tests showed that max. external hip rotation moment in stance was reduced in the FSHD, BMD and LGMD group compared to the control group ($p < .05$) by 40.7%, 74.0% and 92.6%, respectively.

External Knee Moments

Table 5.6: Mean \pm standard deviation of discrete external moments (Nm/kg) at the knee during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
KM1 (Nm/kg)	-0.48 \pm 0.16	-0.50 \pm 0.24	-0.36 \pm 0.15	-0.37 \pm 0.25
KM2 (Nm/kg)	0.83 \pm 0.44	0.26 \pm 0.33*	0.22 \pm 0.34*	0.10 \pm 0.24*
KM3 (Nm/kg)	-0.01 \pm 0.18	-0.25 \pm 0.38	-0.01 \pm 0.44	-0.24 \pm 0.36
KM4 (Nm/kg)	0.57 \pm 0.26	0.41 \pm 0.21	0.43 \pm 0.28	0.38 \pm 0.18
KM5 (Nm/kg)	0.46 \pm 0.13	0.39 \pm 0.18	0.36 \pm 0.28	0.33 \pm 0.16

Key: KM1 = 1st Max. extension moment in loading, KM2 = Max. flexor moment in stance, KM3 = 2nd Max. extension moment in stance, KM4 = 1st Max. varus moment in stance, KM5 = 2nd Max. varus moment in stance.

There was a significant main effect of group on the max. knee flexor moment in stance ($p \leq .01$). No differences were found in the other knee moment variables ($p > .05$).

Post hoc tests showed that the max. knee flexor moment in stance was smaller in the FSHD, BMD and LGMD group compared to the control ($p < .05$) by 68.7%, 73.5% and 88.0%, respectively.

External Ankle Moments

Table 5.7: Mean \pm standard deviation of discrete external moments (Nm/kg) at the ankle during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
AM1 (Nm/kg)	-0.20 \pm 0.12	-0.02 \pm 0.06*	-0.04 \pm 0.10*	-0.07 \pm 0.07*
AM2 (Nm/kg)	1.52 \pm 0.19	1.43 \pm 0.26	1.50 \pm 0.43	1.20 \pm 0.41
AM3 (Nm/kg)	-0.02 \pm 0.02	-0.06 \pm 0.06	-0.02 \pm 0.02	-0.02 \pm 0.02
AM4 (Nm/kg)	0.19 \pm 0.09	0.18 \pm 0.09	0.17 \pm 0.05	0.17 \pm 0.04

Key: AM1 = Max. plantarflexion moment in stance, AM2 = Max. dorsiflexor moment in stance, AM3 = Max. ankle eversion moment, AM4 = Max. ankle inversion moment.

There was a significant main effect of group on the max. plantarflexion moment in stance ($p < .05$). No other differences in ankle moments were found at the ankle joint ($p > .05$).

Post hoc tests showed that the max. plantarflexion moment in stance was smaller in the FSHD, BMD and LGMD group than the control group by 90%, 80% and 65% ($p < .05$), respectively.

5.3.1.4 Joint Powers

Joint powers of the hip, knee and ankle joint during the gait cycle are presented as ensemble averages for the FSHD, BMD and LGMD group in Figure 5.6. Discrete kinetic variables for the control, FSHD, BMD and LGMD group are presented in Table 5.8, 5.9 and 5.10

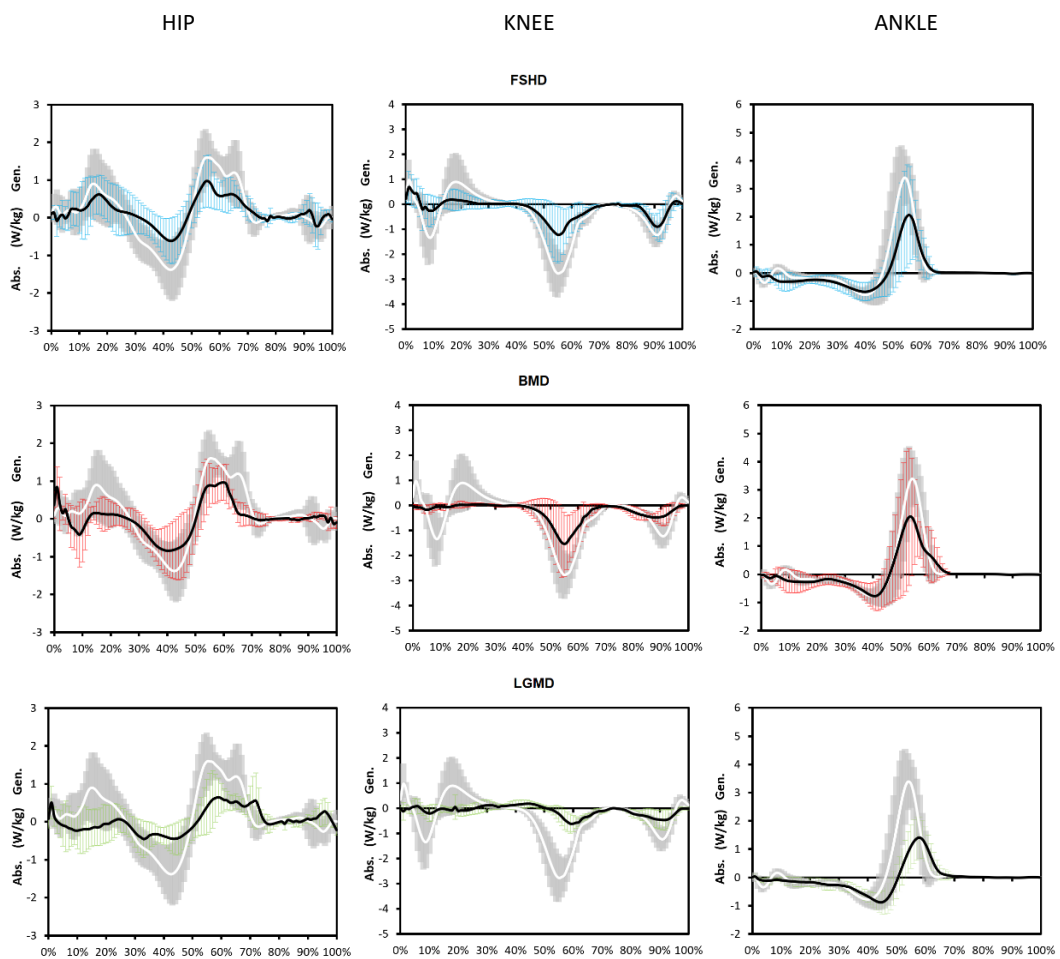


Figure 5.6: Hip, knee and ankle joint powers during the gait cycle of the FSHD (top row), BMD (middle row) and LGMD (bottom row) groups. The white line and grey band represents the control group mean ± 1 standard deviation, and the black line and coloured band represents the MD group mean ± 1 standard deviation. On the x-axis, 0% represents initial contact and 100% the following ipsilateral contact.

Hip Power

Table 5.8: Mean \pm standard deviation of discrete hip power variables (W/kg) during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
Hp1 (W/kg)	1.26 \pm 0.73	0.84 \pm 0.49	0.35 \pm 0.32*	0.26 \pm 0.40*
Hp2 (W/kg)	-1.44 \pm 0.70	-0.73 \pm 0.53	-0.99 \pm 0.71	-0.75 \pm 0.26
Hp3 (W/kg)	1.93 \pm 0.68	1.16 \pm 0.61*	1.28 \pm 0.55*	0.90 \pm 0.50*

Key: Hp1 = Max. hip extensor generation power in early stance, Hp2 = Max. hip flexor absorption power in mid-stance, Hp3 = Max. hip flexor generation power in pre-swing.

There was a significant main effect of group on the max. hip extensor generation power in early stance ($p \leq .01$) and the max. hip flexor generation power in pre-swing ($p < .05$). No effect of group on the max. hip flexor absorption power in mid-stance was found ($p > .05$).

Post hoc tests showed that the max. hip extensor generation power in early stance did not differ between the control and FSHD group ($p > .05$) but that it was 72.2% smaller in the BMD group ($p \leq .01$) and 79.4% smaller in the LGMD group ($p \leq .01$) than the control group.

Post hoc tests showed that the max. hip flexor generation power in pre-swing was 39.9% smaller in the FSHD group ($p < .05$), 33.7% smaller in the BMD group ($p < .05$) and 53.4% smaller in the LGMD group ($p \leq .01$) compared to the control group.

Knee Power

Table 5.9: Mean \pm standard deviation of discrete knee power variables during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
Kp1 (W/kg)	-1.12 \pm 1.43	-0.50 \pm 0.59	-0.28 \pm 0.10	-0.40 \pm 0.29
Kp2 (W/kg)	1.02 \pm 1.12	0.37 \pm 0.35*	0.13 \pm 0.06*	0.33 \pm 0.37*
Kp3 (W/kg)	-3.00 \pm 0.73	-1.59 \pm 0.91*	-1.82 \pm 1.39*	-0.71 \pm 0.34*
Kp4 (W/kg)	-1.31 \pm 0.42	-1.08 \pm 0.49	-0.62 \pm 0.67*	-0.55 \pm 0.38*

Key: Kp1 = Max. knee extensor absorption power in early stance, Kp2 = Max. knee extensor generation power in mid-stance, Kp3 = Max. knee extensor absorption power in pre-swing, Kp4 = Max. knee flexor absorption power in late swing.

There was a significant main effect of group on the max. knee extensor generation power in mid-stance, the max. knee extensor absorption power in pre-swing and the max. knee flexor absorption power in late swing ($p \leq .01$). No effect of group was found for the max. knee extensor absorption power in early stance ($p > .05$).

Post hoc tests showed that the max. knee extensor generation power in mid-stance was smaller in the FSHD, BMD and LGMD group compared to the control group ($p < .05$), by 63.7%, 87.3% and 67.6% respectively.

Post hoc tests showed that the max. knee extensor absorption power in pre-swing was 47.0% smaller in the FSHD group ($p \leq .01$), 39.3% smaller in the BMD group ($p < .05$) and 76.3% smaller in the LGMD group ($p \leq .01$).

Post hoc tests showed that the max. knee flexor absorption power in late swing did not differ between the control and the FSHD group ($p > .05$) but was 52.7%

smaller in the BMD group ($p \leq .01$) and 58.0% smaller in the LGMD group ($p \leq .01$) than controls.

Ankle Power

Table 5.10: Mean \pm standard deviation of discrete ankle power variables during the gait cycle. * represents a significant difference from the control group (CTRL).

	CTRL	FSHD	BMD	LGMD
Ap1 (W/kg)	-0.93 \pm 0.32	-0.81 \pm 0.33	-0.94 \pm 0.43	-0.99 \pm 0.42
Ap2 (W/kg)	4.11 \pm 0.84	2.72 \pm 1.37*	2.92 \pm 1.83*	1.52 \pm 0.84*

Key: Ap1 = Max. plantarflexion absorption power in early stance, Ap2 = Max. plantarflexion generation power in stance.

A main effect of group was found on max. plantarflexion generation power in the stance phase ($p \leq .01$). No main effect of group was found in max. plantarflexion absorption power in early stance ($p > .05$).

A post hoc test showed that max. plantarflexion generation power in stance was smaller in the FSHD, BMD and LGMD group compared to the control group by 33.8%, 29.0% and 63.0% ($p \leq .01$), respectively.

5.3.2 Part B – Effects of RT

5.3.2.1 Participant Characteristics

Individual participant characteristics, including use of walking aids during gait analysis are provided in Table 4.11 in *Chapter 4*.

5.3.2.2 Ground Reaction Forces

Ground reaction forces in the vertical, anterior-posterior and medial-lateral direction during the stance phase of the gait cycle are presented as ensemble averages for each time point (PRE1, PRE2 and POST) in Figure 5.7. Discrete ground reaction force variables for PRE1, PRE2 and POST are presented in Table 5.11.

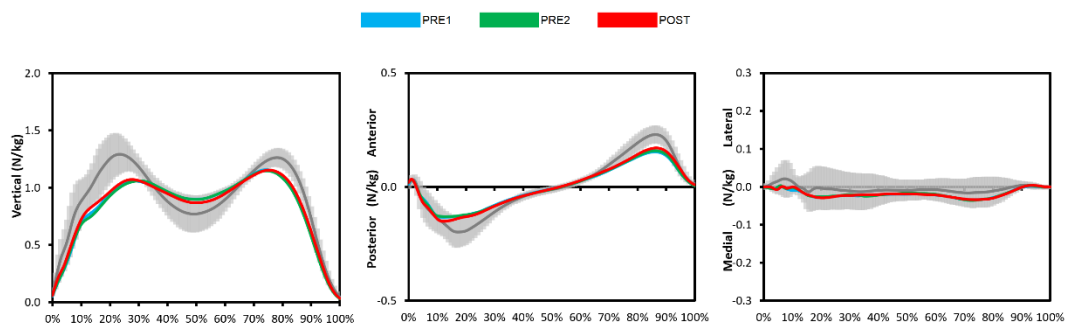


Figure 5.7: Vertical (left), anterior-posterior (middle) and medial-lateral (right) ground reaction force during the stance phase. The black line and grey band represents control data mean ± 1 standard deviation, and the coloured lines represent the MD group mean at PRE1 (blue), PRE2 (green) and POST (red). On the x-axis, 0% represents initial contact and 100% represents toe-off.

Table 5.11: Mean \pm standard deviation of discrete ground reaction force variables (N/kg). * represents a significant difference from PRE1 and § represent a significant difference from PRE2.

	PRE1	PRE2	POST
Fz1 (N/kg)	1.12 \pm 0.24	1.13 \pm 0.23	0.13 \pm 0.23
Fz2 (N/kg)	0.88 \pm 0.18	0.88 \pm 0.18	0.86 \pm 0.17* §
Fz3 (N/kg)	1.18 \pm 0.22	1.18 \pm 0.22	1.18 \pm 0.23
Fy1 (N/kg)	-0.15 \pm 0.07	-0.15 \pm 0.06	-0.17 \pm 0.06* §
Fy2 (N/kg)	0.16 \pm 0.07	0.16 \pm 0.08	0.17 \pm 0.08*
Fx1 (N/kg)	0.02 \pm 0.03	0.03 \pm 0.03	0.02 \pm 0.03
Fx2 (N/kg)	-0.05 \pm 0.04	-0.04 \pm 0.04	-0.05 \pm 0.04
Fx3 (N/kg)	-0.05 \pm 0.03	-0.05 \pm 0.03	-0.05 \pm 0.03

Key: Fz1= Max. vertical force in loading, Fz2 = Min. vertical force in mid-stance, Fz3 = Max. vertical force in terminal stance, Fy1 = Max. braking force, Fy2 = Max. propulsive force, Fx1 = Max. lateral force in loading, Fx2 = Max. medial force in mid-stance, Fy3 = Max. medial force in terminal stance.

There was a significant main effect of time on the min. vertical force in mid-stance ($p \leq .01$), max. braking force ($p \leq .01$, $\eta^2 = .28$) and max. propulsive force ($p < .05$, $\eta^2 = .23$), with the retrospective observed powers ranging from .75 to .86). No other significant effects were found for ground reaction variables ($P > .05$).

Post hoc tests showed that the min. vertical force in mid-stance did not differ between PRE1 and PRE2 ($P > .05$) but was increased by 2.3% from PRE1 to POST ($p < .05$) and from PRE2 to POST ($p \leq .01$).

Post hoc tests showed that the max. braking force did not differ between PRE1 and PRE2 ($p > .05$) but was increased from PRE1 to POST and from PRE2 to POST by 13.3% ($p \leq .01$).

Post hoc tests showed that the max. propulsive force did not differ between PRE1 and PRE2 ($p > .05$) or between PRE2 and POST ($P = .095$) but was increased by 6.3% from PRE1 to POST ($p < .05$).

5.3.2.3 External Joint Moments

External joint moments of the hip, knee and ankle joint in the sagittal, frontal and transverse planes, along with the hip, knee and ankle powers during the gait cycle are presented as ensemble averages for each time point (PRE1, PRE2 and POST), in Figure 5.8. The root mean square differences in sagittal plane external joint moments between PRE1 and PRE2 and between PRE2 and POST are presented in Table 5.12.

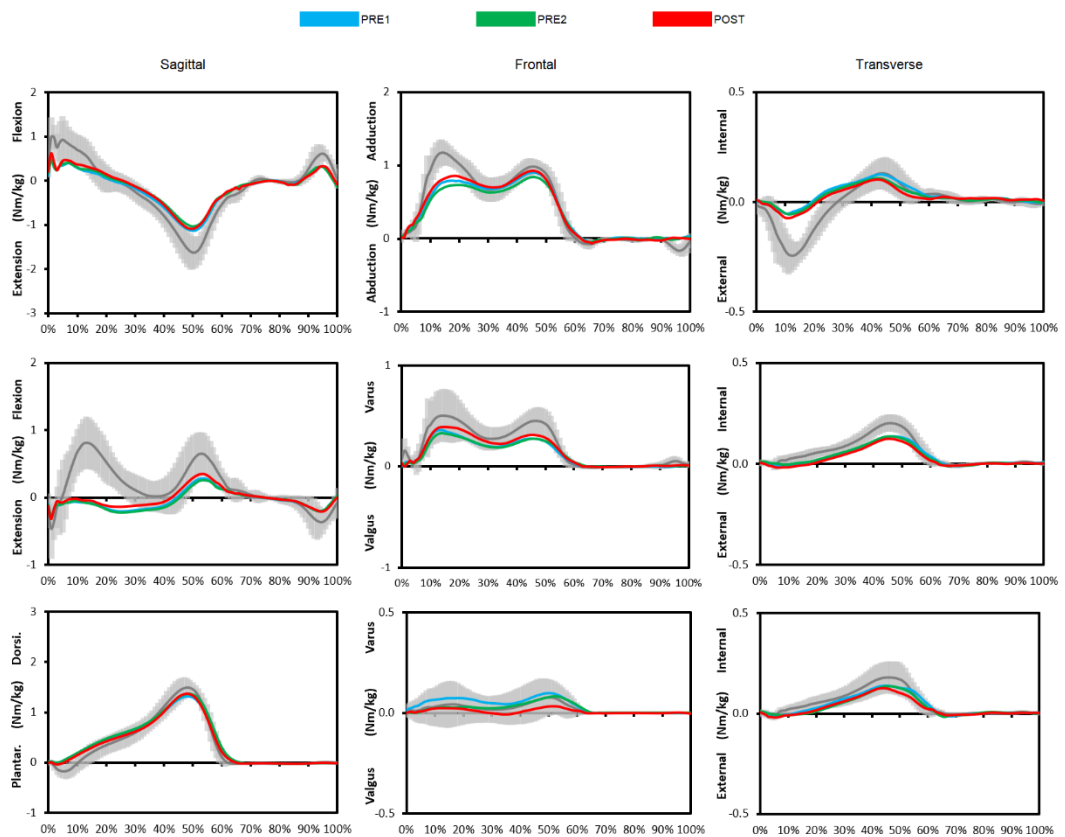


Figure 5.8: Hip (top row), knee (middle row) and ankle (bottom row) joint external moment during the gait cycle in the sagittal (left column), frontal (middle column) and transverse (right column) planes. The black line and grey band represents control data mean \pm 1 standard deviation, and the coloured lines represents the MD group mean at PRE1 (blue), PRE2 (green) and POST (red). On the x-axis, 0% represents initial contact and 100% represents toe-off.

Table 5.12: Root mean square difference in external joint moment between PRE1 and PRE2 and between PRE2 and POST over the entire gait cycle and in the stance phase.

	PRE1-PRE2	PRE2-POST
Hip Extensor Moment (Nm/kg)		
Gait cycle	0.04	0.04
Stance phase	0.05	0.04
Knee Flexor Moment (Nm/kg)		
Gait cycle	0.01	0.04
Stance phase	0.02	0.06
Ankle Plantarflexion Moment (Nm/kg)		
Gait cycle	0.02	0.03
Stance phase	0.04	0.05

Discrete variables at PRE1, PRE2 and POST are presented in Table 5.13, 5.14 and 5.15, for the hip joint, knee joint and ankle joint respectively.

External Hip Moments

Table 5.13: Mean \pm standard deviation of discrete external moments (Nm/kg) at the hip during the gait cycle. * represents a significant difference from PRE1 and \dagger represents a significant difference from PRE2.

	PRE1	PRE2	POST
HM1 (Nm/kg)	0.71 \pm 0.40	0.72 \pm 0.36	0.84 \pm 0.60
HM2 (Nm/kg)	-1.22 \pm 0.53	-0.11 \pm 0.51	-0.19 \pm 0.53
HM3 (Nm/kg)	0.91 \pm 0.31	0.85 \pm 0.31	0.96 \pm 0.36
HM4 (Nm/kg)	0.94 \pm 0.30	0.87 \pm 0.33	0.96 \pm 0.33
HM5 (Nm/kg)	-0.08 \pm 0.07	-0.09 \pm 0.08	-0.11 \pm 0.11
HM6 (Nm/kg)	0.15 \pm 0.16	0.14 \pm 0.06	0.13 \pm 0.07

Key: HM1 = Max. hip flexor moment in stance, HM2 = Max. hip extensor moment in stance, HM3 = 1st Max. hip adductor moment in stance, HM4 = 2nd Max. hip adductor moment in stance, HM5 = Max. external hip rotation moment, HM6 = Max. internal hip rotation moment.

No significant main effect of time was found for any of the discrete hip moment variables ($p > .05$), with the retrospective observed power for these comparisons ranging between .12 and .42.

External Knee Moments

Table 5.14: Mean \pm standard deviation of discrete external moments (Nm/kg) at the knee during the gait cycle. * represents a significant difference from PRE1 and \S represents a significant difference from PRE2.

	PRE1	PRE2	POST
KM1 (Nm/kg)	-0.41 \pm 0.23	-0.45 \pm 0.25	-0.44 \pm 0.28
KM2 (Nm/kg)	0.15 \pm 0.25	0.16 \pm 0.27	0.21 \pm 0.31* \S
KM3 (Nm/kg)	-0.21 \pm 0.37	-0.23 \pm 0.38	-0.15 \pm 0.34
KM4 (Nm/kg)	0.41 \pm 0.22	0.40 \pm 0.20	0.48 \pm 0.25
KM5 (Nm/kg)	0.34 \pm 0.19	0.33 \pm 0.20	0.37 \pm 0.25

Key: KM1 = 1st Max. extension moment in stance, KM2 = Max. flexor moment in stance, KM3 = 2nd Max. extension moment in stance, KM4 = 1st Max. varus moment in stance, KM5 = 2nd Max. knee varus moment in stance.

A significant main effect of time was found for the maximum knee flexor moment during the stance phase ($p < .05$). Post hoc tests showed that no difference between PRE1 and PRE2 was evident ($p > .05$) but a 40% increase from PRE1 to POST ($p < .05$) and a 31.2% increase from PRE2 to POST was found ($p < .05$).

No significant main effect of time was found for any other discrete knee moment variable ($p > .05$). The retrospective observed powers for these comparisons ranged between .11 and .25.

External Ankle Moments

Table 5.15: Mean \pm standard deviation of discrete external moments (Nm/kg) at the ankle during the gait cycle. * represents a significant difference from PRE1 and \S represents a significant difference from PRE2.

	PRE1	PRE2	POST
AM1 (Nm/kg)	-0.04 \pm 0.08	-0.04 \pm 0.05	-0.09 \pm 0.09* \S
AM2 (Nm/kg)	1.38 \pm 0.39	1.44 \pm 0.41	1.42 \pm 0.40
AM3 (Nm/kg)	-0.04 \pm 0.05	-0.04 \pm 0.02	-0.05 \pm 0.04
AM4 (Nm/kg)	0.17 \pm 0.07	0.15 \pm 0.06	0.16 \pm 0.07

Key: AM1 = Max. plantarflexion moment in stance, AM2 = Max. dorsiflexor moment in stance, AM3 = Max. ankle eversion moment, AM4 = Max. ankle inversion moment.

There was a significant main effect of time on the max. plantarflexion moment in early stance ($p < .05$, $\eta^2 = .24$), with an observed power of .78. No main effects of time were found for the other discrete ankle moment variables ($p > .05$).

Post hoc tests showed that max. plantarflexion moment in early stance did not differ between PRE1 and PRE2 ($p > .05$) but was increased by 125% from PRE1 to POST ($p \leq .01$) and from PRE2 to POST ($p \leq .01$).

5.3.2.4 Joint Powers

Joint powers of the hip, knee and ankle joint at PRE1, PRE2 and POST are presented as ensemble averages of the gait cycle in Figure 5.9. Discrete variables at PRE1, PRE2 and POST are presented in Table 5.16, 5.17 and 5.18 for the hip, knee and ankle joint respectively.

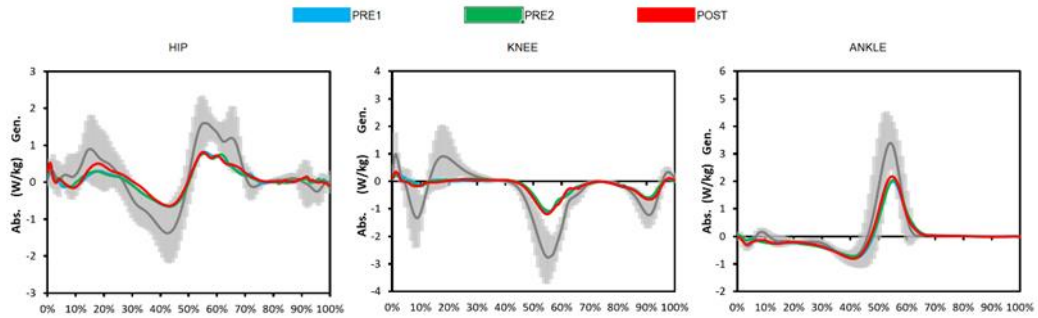


Figure 5.9: Hip (left), knee (middle) and ankle (right) joint power during the gait cycle in the sagittal plane. The black line and grey band represents control data mean \pm 1 standard deviation. Coloured lines represent the MD group mean at PRE1 (blue), PRE2 (green) and POST (red). On the x-axis, 0% represents initial contact and 100% represents toe-off.

Hip Power

Table 5.16: Mean \pm standard deviation of discrete hip power variables (W/kg) during the gait cycle. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

	PRE1	PRE2	POST
Hp1 (W/kg)	0.55 \pm 0.52	0.54 \pm 0.47	0.69 \pm 0.77
Hp2 (W/kg)	-0.82 \pm 0.56	-0.80 \pm 0.62	-0.84 \pm 0.79
Hp3 (W/kg)	1.11 \pm 0.60	1.18 \pm 0.71	1.21 \pm 0.62

Key: Hp1 = Max. hip extensor generation power in early stance, Hp2 = Max. hip flexor absorption power in mid-stance, Hp3 = Max. hip flexor generation power in pre-swing.

No significant main effect of time was found for any discrete hip power variable ($p > .05$), with retrospective observed powers $\leq .15$.

Knee Power

Table 5.17: Mean \pm standard deviation of discrete knee power variables during the gait cycle. * represents a significant difference from PRE1 and $\text{\$}$ represents a significant difference from PRE2.

	PRE1	PRE2	POST
Kp1 (W/kg)	-0.33 \pm 0.23	-0.37 \pm 0.32	-0.43 \pm 0.39
Kp2 (W/kg)	0.27 \pm 0.27	0.25 \pm 0.22	0.27 \pm 0.23
Kp3 (W/kg)	-1.48 \pm 1.11	-1.46 \pm 1.47	-1.60 \pm 0.99
Kp4 (W/kg)	-0.76 \pm 0.48	-0.68 \pm 0.65	-0.88 \pm 0.52* $\text{\$}$

Key: Kp1 = Max. knee extensor absorption power in early stance, Kp2 = Max. knee extensor generation power in mid-stance, Kp3 = Max. knee extensor absorption power in pre-swing, Kp4 = Max. knee flexor absorption power in late swing.

A significant main effect of time on the max. knee flexor absorption power in late swing was found ($p < .05$). No significant main effect was evident in any other discrete knee power variable ($p > .05$).

Post hoc tests showed that max. knee flexor absorption power did not differ between PRE1 and PRE2 ($p > .05$) but was significantly increased by 15.8% from PRE1 to POST ($p \leq .01$) and by 29.4% from PRE2 to POST ($p < .05$).

Ankle Power

Table 5.18: Mean \pm standard deviation of discrete ankle power variables during the gait cycle. * represents a significant difference from PRE1 and \textasciitilde represents a significant difference from PRE2.

	PRE1	PRE2	POST
Ap1 (W/kg)	-0.98 \pm 0.38	-0.94 \pm 0.45	-0.86 \pm 0.56
Ap2 (W/kg)	2.55 \pm 1.66	2.56 \pm 1.52	2.79 \pm 1.72* \textasciitilde

Key: Ap1 = Max. plantarflexion absorption power in early stance, Ap2 = Max. plantarflexion generation power in stance.

A significant main effect of time was found in the max. plantarflexion generation power during stance ($p < .05$, $\eta^2 = .23$), with an observed retrospective power of .76. No main effect of time was found for the max. plantarflexion absorption power in early stance ($p > .05$).

Post hoc tests showed that max. plantarflexion generation power did not differ between PRE1 and PRE2 ($P > .05$) but increased by 9.4% from PRE1 to POST ($p < .05$) and increased by 9.0% from PRE2 to POST ($p < .05$).

5.3.2.5 Additional Kinetic Analysis – Knee Moment and Knee Power

The knee flexion-extension moment and power for the sub-group of participants categorised as hyperextending the knee joint in *Chapter 4* (see *Chapter 4* for more details) are presented in Figure 5.10 and 5.11, respectively. Discrete knee moment and knee power variables from this data set are presented in Table 5.19 and 5.20, respectively.

A main effect of time was found in the 2nd max. extension moment during stance ($p < .05$, $\eta^2 = .42$), with an observed retrospective power of .73. No main effect of time was found for the 1st max. extension moment in stance or the max flexor moment in stance ($p > .05$), with observed powers of .21 and .18, respectively.

Post hoc tests showed that there was no difference in the 2nd max. extension moment during stance between PRE1 and PRE2 ($p > .05$) but that it decreased by 30.4% from PRE1 to POST and 37.3% from PRE2 to POST ($p < .05$).

There was a main effect of time on the max. knee extensor absorption power at pre-swing ($p < .01$, $\eta^2 = .49$), with an observed retrospective power of .86. No significant main effect of time was found in the max. knee extensor absorption power in early stance, the max. knee extensor generation power in mid-stance or the max. knee flexor absorption power in late swing ($p > .05$), with observed powers between .11 and .26.

Post hoc tests showed that the max. knee extensor absorption power at pre-swing did not differ between PRE1 and PRE2 ($p > .05$) but that it increased by 49.2% from PRE1 to POST and 30.0% from PRE2 to POST ($p < .05$).

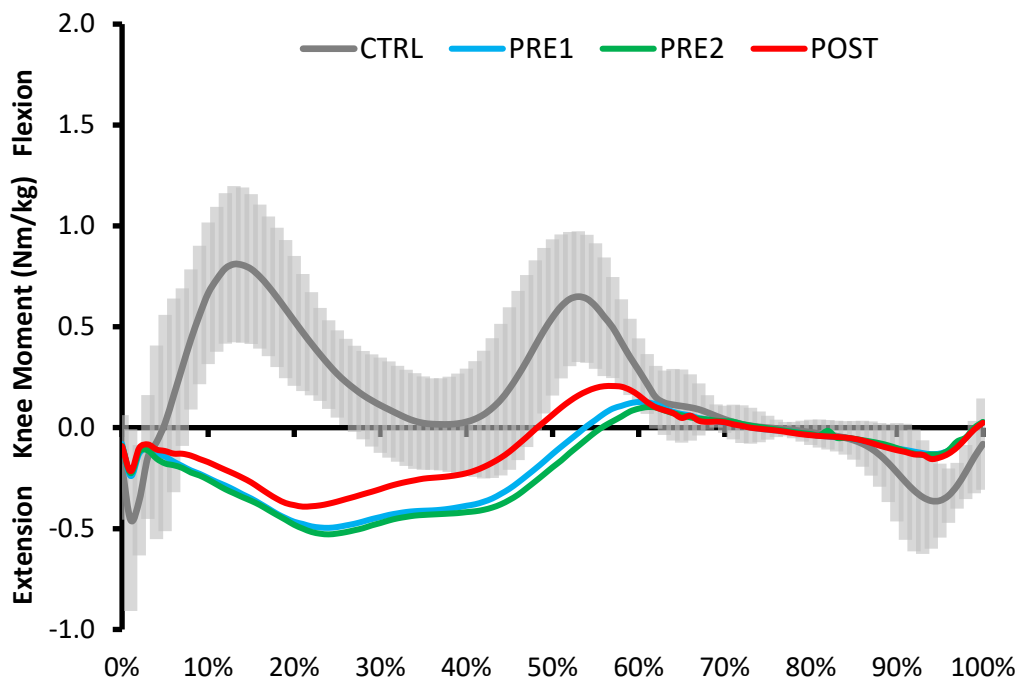


Figure 5.10: Mean knee flexion (+) and extension (-) external moment during the gait cycle in MD participants categorised as hyperextending the knee, at PRE1 (blue line), PRE2 (green line) and POST (red line) completion of a RT programme. The grey line (\pm grey band) represents control data mean (\pm 1 standard deviation) for visual comparison. On the x-axis, 0% represents initial ground contact and 100% the following ipsilateral ground contact.

Table 5.19: Mean \pm standard deviation of discrete external knee moment data for the subgroup of MD participants that exhibited excessive hyperextension of the knee during stance. * represents a significant difference from PRE1 and \textasciitilde represents a significant difference from PRE2.

	PRE1	PRE2	POST
KM1 (Nm/kg)	-0.47 \pm 0.25	-0.48 \pm 0.25	-0.39 \pm 0.20
KM2 (Nm/kg)	-0.02 \pm 0.10	-0.02 \pm 0.10	0.02 \pm 0.15
KM3 (Nm/kg)	-0.46 \pm 0.27	-0.51 \pm 0.26	-0.32 \pm 0.19* \textasciitilde

Key: KM1 = 1st Max. extension moment in stance, KM2 = Max. flexor moment in stance, KM3 = 2nd Max. extension moment in stance.

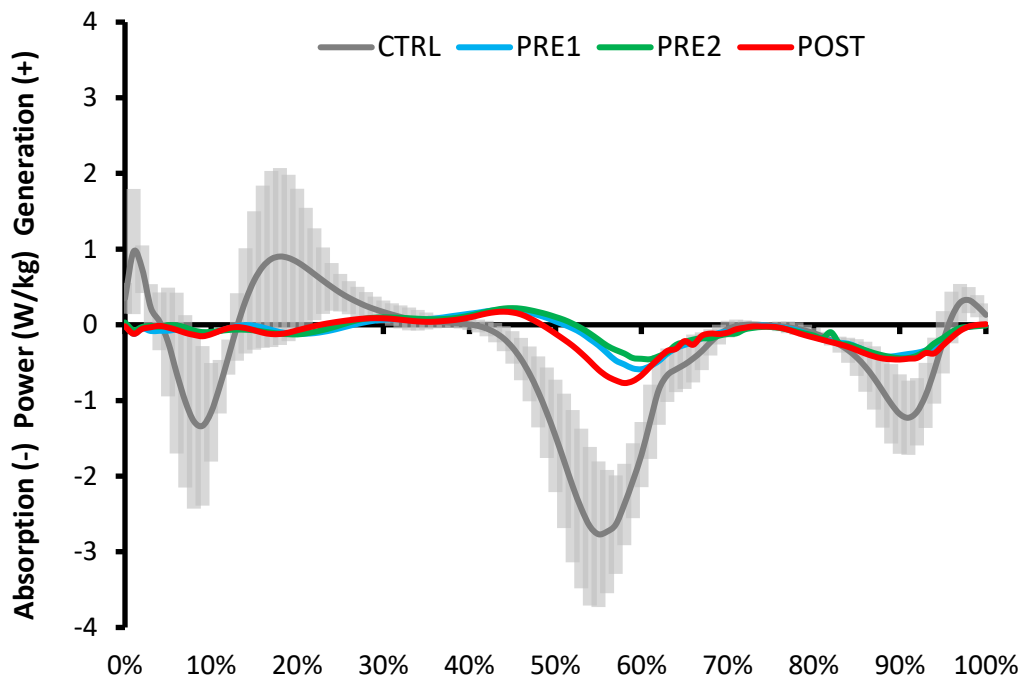


Figure 5.11: Mean knee power during the gait cycle in MD participants categorised as hyperextending the knee, at PRE1 (blue line), PRE2 (green line) and POST (red line) completion of a RT programme. The grey line (\pm grey band) represents control data mean (\pm 1 standard deviation) for visual comparison. On the x-axis, 0% represents initial ground contact and 100% the following ipsilateral ground contact.

Table 5.20: Mean \pm standard deviation of discrete knee power data for the sub-group of MD participants that exhibited excessive hyperextension of the knee during stance. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

	PRE1	PRE2	POST
Kp1 (W/kg)	-0.31 \pm 0.19	-0.26 \pm 0.14	-0.27 \pm 0.20
Kp2 (W/kg)	0.15 \pm 0.14	0.13 \pm 0.15	0.16 \pm 0.17
Kp3 (W/kg)	-0.61 \pm 0.40	-0.70 \pm 0.35	-0.91 \pm 0.43* §
Kp4 (W/kg)	-0.54 \pm 0.32	-0.31 \pm 0.59	-0.67 \pm 0.34

Key: Kp1 = Max. knee extensor absorption power in early stance, Kp2 = Max. knee extensor generation power in mid-stance, Kp3 = Max. knee extensor absorption power in pre-swing, Kp4 = Max. knee flexor absorption power in late swing.

5.4 Discussion

5.4.1 Part A- MD versus Controls

This study is novel in the description of the kinetics of gait in adults with BMD and LGMD, along with the presentation of ground reaction forces and joint powers during FSHD gait compared to controls. Several peak vertical and anterior-posterior ground reaction forces were small in one or all of the MD groups compared to the controls. Specifically, peak vertical ground reaction force in loading in all MD groups; peak vertical force in terminal stance in LGMD and peak propulsive force in LGMD. Peak lateral force in terminal stance however, was greater in the BMD group than the controls. Numerous differences in joint moments between the MD groups and the control group were evident at the hip in the sagittal, frontal and transverse planes, along with differences in the knee and ankle moments in the sagittal plane. In addition, deviations in joint powers were found in the MD groups compared to the controls, including; a smaller maximum hip extensor generation power in BMD and LGMD; a smaller maximum hip flexor generation power in all MD groups; a smaller maximum knee extensor generation power in all MD groups; a smaller maximum knee extension absorption power in all MD groups; a smaller maximum knee flexor absorption power in BMD and LGMD and a smaller maximum plantarflexion generation power in all MD groups.

5.4.1.1 Ground Reaction Forces

It is unsurprising that numerous peak ground reaction forces in the vertical and horizontal direction were smaller in one or some of the MD groups in comparison to the controls, given the slower self-selected gait speed of the MD groups

presented in *Chapter 5* (control: 1.44 m/s, FSHD: 1.06 m/s, BMD: 0.96 m/s, LGMD: 0.80 m/s).

In the vertical direction, peak force during loading was smaller in all MD groups than in the control group. In terminal stance, peak vertical force was smaller in all MD groups but only reached significance in the LGMD group. Interestingly, peak force in loading was 3% lower than body weight in LGMD (1 = body weight). This suggests that full weightbearing on the legs at loading did not happen in this group. It is likely that a proportion of bodyweight was supported by the upper body in some individuals through their walking aids. Thus, in the LGMD group the centre of mass may not be accelerated upwards as much as controls; at least not by the lower body. This evidence provides some support for the explanation that was proposed in *Chapter 5* regarding no change to the oxygen cost of gait post RT. Similar findings to these (lower peak vertical forces) have previously been shown in children with Duchenne MD compared to controls (Gaudreault et al., 2010), however the differences in vertical ground reaction forces were dissipated once control gait speed was matched to MD gait speed. Typically, the vertical ground reaction force decreases from the initial peak to mid-stance as the knee flexes and the vertical lift in the centre of mass decelerates (Chung and Wang, 2010). No significant difference in this minimum vertical force at mid-stance was found between the groups, but the decrease in vertical force from the initial peak to mid-stance was observably smaller in all MD groups than the control. This parallels the reduced, or lack of knee flexion in mid-stance that was presented in *Chapter 5* in the MD groups.

In the anterior-posterior direction, the peak braking force was smaller in all MD groups than controls, but this difference did not reach significance. The peak propulsive force however was significantly smaller in LGMD than controls, which parallels the slowest gait speed in this group. Numerous studies have shown that the plantar flexor muscles are the main contributor towards forward propulsion of the mass centre during late stance in normal walking (Liu et al., 2006; Gottschall and Kram, 2003; Neptune et al., 2001). Therefore, the smaller propulsive force in LGMD is likely related to the weak plantar flexor MVC torque presented in *Chapter 4*, which was the most severe in LGMD than all other groups.

Interestingly, peak medial ground reaction force during terminal stance was 13% greater in the BMD group than the control group, despite the slower gait speed in BMD. This finding agrees with a study by Gaudreault et al. (2010), which also reported a greater peak medial force during stance in Duchenne MD compared to controls walking at both their natural and a matched gait speed to the MD group. This finding provides evidence towards the previously presumed notion of similar gait patterns between Duchenne MD and BMD. It is important to note the greater step width reported in the BMD group compared to controls in *Chapter 5*, as this may be related to the greater medial ground reaction force found in this group. This is suspected as the medial ground reaction force during terminal stance acts to transfer body weight onto the opposite foot (Browning and Kram, 2007). Therefore, the greater step width in BMD likely requires a greater force to complete this transition. Furthermore, enforced increases in step width have previously been shown to increase peak medial ground reaction forces during stance in healthy adults (Donelan et al., 2001).

5.4.1.2 External Joint Moments

Differences in hip joint moments were found in the MD groups compared to controls. Most notable was the reduced maximum hip extensor moment in late stance, which was 41% lower in the FSHD and 33% lower in the LGMD group than controls. However, no significant difference in this variable was evident in BMD compared to controls. Similar findings of a lower hip extensor moment in late stance have previously been reported in other populations, such as elderly individuals compared to young adults (Monaco et al., 2009).

The smaller hip extensor moment in FSHD than controls coincides with the lack of hip extension at toe-off in the FSHD group reported in *Chapter 4*. The combination of a reduced hip extensor moment acting on the hip joint, and the weakness of the hip extensor muscles, as reported in *Chapter 3*, likely limits the degree of hip extension that is achievable. In BMD however, no difference in maximum hip extensor moment was evident, yet a lack of hip extension at toe-off was also found in this group (*Chapter 3*). Thus, these findings demonstrate that the lack of hip extension at toe-off in the BMD group is not a function of low hip extensor moments acting on the hip joint. Instead, the reduced hip extension position in BMD must be related to an alternative abnormality. One such alternative may be tightness in the muscles that are anterior to the hip, such as the hip flexors, which may reduce the degree of hip extension that is attainable. Although it is not possible to verify this explanation from our study, it is clear that the magnitude of the hip extensor moment in stance is not the cause of limited hip extension in BMD.

Deviations in the knee flexor/extensor moment during the gait cycle, for each MD group compared to the control group, are observable in Figures 5.3, 5.4 and 5.5. The root mean square difference in knee moment shows considerable differences between each MD group and the controls over the stance phase as a whole (FSHD: 0.34 Nm/kg, BMD: 0.25 Nm/kg, LGMD: 0.41 Nm/kg). In addition, analysis of discrete variables demonstrate significantly lower knee flexor moments during the loading response compared to controls by 69%, 74% and 88%, in FSHD, BMD and LGMD, respectively. Furthermore, although no significant difference was found in the maximum knee extensor moment during mid-stance, it was 0.24 Nm/kg and 0.23 Nm/kg greater in the FSHD and LGMD group than the controls. However, no difference in the maximum knee extensor moment was evident between BMD and controls (-0.01 versus -0.01), which disagrees with previous studies in children with Duchenne MD that reported greater peak knee extensor moments during stance compared to controls (D'Angelo et al., 2009; Gaudreault et al., 2010). This discrepancy highlights that gait patterns between children with Duchenne MD and adults with BMD are not entirely alike, which is most likely a function of the greater severity and progression of Duchenne MD than BMD.

In *Chapter 4* we proposed that the greater severity of knee extension/hyperextension during midstance in LGMD than BMD despite similar strength deficits, was either a function of greater abnormalities in the knee flexor/extensor moment, or a reduced resistance to hyperextension from the internal structures of the knee. The findings from this study confirm that the LGMD group experience a lower knee flexor moment acting on the knee joint at loading than the BMD group, and a greater knee extensor moment acting on the knee joint

during mid-stance than the BMD group. Thus, it appears that the greater severity of hyperextension in LGMD than BMD is a function of a larger external extensor moment acting on the knee joint during stance.

The smaller knee flexor moments during loading in FSHD, BMD and LGMD than controls coincides with less flexed knee positions during loading that were reported in *Chapter 4* for these groups. In addition, the heightened knee extensor moment during mid-stance in LGMD coincides with the hyperextension of the knee joint that was reported in LGMD (*Chapter 4*). However, a high knee extensor moment during stance was also found in the FSHD group, but hyperextension of the knee was not evident in this group, as shown in *Chapter 4*. Thus, both the LGMD and FSHD group experienced an excessive external knee extensor moment during mid-stance but it appears that the FSHD group were able to counter this external knee extensor moment to keep the knee in a slightly flexed position. This reflects the less severe strength deficits (in the knee flexors and knee extensors) of the FSHD group than the LGMD group (*as shown in Chapter 3*).

At heel contact with the ground, the vertical projection of the ground reaction force is typically located posterior to the ankle joint, which results in an external plantarflexion moment during early stance (Webster and Darter, 2019). This plantarflexion moment can be seen in the control group in Figure 5.3. However, there is a complete absence of this external moment in the FSHD, BMD and LGMD group, which is observable in Figures 5.3, 5.4 and 5.5, respectively. As such, the maximum plantarflexion moment in early stance was 90%, 80% and 65% lower in the FSHD, BMD and LGMD group respectively compared to controls. This finding

coincides with the lack of dorsiflexion at initial contact (flat foot) that was reported in the MD groups in *Chapter 4*. With this flat foot position at initial contact, an immediate dorsiflexor moment occurs instead. This abnormality has previously been reported in children with Duchenne MD (Gaudreault et al., 2010).

5.4.1.3 Joint Powers

It is clear that the propulsive generating capacity during late stance is impaired in all MD groups. This is demonstrated at the hip, knee and ankle. The maximum hip flexor generation power in late stance was 40%, 34% and 53% smaller in the FSHD, BMD and LGMD groups compared to controls, respectively. In addition, the knee extensor generation power in stance was 34%, 87% and 68% smaller in the FSHD, BMD and LGMD groups compared to controls. Finally, the maximum plantarflexion generation power in late stance was 34%, 29% and 63% lower in the FSHD, BMD and LGMD group, respectively. The greater deficit in hip flexor power generation and plantarflexion generation power in the LGMD group compared to FSHD and BMD parallels the smaller maximum propulsive force reported in LGMD. This is particularly pertinent as numerous studies have shown that the plantar flexors are the main contributor towards forward propulsion during late stance in normal walking (Liu et al., 2006; Gottschall and Kram, 2003; Neptune et al., 2001).

Previous studies that have measured joint powers in other types of MD, namely Duchenne MD, have reported similar findings to ours. These findings include lower plantar flexion generation powers in late stance (D'Angelo et al., 2009; Gaudreault et al., 2009; Gaudreault et al., 2010) and a lower hip flexor generation power in late stance (Gaudreault et al., 2010), compared to controls. In addition, reduced

plantarflexion generation power in late stance is well documented in elderly populations compared to young (Schloemer et al., 2017; Monaco et al., 2009; Silder et al., 2008), and has been reported in a study involving adults with Myotonic MD (Galli et al., 2012). However, in the latter two populations (elderly and Myotonic MD) a greater hip flexor generation power compared to controls was also reported (Galli et al., 2012; Schloemer et al., 2017; Monaco et al., 2009; Silder et al., 2008). This strategy demonstrates a proximal compensation for the reduced plantar flexion generation power in elderly individuals and adults with Myotonic MD. However, this compensatory shift is not evident in our populations of FSHD, BMD or LGMD as hip flexor generation power was also lower than it was in the control group.

5.4.1.4 Clinical Implications

This study demonstrates numerous kinetic abnormalities in individuals with FSHD, BMD and LGMD compared to controls. These abnormalities have numerous clinical implications including the potential for increased pain and damage through excessive forces acting on the joints. For example, the lower knee flexor moment in loading and the heightened knee extensor moment in mid-stance in the MD groups, LGMD in particular, exposes the internal structures of the knee joint to excessive forces during the stance phase. Another clinical implication is the deterioration of gait speed due to a reduced capacity to generate propulsion. The inferior joint powers at the hip, knee and ankle joint from mid-stance to terminal stance indicate that the capacity to generate propulsion is diminished proximally and distally for all MD groups. Therefore, a full lower-body RT programme may be advantageous towards maintaining ambulation in these types of MD.

5.4.1.5 Conclusion

In conclusion, several peak vertical and horizontal ground reaction forces differed to controls. Peak vertical force in loading was smaller in all MD groups, peak vertical force in terminal stance and propulsive force was smaller in LGMD and peak lateral force in terminal stance was greater in BMD. In addition, deviations in joint moments were evident at all lower-limb joint levels (hip, knee and ankle) between the MD groups and controls, with the most striking abnormalities occurring in the knee flexor/extensor moment and the plantarflexor/dorsiflexor moment in each MD group. On the other hand, hip moment abnormalities varied between the MD groups, with only the FSHD and LGMD group demonstrating an inferior hip extensor moment compared to controls. Despite these differences between the MD groups, propulsive force generating capacity was diminished in all MD groups at the ankle, knee and hip joint. Overall, these findings suggests that several kinetic abnormalities are common to all three types of MD whereas others are individual to the specific groups. Thus, individualised RT programmes would be advantageous in these individuals.

5.4.2 Part B – Effects of RT

This is the first study to examine the effect of a RT programme on key kinetic gait parameters in individuals with MD. Alongside the increase in gait speed and changes in numerous kinematic variables presented in *Chapter 4*, several kinetic variables were altered after completion of the RT programme. Peak vertical and horizontal ground reaction forces including the minimum vertical force in mid-stance, the maximum braking force and the maximum propulsive force increased post RT. In

addition, adaptations were also found in several joint moments, including an increase in the maximum plantarflexion moment during early stance and the maximum knee flexor moment in stance. The only change in joint power occurred at the ankle joint as an increase in maximum plantarflexion generation power in late stance. Importantly the additional analysis completed in the subgroup of MD participants that hyperextended the knee during stance, found that the maximum knee extensor moment during mid-stance was reduced in these individuals post RT. It is important to note, as mentioned in *Chapter 4* of this thesis, the discrete kinetic variables in which significant differences were found post RT all showed sufficient retrospective statistical power (between .75 and .86). However, some of the variables that did not differ were found to have insufficient retrospective observed power (between .11 and .42). Thus, it is viable that a greater sample size would reveal additional kinetic differences alongside the ones found in this study, but the key finding that RT does influence variables of gait in a positive direction remains valid.

5.4.2.1 Ground Reaction Forces

Increases in peak vertical and horizontal ground reaction forces were found in the MD group post RT. In the vertical direction, the minimum vertical force during mid-stance increased by 2.3% (i.e. a lower magnitude of force), shifting the vertical force curve closer to that of non-dystrophic controls. This reduction in vertical force coincides with the increased knee flexion that occurred in this group post RT (*Chapter 4*). A 13% increase in maximum braking force during early stance was also found, which makes sense given the increase in gait speed that occurred post RT. In

addition, a 6.3% increase in maximum propulsive force during late stance was found from PRE1 to POST RT. This finding signifies that RT improved the propulsive force generating capacity of this MD group. As already mentioned, it has previously been shown that the plantar flexor muscles are the main contributors towards forward propulsion in late stance (Liu et al., 2006). Thus, the 65% increase in plantarflexion MVC torque that was found post RT (*Chapter 3*) is in line with this.

5.4.2.2 External Joint Moments

The root mean square difference in sagittal plane external joint moments offers a value of the global difference in joint moment over the gait cycle as a whole, and over the stance phase as a whole rather than at discrete time points or peaks. The mean variance in the hip flexor/extensor moment was relatively equal between the control period and post completion of the RT programme, both over the entire gait cycle (0.04 versus 0.04 Nm/kg) and over the stance phase (0.04 versus 0.05 Nm/kg). This demonstrates that on the whole the hip flexor/extensor moment did not change considerably post RT, relative to the variance within the initial control period. The largest difference in overall joint moment post RT occurred in the knee flexor/extensor external moment, which differed by a mean of 0.04 Nm/kg overall and 0.06 Nm/kg in the stance phase post RT, compared to small variances of 0.01 and 0.02 Nm/kg in the control period. The mean difference in plantarflexion moment post RT was only slightly greater than the variance observed in the control period (0.03 versus 0.02 Nm/kg, respectively). Therefore, the overall ankle plantarflexion moment did not differ considerably between the control period and post RT. Overall, only the knee flexion/extension moment changed post RT when

analysed over the entire gait cycle, but additional adaptations were evident in discrete variables which will be now be discussed.

Analysis of discrete variables at the hip found no change in hip moments in the sagittal, frontal or transverse planes. However, it is important to note the low observed powers in these comparisons (between .12 and .42). Thus, a greater sample size and in turn a greater statistical power may detect adaptations in hip moments post RT.

Most notable among the adaptations in external joint moments was the 31.2% increase in maximum knee flexor moment during stance, post completion of the RT programme. This finding parallels the increase in the knee flexion position during mid-stance that was found post RT and is presented in *Chapter 4*. These adaptations also coincide with the greater reduction in vertical ground reaction force following the initial peak in vertical force, which was described above. Together these findings demonstrate a superior attenuation of the vertical forces acting on the body during mid-stance. Additionally in the sub-group of participants that hyperextended at the knee joint, a 37.3% reduction in the maximum external knee extensor moment during mid-stance was found. This finding parallels the 4.1° (38.4%) reduction in the severity of hyperextension during mid-stance that was presented in *Chapter 4*. We noted that this reduction in knee hyperextension may be related to changes in the knee extensor moment or other adaptations such as an increased resistance to hyperextension from the internal structures of the knee. The findings from this study confirm that the reduction in the severity of hyperextension is a function of a reduced external knee extensor moment acting on the knee joint during mid-stance.

Although it is possible that an increase in internal resistance to hyperextension also occurred post RT, it is not possible to determine this from our study,

At the ankle, an increase in maximum plantarflexion moment in early stance was found post RT, with stable values in the control period. This adaptation occurs in parallel with the 2.2° increase in ankle dorsiflexion at initial contact presented in *Chapter 4*. This greater dorsiflexed position at initial contact, together with the increase in plantarflexion moment during loading, reflects a more posterior trajectory of the vertical ground reaction force in relation to the ankle joint during loading (Webster and Darter, 2019).

5.4.2.3 Joint Powers

An increase in the propulsive generating capacity at push-off was observed post RT. Specifically, the maximum plantarflexion generation power increased by 9% post completion of the RT programme, with stable values in the initial control period. This finding represents an increase in the propulsive generating capacity of individuals with MD during the late stance phase, which is observable in the increased propulsive ground reaction force post RT that was described earlier in this discussion. This increase in ankle power corresponds well with, and may be related to, the 65% increase in plantarflexion MVC torque that was presented in *Chapter 3*. Interestingly, similar findings have previously been reported in children with cerebral palsy following a programme of 8 weeks' individually designed RT (Eek et al., 2008). No other changes in joint powers were found post completion of the RT programme, but it should be noted that although not significantly different, the maximum hip extensor generation power in early stance increased by 27.8% and is

noticeably larger in Figure 5.9. This variable had a considerably low retrospective statistical power and therefore may significantly differ in future studies with a greater sample size.

Overall, analysis of joint powers pre and post the RT programme demonstrated that adaptations occurred predominantly in the distal joints at the push-off phase of gait rather than the proximal joints.

5.4.2.4 Clinical Implication

The implication of these findings is that RT is a practical option to help improve walking ability in adults living with MD. As an intervention, RT has the potential to reduce excessive forces at the joints during gait which often result in abnormal joint positions. For instance, the excessive knee extension moment observed during mid-stance in this MD population was reduced. In addition, RT also has the potential to improve walking speed in MD through an increase in propulsive generating capacity, such as the increase in plantarflexion generation power at push-off shown within this study.

5.4.2.5 Limitations

This study has a key limitation that cannot be ignored. Whilst statistical power was sufficient for some of the variables of interest in this study, low retrospective statistical power was observed in quite a few other kinetic variables, particularly those at the hip. Therefore, it is highly likely that adaptations occurred in additional kinetic variables post RT in this population but were concealed due to this limitation. Whilst statistical power was sufficient for variables of MVC torque presented in *Chapter 4*, and the vast majority of kinematic variables presented in *Chapter 4*,

greater power would have been advantageous in this study. Nevertheless, the variables that were sufficiently powered in this study demonstrate that RT is a successful intervention for gait adaptations in MD.

5.4.2.6 Conclusion

In conclusion, this is the first study to demonstrate positive effects of a 12-week RT programme on a number of kinetic gait abnormalities in adults with MD. Overall, RT is an innovative approach to improving gait abnormalities and to enhancing propulsive capacity in MD, which was shown specifically by an increase in the maximum external knee flexor moment during stance, a reduction in the excessive external knee extensor moment during stance and an increase in peak plantarflexor power generation during late stance.

Chapter 6

Influence of resistance training on quality of life and mental health in adults with Facioscapulohumeral, Limb-girdle and Becker muscular dystrophy

6.1 Introduction

MD encompasses a number of neuromuscular conditions which are caused by a variety of genetic mutations (Huml, 2015). Such mutations give rise to a reduced or absent expression of proteins within the muscle cell which ultimately causes progressive weakening and deterioration of the muscles (Mercuri and Muntoni, 2013). This results in increasing levels of disability and reduced physical function (Huml, 2015). In addition, chronic conditions, such as MD, may result in not just physical but also mental challenges. A higher prevalence of poor mental health has previously been demonstrated in a variety of groups with chronic medical conditions (Katon, 2011).

Duchenne MD is the most severe form of MD, characterised by an absence of the protein dystrophin (Koenig et al., 1989), early childhood onset, rapid progression, loss of ambulation in childhood and premature death (Bushby et al., 2010). Other types of MD vary between childhood and adult onset, progress more slowly and do not typically lead to a loss of ability to walk, at least until the second decade of life and onwards (Emery, 2002). Three common types of MD that fit the latter description are FSHD, LGMD and BMD (Emery, 2002). Similar to Duchenne MD, BMD is also due to a defect in the dystrophin protein, but the protein is reduced or dysfunctional rather than absent (Koenig et al., 1989), rendering BMD a less severe variant of Duchenne MD with the loss in ambulation typically occurring from the second decade of life onwards (Mercuri and Muntoni, 2013). FSHD and LGMD are both heterogeneous conditions with various subtypes in each condition that affect different proteins at several molecular levels of the muscle cell (Sacconi et al., 2015;

Liewluck and Milone, 2018). FSHD and LGMD typically occur in adulthood, with the loss in ability to walk occurring much later in life, if at all (Emery, 2002).

6.1.1 Part A

Understanding quality of life (QoL) and mental health in MD is of vital importance. QoL has of late become a major focal point in long-term disease management, as lower QoL has been demonstrated across a variety of muscle diseases (Graham et al., 2011). In MD populations the research is conflicting. Some studies have reported reduced QoL (both physical and mental dimensions), in children and adults with Duchenne MD (Davis et al., 2010; Uzark et al., 2012; Landfeldt et al., 2016; Lue et al., 2016), a combined group of children and adults with Duchenne MD, BMD and LGMD (Grootenhuis et al., 2007), adults with Myotonic MD (Antonini et al., 2006) and adults with FSHD (Winter et al., 2010; Padua et al., 2009). In contrast, other studies have reported that whilst physical aspects of QoL are impaired, QoL in the mental domain is similar between individuals with Duchenne MD and control groups or normative reference values (Kohler et al., 2005; Pangalila, van den Bos, Bartels, Bergen, Kampelmacher, et al., 2015; Elsenbruch et al., 2013). The latter findings reflect the disability paradox phenomenon (Albrecht and Devlieger, 1999) where perceived QoL is high despite substantial physical disability.

The relationship between MD and QoL is clearly complicated, and it is likely mediated by additional factors. Previous investigations have shown that numerous disease-specific parameters are related to QoL in MD in the physical domain, including current age (Uzark et al., 2012), disease severity (Landfeldt et al., 2016; Padua et al., 2009; Otto et al., 2017; Peric et al., 2018), functional status (Lue et al.,

2016), wheelchair use (Wei et al., 2016) and age at disease onset (Peric et al., 2018). Other variables are negatively associated with both domains (physical and mental) of QoL in MD; pain (Padua et al., 2009; Abresch et al., 2002) and fatigue (Wei et al., 2016; Kalkman, 2005; Pangalila, van den Bos, Bartels, Bergen, Stam, et al., 2015). Interestingly, these two variables are aspects of the condition that may be manageable through interventions such as medication. Of particular interest to this study is the relationship of QoL to variables that may be managed to some extent through RT, such as physical activity level, depressive symptoms, anxiety and self-esteem.

The relationships between physical activity and QoL and between self-esteem and QoL remain un-investigated in individuals with MD. On the other hand, negative relationships have been presented between anxiety and both domains of QoL, and between depression and the physical domain of QoL, in Duchenne MD (Pangalila, van den Bos, Bartels, Bergen, Stam, et al., 2015). Furthermore, Peric et al. (2018) established a negative association between depression and total QoL score in adults with LGMD, but details regarding individual QoL subscales were not provided. The relationship of depression and anxiety with QoL is yet to be investigated in FSHD or BMD, and nothing is known of the relationship between anxiety and QoL in LGMD.

It is known that poor mental health is often present in individuals with long-term physical disease. Moussavi et al. (2007) established that between 9.3% and 18.1% of individuals with a physical disease exhibit depression, which was significantly higher than the 4.4% in the general population with no physical condition. Similarly, higher levels of moderate depression have been established in adults with

Duchenne MD (18%), compared to a control group (8%;(Pangalila, van den Bos, Bartels, Bergen, Stam, et al., 2015). However, investigation of mental health in FSHD, BMD and LGMD is particularly limited. Caregivers of non-ambulatory males with BMD perceived that depression and anxiety were present in 18% and 26% of their patients, respectively (Latimer et al., 2017). In addition, the frequency of anxiety and depression experienced by adults with BMD and LGMD does not differ (Melo et al., 1995), but in adults with Myotonic MD the severity of depression was higher than in adults with FSHD (Alschuler et al., 2012). Studies quantifying anxiety and depression in comparison to control or normative reference data have yet to be conducted in FSHD, LGMD and BMD.

Investigation into levels of self-esteem in MD are also extremely limited, with only two examinations of this being published to date. Authors reported lower levels of self-esteem in children with LGMD compared to an age and sex-matched control group (Miladi et al., 1999), whilst no difference in self-esteem was established between adults with Myotonic MD and normative reference data (Bertrand et al., 2015). It has previously been established that self-esteem increases from adolescence to adulthood in healthy populations (Huang, 2010). Thus, age may play a role in the mediation of self-esteem in MD too, but the research is too sparse to confirm this. What is more, these studies were limited to measures of global self-esteem. Given the multidimensional nature of self-esteem (Raustorp et al., 2005), domain-specific levels of self-worth may be more sensitive to investigation. In particular, physical self-worth is of interest in individuals with MD due to the typical influence of MD on physical elements of the body and function. However, this is yet to be investigated in any form of MD.

It has been shown that individuals with FSHD, BMD and LGMD experience a high frequency of body pain that is symptomatic of their condition (Jacques et al., 2019). Kinesiophobia is consistently elevated in other populations with chronic pain, such as those with low back pain, (Ishak et al., 2017), chronic musculoskeletal pain (Bränström and Fahlström, 2008), neck pain (Demirbüken et al., 2015) and post-surgery disk herniation (Svensson et al., 2011). Kinesiophobia describes an elevated fear of physical movement or injury/re-injury (Woby et al., 2005) and is commonly measured using The Tampa Scale of Kinesiophobia (Miller et al., 1991). However, kinesiophobia remains un-investigated in individuals with FSHD, BMD and LGMD. Given the presence of significant pain in these populations, it is possible that kinesiophobia is also elevated which may have important implications for MD management techniques, such as physiotherapy, and long-term physical activity limitations.

Thus, the first aim of this study is to quantify QoL and the mental health profiles (depressive symptoms, trait anxiety, global self-esteem and physical self-worth) of adults living with MD (FSHD, BMD and LGMD), compared to age-matched control adults. In addition, the physical activity and mental health factors that may be related to QoL in these individuals will be examined, along with the severity of kinesiophobia.

6.1.2 Part B

Along with the quantification of QoL and mental health in adults with MD, of particular interest is the suitability of RT as an intervention for these areas. RT is a form of exercise that has previously been shown to positively influence QoL and

mental health in a range of clinical populations. QoL was improved post RT in adults with Parkinson's disease (Ferreira et al., 2018), older adults (Kekalainen et al., 2018) and patients with chronic heart failure (Lans et al., 2018). In addition, systematic reviews and meta-analyses have revealed that RT programmes positively influence anxiety, depression and self-esteem. O' Connor et al. (2010) revealed a moderate effect of RT on the reduction of anxiety symptoms across older adults, breast cancer patients and adults with osteoarthritis, with a large effect when older adults were analysed independently. Furthermore, Mead et al. (2010) reported large reductions in the severity of depressive symptoms post RT amongst clinically depressed patients. Reductions have also been established in participants with fibromyalgia (Jones et al., 2002; Hakkinen et al., 2001), spinal cord injury (Hicks et al., 2003) and osteoarthritis (O' Reilly et al., 1999), whilst results in older adults are inconclusive. Some studies have found a positive effect of RT in older adults, (Cassilhas et al., 2007; Timonen et al., 2002; Singh et al., 1997), whilst other studies have reported no change in depression with RT in elderly populations (Jette et al., 1996; Sims et al., 2006; Chin A Paw et al., 2004; Penninx et al., 2002). However, low adherence rates (ranging from 58-71%) were evident in the latter group of studies. With regard to self-esteem, Spence et al. (2005) found a small effect of RT on improvements in global self-esteem. More recently, improvements in global self-esteem post 12 weeks' RT were shown to be accompanied by larger improvements in physical self-worth in obese women (Megakli et al., 2015).

Based on previous research in other populations, RT may also elicit beneficial effects on mental health and QoL in individuals with MD. However this is yet to be investigated, which is likely due to historical discouragement of RT in adults living

with MD. This discouragement was due to claims that RT may be harmful to the muscle cells of individuals with MD (Ansved, 2001). However, the evidence for this is limited to anecdotal case reports of overwork weakness in FSHD (Johnson and Braddom, 1971) and scapuloperoneal MD (Wagner et al., 1986), and murine evidence in MDX mice (Weller et al., 1990; Petrof et al., 1993). MDX mice represent one type of MD only (Duchenne) and in any case, the replicability of the MDX mutation to Duchenne MD is limited (Partridge, 2013). Given the stark differences in genotype and severity of Duchenne MD compared to other types of MD, along with questionable applicability of MDX mice to humans, it is illogical to presume that RT should be avoided in all types of MD. Yet, there remains a serious lack of experimental investigation into RT in individuals with MD.

A meta-analysis conducted by Gianola et al. (2013) was unable to determine whether RT was beneficial or not in MD, due to there being only four studies that investigated maximum voluntary contraction (MVC) strength following a period of RT in individuals with MD (Lindeman et al., 1995; Tollback et al., 1999; Van der Kooi et al., 2004; de Lateur and Giaconi, 1979). Nevertheless, the authors did establish that despite no overall effect of RT, the direction of the effect in each of the studies was positive (Gianola et al., 2013). It remains uncertain from published research whether RT can increase muscle strength in MD, but it does appear that RT is at the very least not harmful to adults living with MD, with likely benefits to muscle strength.

Results presented in Chapter 3 of this thesis show a significant increase in MVC torque in six out of a possible eight lower limb muscle groups following RT, in adults

with FSHD, BMD and LGMD. In addition to these strength gains from RT in FSHD, BMD and LGMD, there may be other benefits of a RT programme in these adults that are equally as important to health. More specifically, the positive influence of RT on QoL and mental health already discussed may apply to adults with MD too, but this is yet to be investigated in any depth. One experimental study has considered this in adults with Myotonic MD (Kierkegaard et al., 2011), but it was limited to the measure of QoL. Nevertheless, the authors reported no effect of a 14-week RT programme. The influence of RT on QoL in adults with FSHD, LGMD and BMD, along with the effects of RT on the more detailed measures of mental health in these populations, remain unknown.

Thus, the second aim of this study is to examine whether a 12-week programme of supervised RT influences QoL and aspects of mental health (depressive symptoms, trait anxiety, global self-esteem, physical self-worth and fear of movement), in ambulatory adults with MD (FSHD, BMD and LGMD).

6.2 Method

6.2.1 Participants & Study Design

The experimental design for this study is presented in two parts. Part A presents group comparisons between adults with FSHD (9), BMD (7), LGMD (6) and a group of 10 control adults matched in age, stature and body mass.

Part B is a within-participant design, involving a group of 17 adults with MD, inclusive of FSHD (6), BMD (5) and LGMD (6). Data were collected at three time points: PRE1 (before a 12-week control period), PRE2 (immediately after the 12-week control period) and POST (immediately after a 12-week RT programme). All 17 MD participants completed a 12-week, twice a week, RT programme. One additional testing session took place halfway through the RT programme (Mid-Train), in which questionnaire data were also collected.

Detailed descriptions of the study design, participants and the RT programme are provided in *Chapter 3.2 Method*.

Manchester Metropolitan University Ethics Committee granted ethical approval and all participants provided written informed consent after which data collection took place at Manchester Metropolitan University on all occasions.

6.2.2 Procedure

6.2.2.1 Part A - MD versus Controls

Participants were given seven questionnaires (outlined below) which were each explained by one investigator. Participants were asked to complete the questionnaires in their own time and to return them to the investigators within one-

two weeks. The participants were able to ask questions about each questionnaire if required and were informed that the investigator was available via phone or email should they require assistance.

6.2.2.2 Part B - Effects of RT

Participants were given seven questionnaires on four different occasions: PRE1, PRE2, Mid-Train and POST. They were asked to complete the questionnaires (outlined below) in their own time and to return the questionnaires to the investigators within one week. The participants were able to ask questions about each questionnaire if required and were informed that the investigator was available via phone or email should they require assistance.

6.2.3 Measures

Seven questionnaires that assessed QoL and multiple aspects of mental health, along with one questionnaire that quantified physical activity levels, were included within this study. Appendix 4 contains copies of the questionnaires. Each measure is described below:

6.2.3.1 The 36-item Short Form Health Survey

The 36-item Short Form Health Survey is a self-report generic survey that covers 36 questions on functional health and wellbeing to assess QoL, from the participant's perspective (Ware, 2000). Each question has a multiple-choice Likert scale on which participants rate themselves. The answers are summarised into a physical component health score and a mental component health score, such that higher scores indicate better health. The scale has excellent test-retest reliability in both components, with a correlation coefficient above .80 (Ware, 2000).

6.2.3.2 Beck Depression Inventory

The Beck Depression Inventory is a 21 question, multiple choice, self-report questionnaire that measures depressive symptoms. It has good reliability, with test-retest correlation coefficients of .96 (Sprinkle et al., 2002). The questionnaire includes items relating to symptoms of depression and participants score each question from 0 (least) to 3 (most), with a total sum score indicating overall depressive symptoms from 0-63. Higher scores indicate increased severity of depressive symptoms. The cut scores for the Beck Depression Inventory are as follows: ≤ 10 indicates zero to minimal depressive symptoms, 11-20 indicates mild depressive symptoms, 21-30 indicates moderate depressive symptoms, and ≥ 31 indicates severe depressive symptoms.

6.2.3.3 State-Trait Anxiety Inventory

The trait sub-scale of the State-Trait Anxiety Inventory (Spielberger et al., 1983) is a 20 question, multiple choice, self-report questionnaire that measures trait-anxiety, which is a predisposition to long-lasting and persistent feelings of anxiety that are not restricted to particular circumstances. The trait scale has excellent test-retest reliability, with a correlation coefficient of .86 (Spielberger et al., 1983). The scale includes statements for participants to score between 1 (not at all) to 4 (very much so). Total scores can range between 20-80, with higher scores indicating more severe anxiety symptoms.

6.2.3.4 Rosenberg Self-Esteem Survey

The Rosenberg Self-Esteem Scale is a measure of global self-esteem (Rosenberg, 1965) with excellent reliability (correlation coefficient of .90; (Sinclair et al., 2010).

The scale has 10 questions that assess both the positive and negative feelings towards the self. Participants rate themselves on a 4-point Likert scale, with total scores ranging from 10 to 40. The higher the score the higher the self-esteem.

6.2.3.5 Physical Self-Perception Profile

The Physical Self-Perception Profile is a reliable (test-retest correlation coefficient between .74 and .91) (Fox and Corbin, 1989) self-report questionnaire that is comprised of thirty questions that assess physical self-worth in the global domain and self-perceptions in four sub-scales: sport competence, body attractiveness, physical strength and physical conditioning and exercise. An additional eight questions relate to perceived importance in the four sub-scales (sport competence, body attractiveness, physical strength and physical conditioning and exercise) and provide a measure of importance attached by the participant to the respective sub-scale.

6.2.3.6 Tampa Scale of Kinesiophobia

The Tampa Scale of Kinesiophobia is a self-report, multiple choice questionnaire that evaluates fear of movement or injury in individuals who experience chronic pain (Miller et al., 1991). The questionnaire has 17-items which participants answer using a Likert scale ranging from strongly agree to strongly disagree. The scale has good test-retest reliability, with a correlation coefficient $\geq .82$ (Woby et al., 2005). Total score can range between 17 and 68, with higher scores indicating a higher fear of movement. An exact cut-off value for high kinesiophobia has not been established, but values used consistently within the literature to define high

kinesiophobia range from ≥ 35 to 37 (Larsson et al., 2016; Demirbüken et al., 2015; Mahmood et al., 2018).

6.2.3.7 Physical Activity Score for Individuals with Physical Disability

The Physical Activity Scale for Individuals with Physical Disability measures levels of participation in physical activities over the last 7 days, in individuals with physical disabilities (Washburn et al., 2002), with good (ICC = .77) test-retest reliability (van der Ploeg et al., 2007). The scale assesses engagement in leisure activities, light, moderate and strenuous sport and recreation, exercise for muscle strength and endurance, household activities, home repairs, gardening, caring for others and non-sedentary occupational activities. Participants state the amount of days over the last 7 that they participated in each activity, including never, seldom (1-2 days per week), sometimes (3-4 days per week) or often (5-7 days per week), and how many hours they typically participated in each activity per day, ranging from < 1 hour, 1 but < 2 hours, 2-4 hours and > 4 hours.

6.2.4 Data Analysis

Each questionnaire was scored according to the relevant manual and analysed in Microsoft Excel. In part A, data are presented as means and standard deviations for the control group, overall MD group and the MD sub-groups: FSHD BMD and LGMD, but statistical analysis is restricted to comparison between the overall MD group and control group. For part B, data are presented as means and standard deviations for the overall MD group at four-time points: PRE1, PRE2, Mid-Train and POST, but statistical analysis is limited to comparison between PRE1, PRE2 and POST. In all instances, two data points were missing from the Mid-Train time point. As the

Tampa Scale of Kinesiophobia is designed for individuals with chronic pain, data were not collected in the healthy control group. In MD participants, kinesiophobia data were collected in thirteen participants (6 FSHD and 7 BMD) for part A and in 9 MD participants (4 FSHD and 5 BMD) for part B, due to an error in the questionnaire packs provided for participants.

6.2.5 Statistical Analysis

All statistical analysis was completed using IBM SPSS Statistics 22 software. The critical level of significance was set at $p \leq .05$.

6.2.5.1 Part A – MD versus Controls

For all dependent variables that passed the parametric assumptions, independent samples t-tests were performed between the control and overall MD group, except for kinesiophobia. For all dependent variables that did not pass the parametric assumptions, Mann-Whitney U tests were performed. The following dependent variables did not satisfy the parametric assumptions: physical and mental health quality of life, depressive symptoms, global physical self-worth, body physical self-perception, strength physical self-perception and all four importance domains of the physical self-perception profile. For analysis of kinesiophobia, an independent samples t-test was performed between the FSHD and BMD group.

To investigate any associations between QoL (in both the physical and mental health components) and physical activity, depressive symptoms, trait anxiety, global self-esteem, global physical self-worth and kinesiophobia, Pearson's correlation coefficients were conducted using data for the overall MD group. In cases where data were non-parametric, Kendall Tau correlations were conducted.

6.2.5.1 Part B – Effects of RT

For all dependant variables that passed the parametric assumptions, a one-way repeated measures ANOVA was performed between the time points. If the data did not pass Mauchly's test of sphericity ($P < .05$), a Greenhouse-Geisser correction was applied. From the ANOVA, both the retrospective observed power and the effect size, calculated as partial eta squared (η^2), were reported. Post hoc analysis was completed using least significant difference pairwise comparisons. Data that were not normally distributed were analysed using a Friedman's ANOVA, followed by post hoc analysis using Wilcoxon-signed rank tests (least significant difference). The following dependent variables did not satisfy the parametric assumptions: sport physical self-perception, strength physical self-perception, body physical self-perception and all four domains of the importance physical self-perception profile.

6.3 Results

6.3.1 Part A – MD versus Controls

Participant characteristics, including age, stature and body mass, for the control, MD group and subdivided MD groups (FSHD, BMD and LGMD) are presented in *Chapter 3.2 Method*. No significant differences ($p > .05$) in age, stature or body mass were found between any of the groups.

6.3.1.1 Quality of Life

QoL scores in the physical domain were 38.5% lower ($p \leq .001$) in the MD compared to the control group (Figure 6.1). QoL scores in the mental domain were not significantly different ($p > .05$) between the MD and the control group (Figure 6.1).

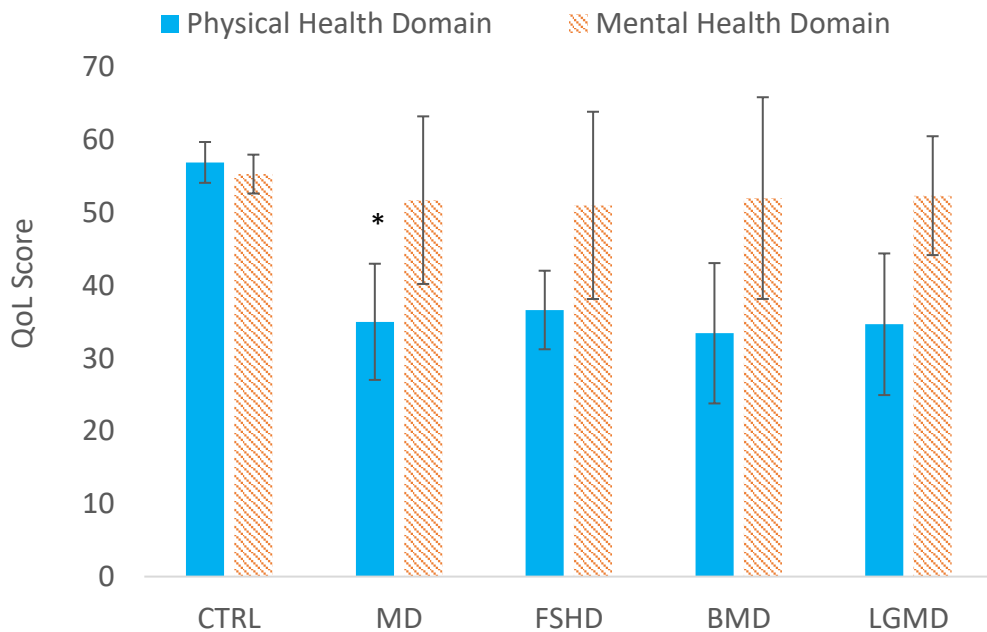


Figure 6.1: Physical health and mental health quality of life (QoL) scores for the control (CTRL) and MD group, along with the MD subgroups: FSHD, BMD and LGMD. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from the control group.

6.3.1.2 Depressive Symptoms

All control participants scored ≤ 10 on the Beck Depression Inventory, which is categorised as zero to minimal depressive symptoms. Of the MD participants, 36.4% scored between 11 and 20 (mild depressive symptoms), and 4.5% scored between 21-30 (moderate depressive symptoms) and 4.5% scored ≥ 31 (severe depressive symptoms) on this inventory. Severity of depressive symptom scores were 14% greater ($p \leq .01$) in the MD than the control group (Figure 6.2).

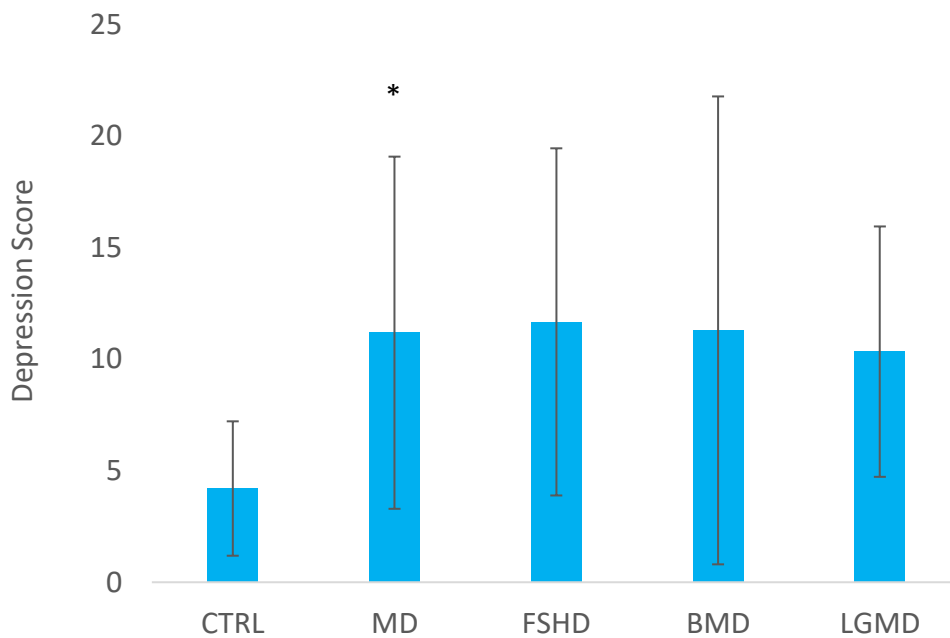


Figure 6.2: Beck Depression scores for the control CTRL) and MD group, along with the MD subgroups: FSHD, BMD and LGMD. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from the control group.

6.3.1.3 Trait Anxiety

Trait anxiety scores were 22.7% greater in the MD than the control group but this was not significantly different ($p = .054$; Figure 6.3).

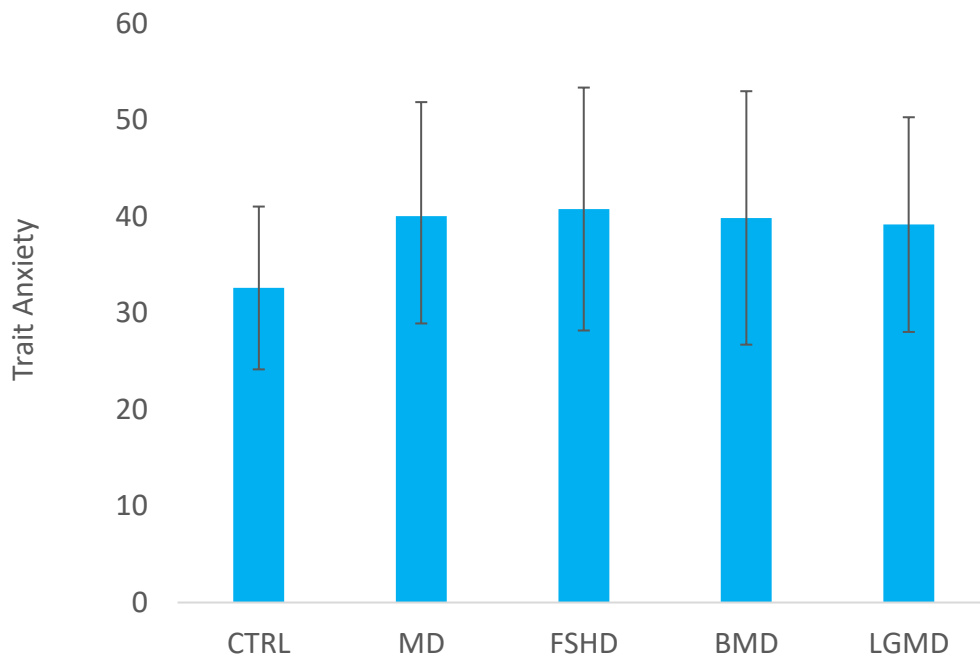


Figure 6.3: Trait anxiety scores for the control (CTRL) and MD group, along with the subdivided MD groups: FSHD, BMD and LGMD. Bars represent the mean and error bars represent the standard deviation.

6.3.1.4 Self-Esteem

Rosenberg self-esteem scores were not significantly different between the control and MD group ($p = .095$; Figure 6.4).

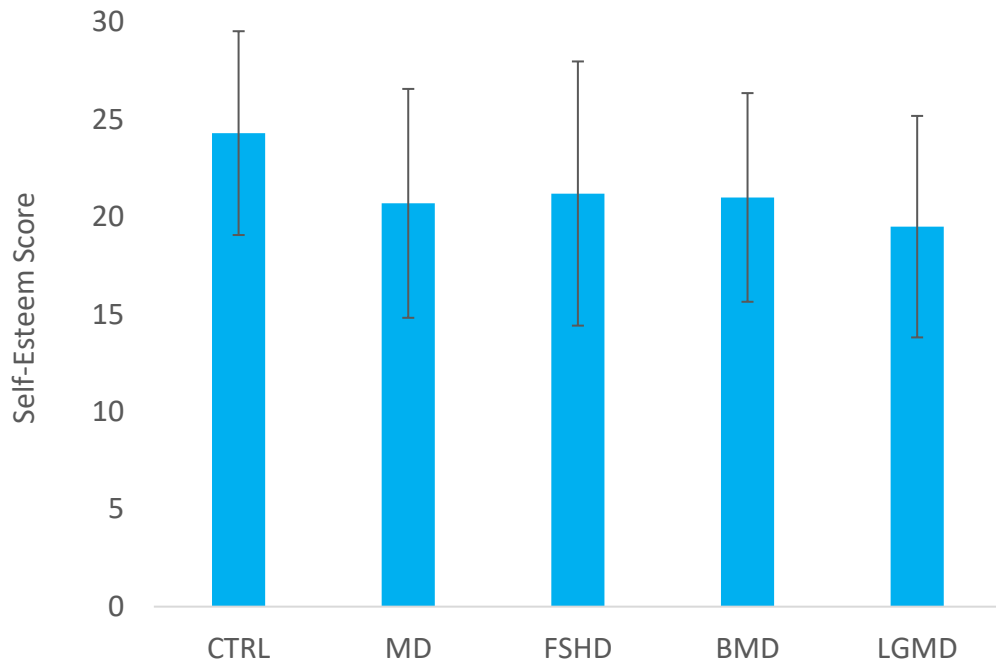


Figure 6.4: Rosenberg self-esteem scores for the control (CTRL) and MD group, along with the MD subgroups: FSHD, BMD and LGMD. Bars represent the mean and error bars represent the standard deviation.

6.3.1.5 Physical Self-Perception Profile

Physical self-perception profile score in the global domain was 35.3% lower ($p \leq .001$) in the MD compared to the control group (Figure 6.5). Physical self-perception profile scores were lower in the sport, condition and strength domains by 35.3% ($p \leq .01$), 28% ($p \leq .01$) and 42.9% ($p \leq .001$), respectively, in the MD compared to the control group (Table 6.1). There was no difference between the MD and control group in the body domain or any of the importance domains ($p > .05$; sport importance, condition importance, body importance or strength importance).

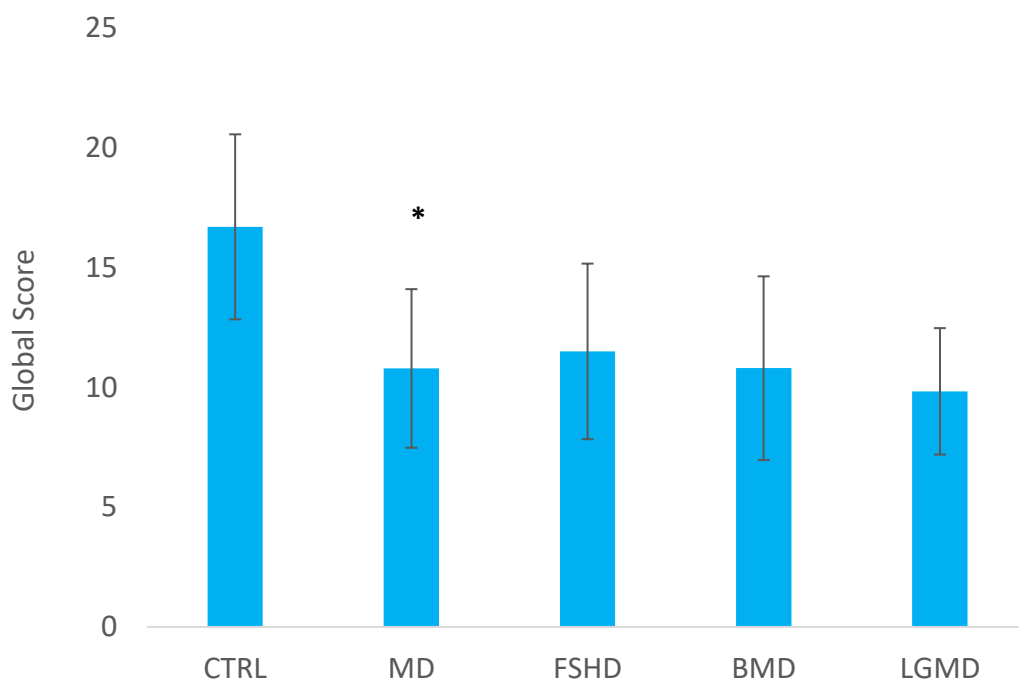


Figure 6.5: Global physical self-worth scores for the control (CTRL) and MD group, along with the MD subgroups: FSHD, BMD and LGMD. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from the control group.

Table 6.1: Physical Self-Perception Profile scores in the sport, condition body and strength domains for the control (CTRL) and MD group, along with the MD subgroups: FSHD, BMD and LGMD. * represents a significant difference from the control group (CTRL). S = score, I = Importance.

	Sport		Condition		Body		Strength	
	S	I	S	I	S	I	S	I
CTRL	15.6 ± 5.0	4.7 ± 1.7	16.4 ± 4.4	5.9 ± 1.7	13.5 ± 2.8	4.5 ± 1.4	15.4 ± 3.9	5.1 ± 2.0
MD	10.1 ± 3.6*	4.3 ± 1.0	11.8 ± 3.2*	5.4 ± 1.2	11.0 ± 3.2	4.8 ± 1.1	8.8 ± 3.0*	5.1 ± 1.1
FSHD	12.4 ± 2.7	4.4 ± 0.5	12.5 ± 1.8	5.5 ± 1.3	10.9 ± 3.6	5.0 ± 0.8	9.6 ± 3.0	4.8 ± 0.9
LGMD	9.2 ± 4.2	4.8 ± 2.6	12.0 ± 5.3	5.2 ± 2.6	10.3 ± 2.7	5.0 ± 2.6	7.8 ± 2.6	5.2 ± 2.6
BMD	7.6 ± 1.8	3.4 ± 0.5	10.4 ± 1.7	5.4 ± 0.9	12.0 ± 3.4	4.4 ± 1.5	8.8 ± 3.1	5.6 ± 1.5

6.3.1.6 Tampa Scale of Kinesiophobia

A high level of kinesiophobia (≥ 35) was present in 54% of the MD participants overall. There was no difference in severity of kinesiophobia between the FSHD and BMD group ($p > .05$), with mean scores of 36 ± 5 and 36 ± 6 in each group, respectively (Figure 6.6).

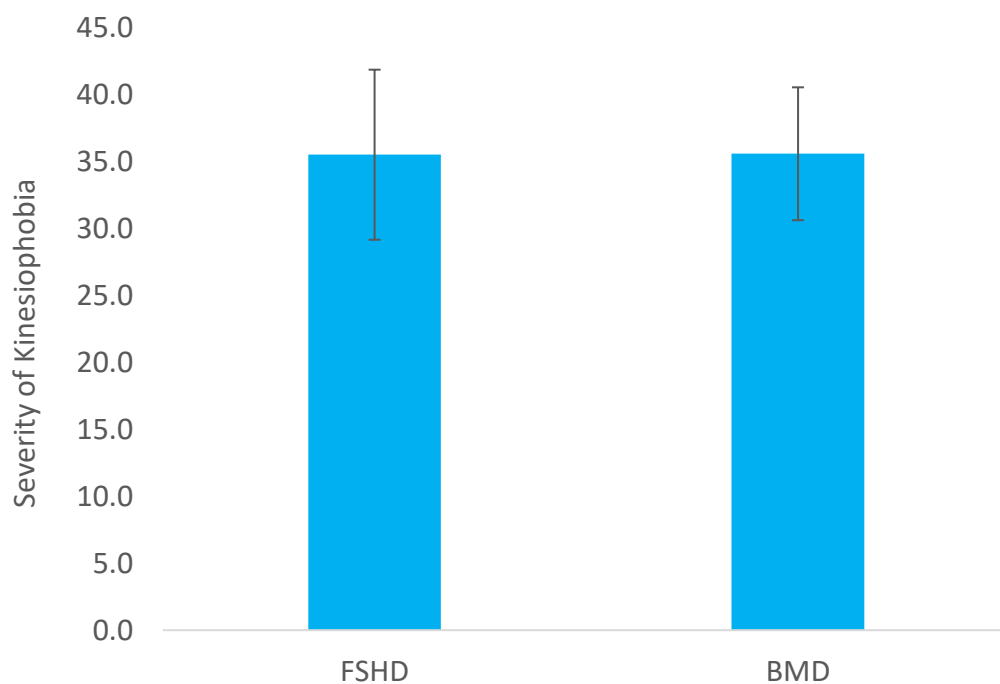


Figure 6.6: Scores on the Tampa scale of kinesiophobia for the FSHD and BMD group. Bars represent the mean and error bars represent the standard deviation.

6.3.1.6 Correlations with QoL

6.3.1.6.1 Physical Activity

Physical activity score was not related to QoL in the physical ($r = .168$, $p > .05$; Figure 6.7) or the mental health domain ($r = -.191$, $p > .05$; Figure 6.8).

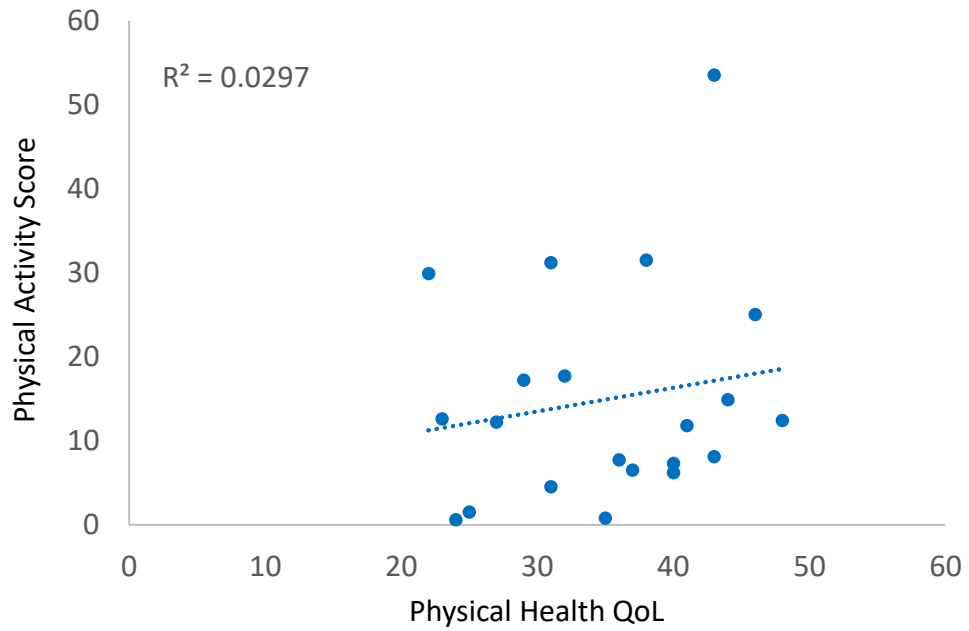


Figure 6.7: Physical activity score and physical health QoL in MD participants.

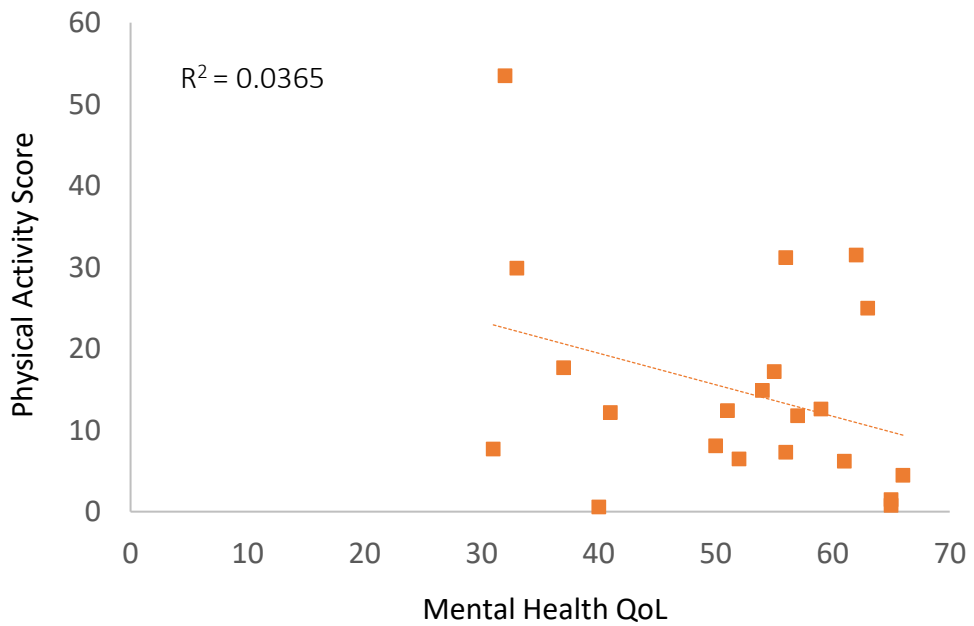


Figure 6.8: Physical activity score and mental health QoL in MD participants.

6.3.1.6.2 Depressive Symptoms

Depression was not related to QoL in the physical health domain ($r = -.068$, $p > .05$; Figure 6.9). Depression was significantly negatively related to QoL in the mental health domain ($r = -.706$, $p \leq .001$; Figure 6.10).

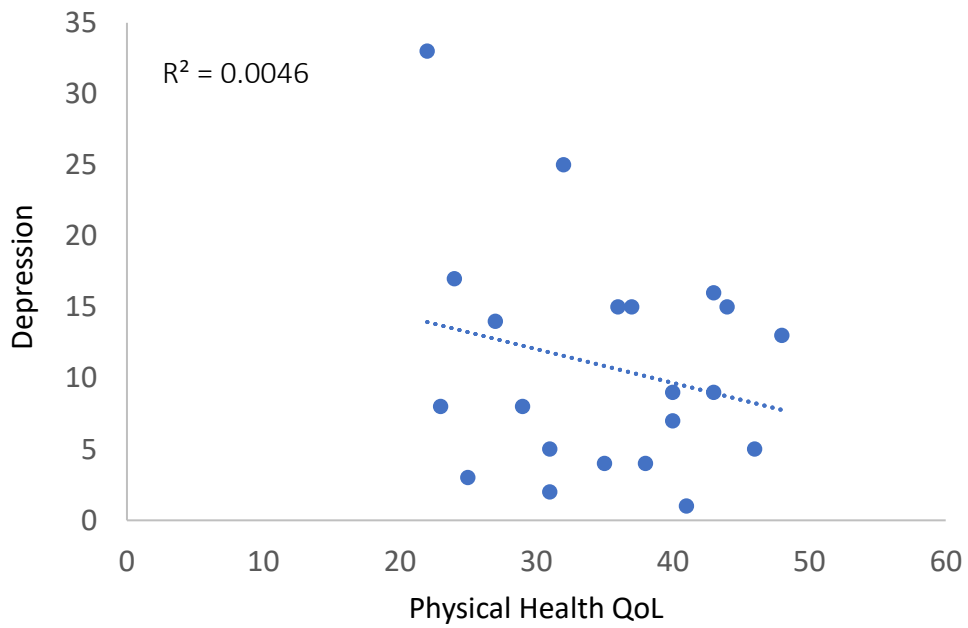


Figure 6.9: Depression score and physical health QoL in MD participants.

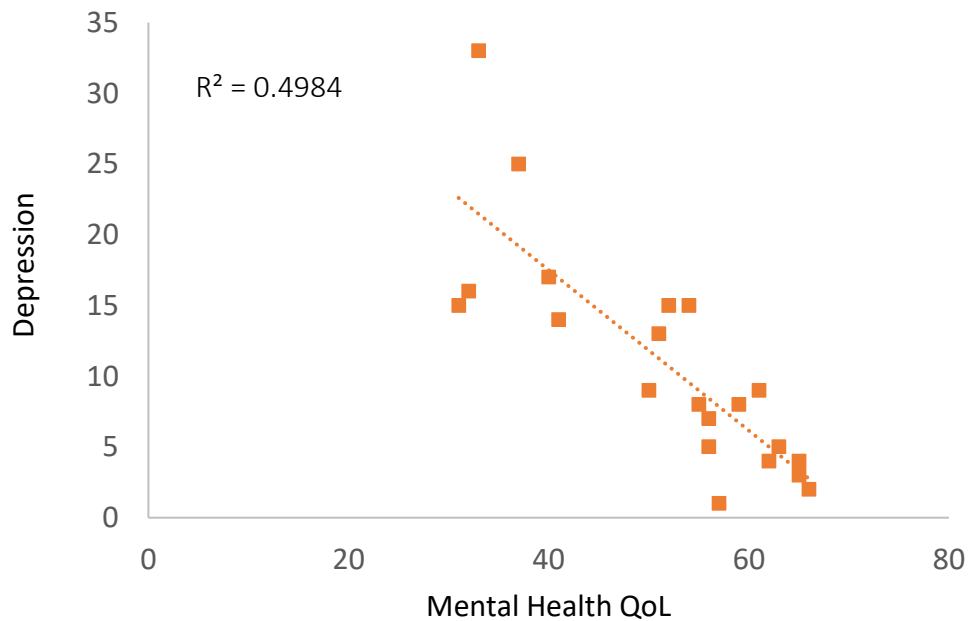


Figure 6.10: Depression score and mental health QoL in MD participants

6.3.1.6.3 Anxiety

Anxiety was not related to QoL in the physical health domain ($r = -.154$, $p > .05$; Figure 6.11). Anxiety was significantly negatively related to QoL in the mental health domain ($r = -.638$, $p \leq .001$; Figure 6.12).

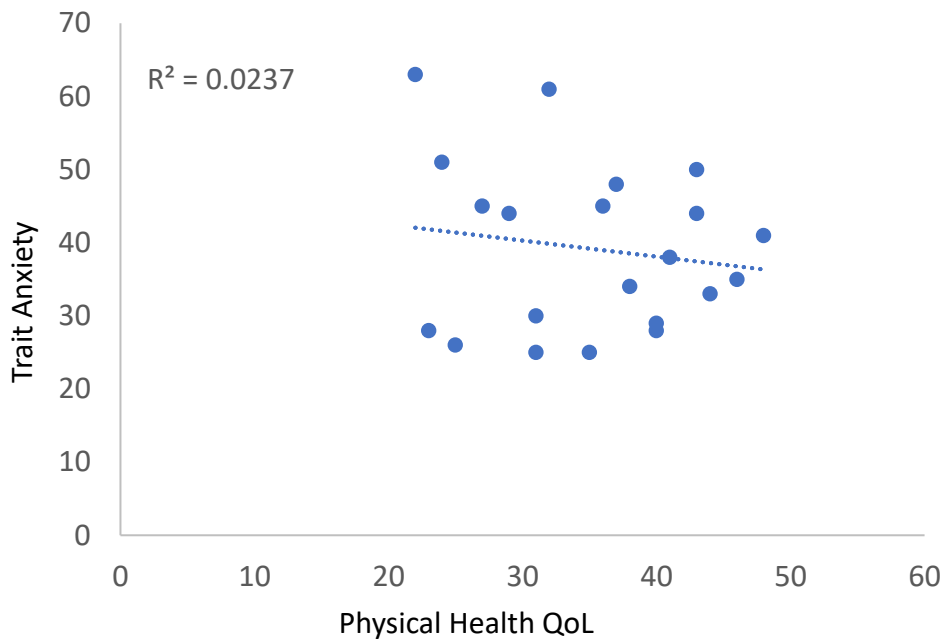


Figure 6.11: Trait anxiety and physical health QoL in MD participants.

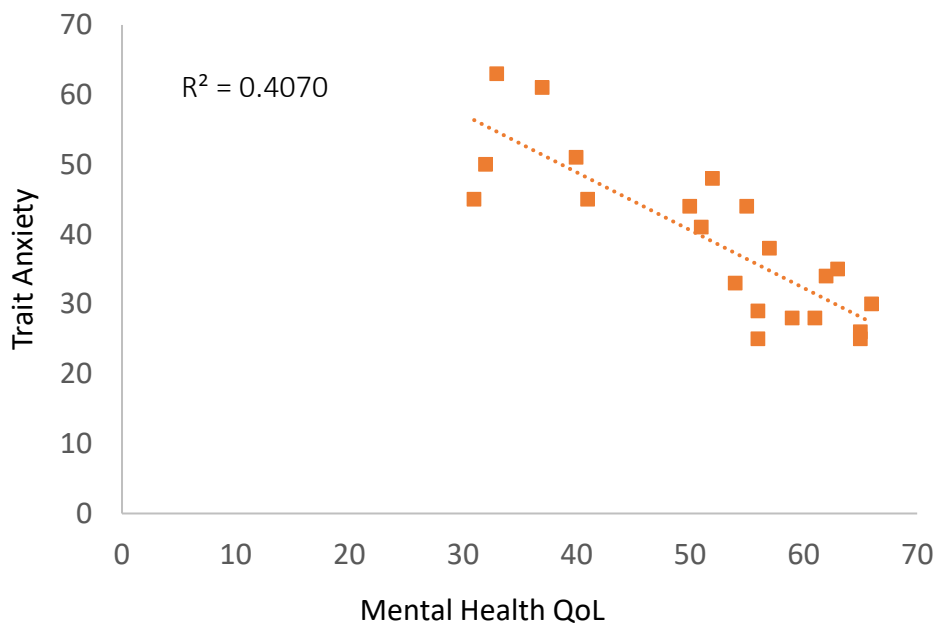


Figure 6.12: Trait anxiety and mental health QoL in MD participants.

6.3.1.6.4 Self-Esteem

Self-esteem was not related to QoL in the physical health domain ($r = -.096$, $p > .05$; Figure 6.13). Self-esteem was significantly positively related to QoL in the mental health domain ($r = .521$, $p \leq .001$; Figure 6.14).

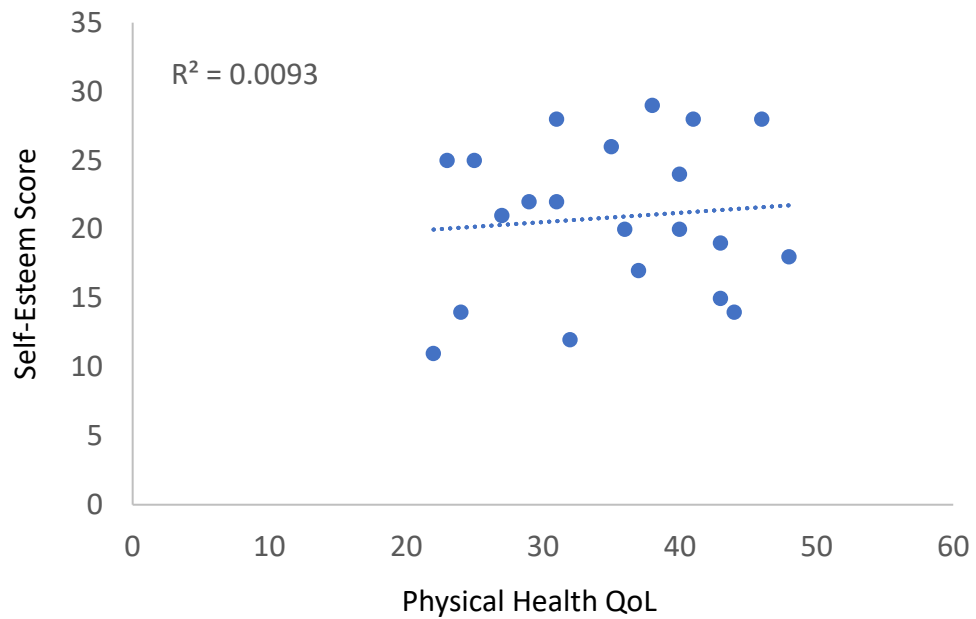


Figure 6.13: Self-esteem score and physical health QoL in MD participants.

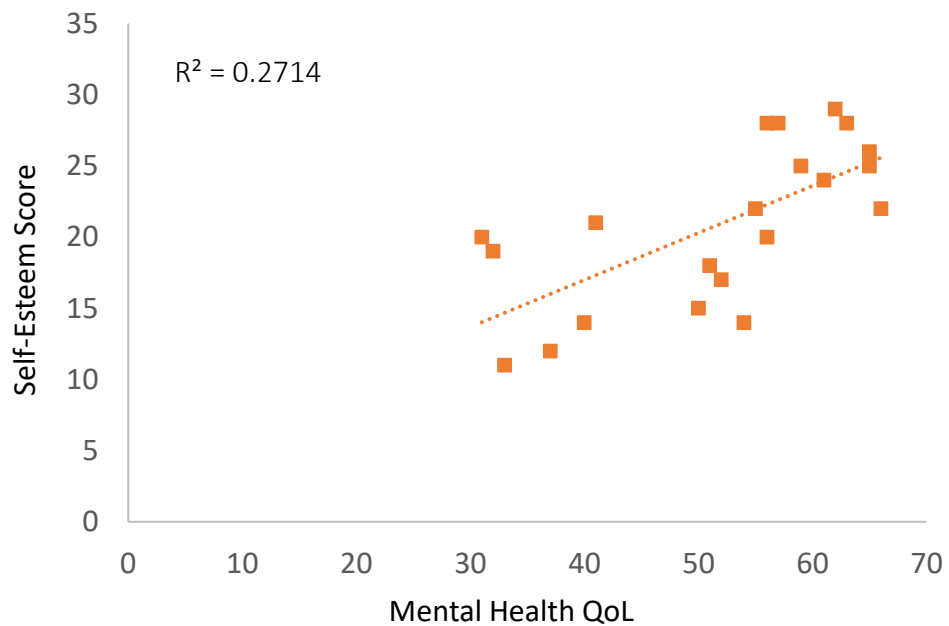


Figure 6.14: Self-esteem score and mental health QoL in MD participants.

6.3.1.6.5 Physical Self-Perception (Global)

Global physical self-perception was not related to QoL in the physical health domain ($r = -.258, p > .05$; Figure 6.15) but it was significantly positively related to QoL in the mental health domain ($r = .594, p = .007$; Figure 6.16).

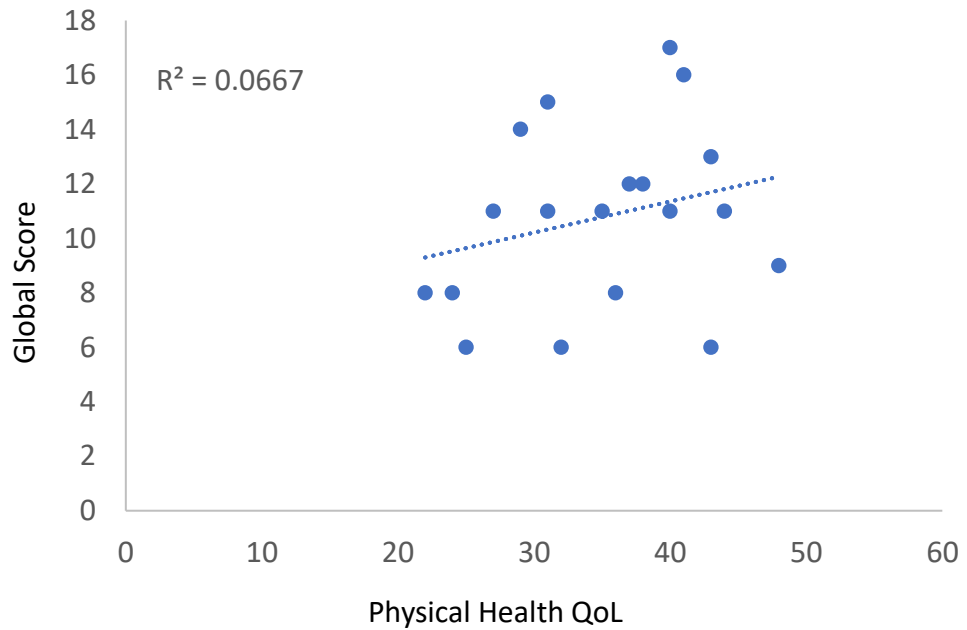


Figure 6.15: Physical self-perception profile in the global domain and physical health QoL in MD participants.

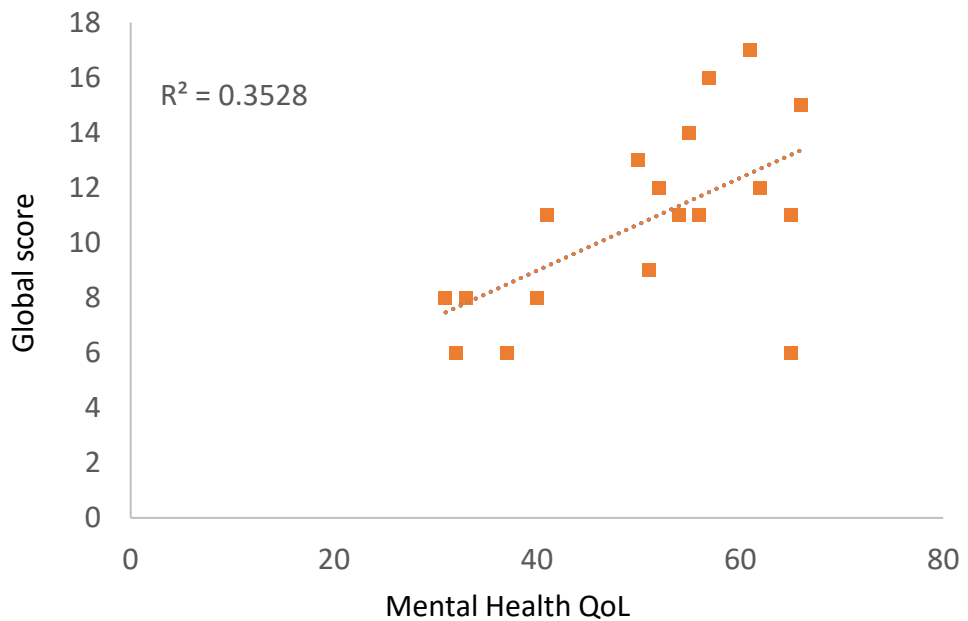


Figure 6.16: Physical self-perception profile in the global domain and mental health QoL in MD participants

6.3.1.6.6 Tampa Scale

Tampa scores were not related to QoL in the physical health domain ($r = .415$, $p > .05$; Figure 6.17) or in the mental health domain ($r = .042$, $p > .05$; Figure 6.18).

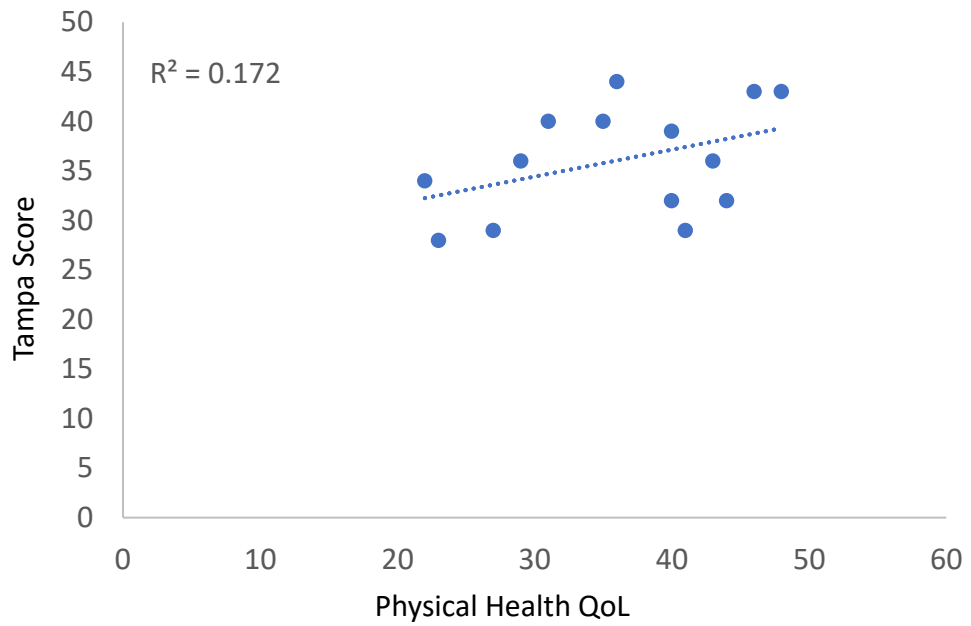


Figure 6.17: Tampa score and physical health QoL in MD participants

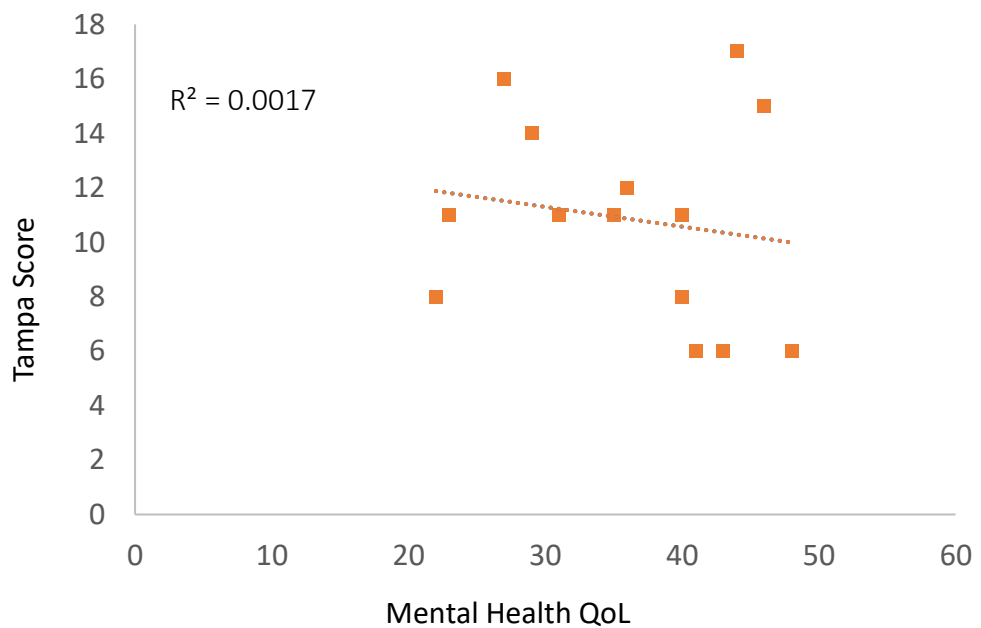


Figure 6.18: Tampa score and mental health QoL in MD participants

6.3.2 Part B – Effects of RT

6.3.2.1 Quality of Life

There was an overall main effect of time on physical health QoL scores ($p = .024$, $\eta^2 = .21$; Figure 6.19), with an observed power of .70. Post hoc analysis revealed that physical health QoL scores did not differ between PRE1 and PRE2 ($p > .05$) but significantly increased by 11.5% from PRE1 to POST the RT programme ($P = .017$) and by 10.5% from PRE2 and POST ($P = .022$).

There was an overall main effect of time on mental health QoL scores ($p = .048$, $\eta^2 = .17$; Figure 6.19), with an observed power of .60. Post hoc analysis revealed that mental health QoL scores did not differ between PRE1 and PRE2 ($p > .05$), but significantly increased by 11.6% from PRE1 to POST ($p = .038$) with no difference between PRE2 and POST ($p = .071$), although the p value was close to the significance threshold of $< .05$.

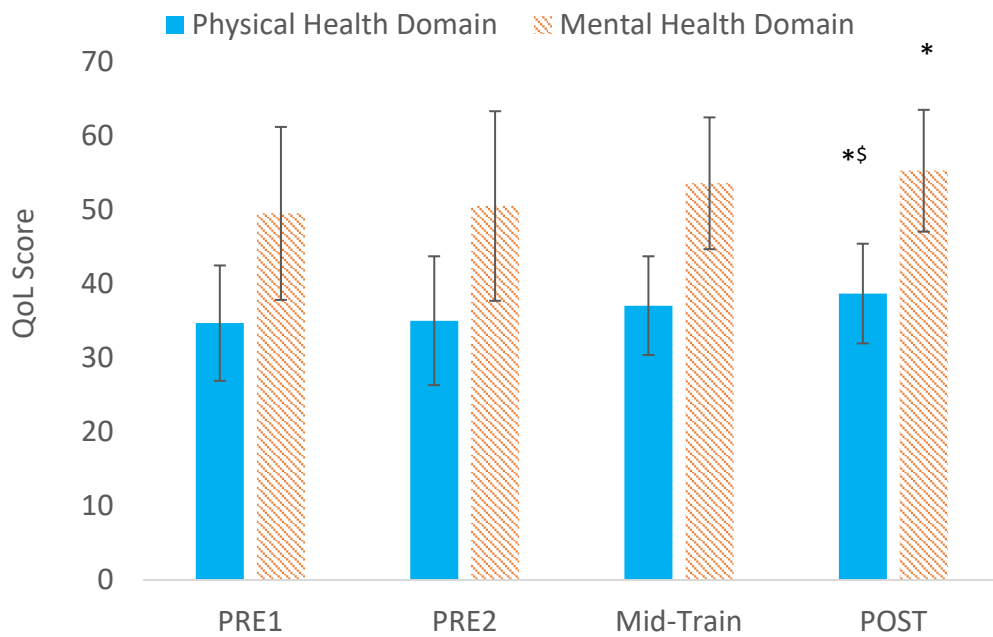


Figure 6.19: Quality of life scores in the physical health and mental health domains at PRE1, PRE2, Mid-Train and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and [§] represents a significant difference from PRE2.

6.3.2.2 Depressive Symptoms

There was a main effect of time on depression ($p \leq .01$, $\eta^2 = .32$; Figure 6.20), with an observed power of .79. Post hoc analysis showed that depression symptom severity decreased between PRE1 and PRE2 by 8.7% ($p < .05$), and by 26.2% from PRE1 to POST ($P \leq .01$), with a 19.2% reduction from PRE2 to POST ($p = .049$). The number of participants that scored ≤ 10 (no depressive symptom), between 11-20 (mild depressive symptoms), between 21-30 (moderate depressive symptoms) are ≥ 31 (severe depressive symptoms) are presented in Table 6.2.

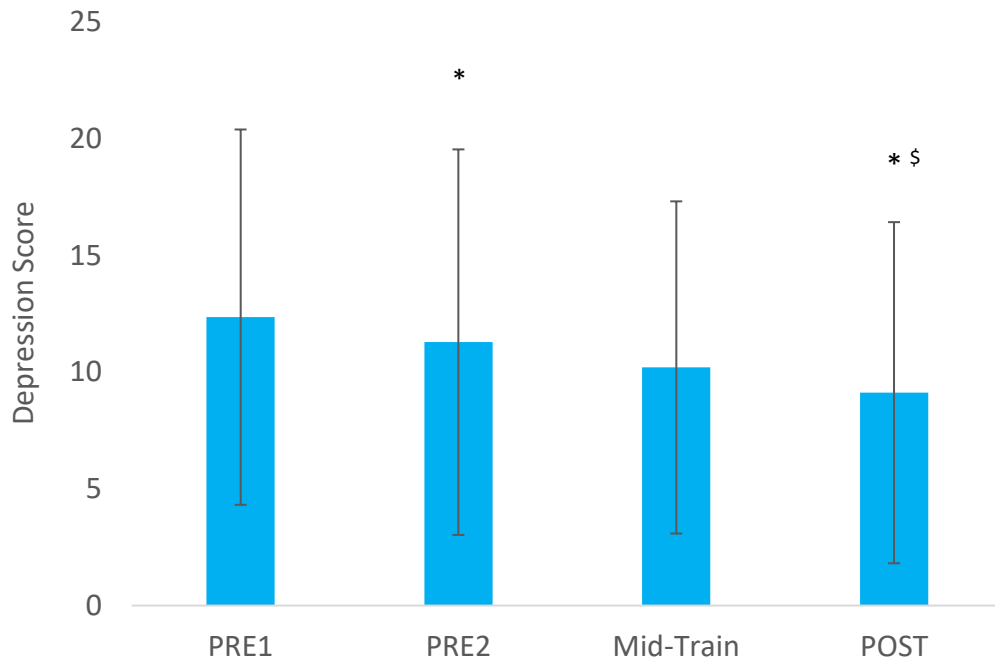


Figure 6.20: Depression scores at PRE1, PRE2, Mid-Train and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

Table 6.2: Number (percentage) of participants that scored no depressive symptoms (≤ 10), mild symptoms (11-20), moderate symptoms (21-30) and severe depressive symptoms (≥ 31) on the Beck Depression Inventory Scale.

	PRE1	PRE2	POST
≤ 10	8 (47)	8 (47)	11 (65)
11-20	7 (41)	7 (41)	4 (23)
21-30	1 (6)	1 (6)	2 (12)
≥ 31	1 (6)	1 (6)	0 (0)

6.3.2.3 Trait Anxiety

There was an overall main effect of time on trait anxiety ($p \leq .01$, $\eta^2 = .27$; Figure 6.21), with an observed power of .83. Post hoc analysis showed that anxiety scores did not significantly differ between PRE1 and PRE2 ($p \geq .05$), but significantly decreased by 11.5% from PRE1 to POST ($P = .016$) and by 11.2% from PRE2 to POST ($p = .021$) completion of the RT programme.

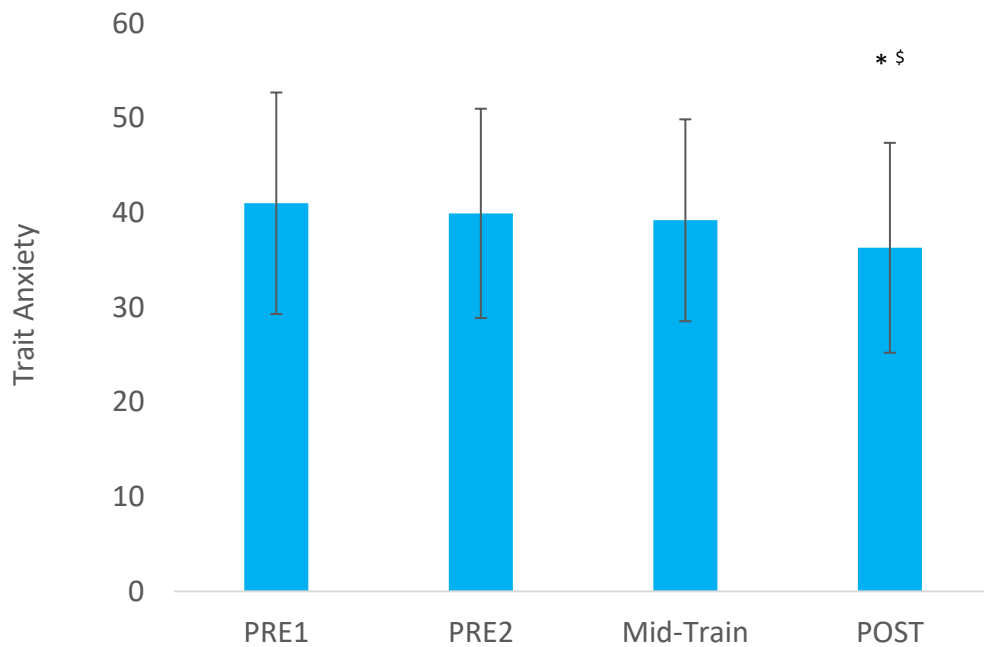


Figure 6.21: Trait anxiety scores at PRE1, PRE2, Mid-Train and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

6.3.2.4 Self-Esteem

There was an overall main effect of time on self-esteem ($p < .01$, $\eta^2 = .37$; Figure 6.22), with an observed power of .89. Post hoc analysis showed that self-esteem scores did not significantly differ between PRE1 and PRE2 ($p > .05$) but significantly increased by 9.6% between PRE2 and POST ($p = .036$) and increased by 14.0% from PRE1 to POST completion of the RT programme ($P \leq .001$).

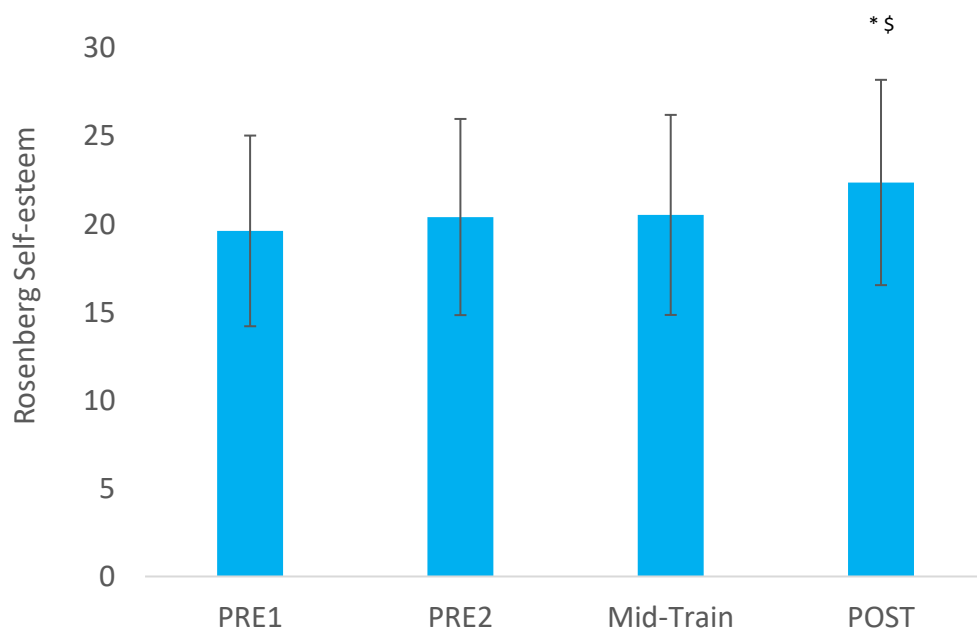


Figure 6.22: Rosenberg Self-Esteem Scale scores at PRE1, PRE2, Mid-Train and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and § represents a significant difference from PRE2.

6.3.2.5 Physical Self-Perception Profile

There was an overall main effect of time on global physical self-perception profile ($p = .023$, $\eta^2 = .22$; Figure 6.23), with an observed power of .70. Post hoc analysis showed that scores did not significantly differ between PRE1 and PRE2 ($p > .05$) but did increase by 14.5% from PRE2 to POST ($p = .023$) and by 14.5% between PRE1 and POST ($p = .043$).

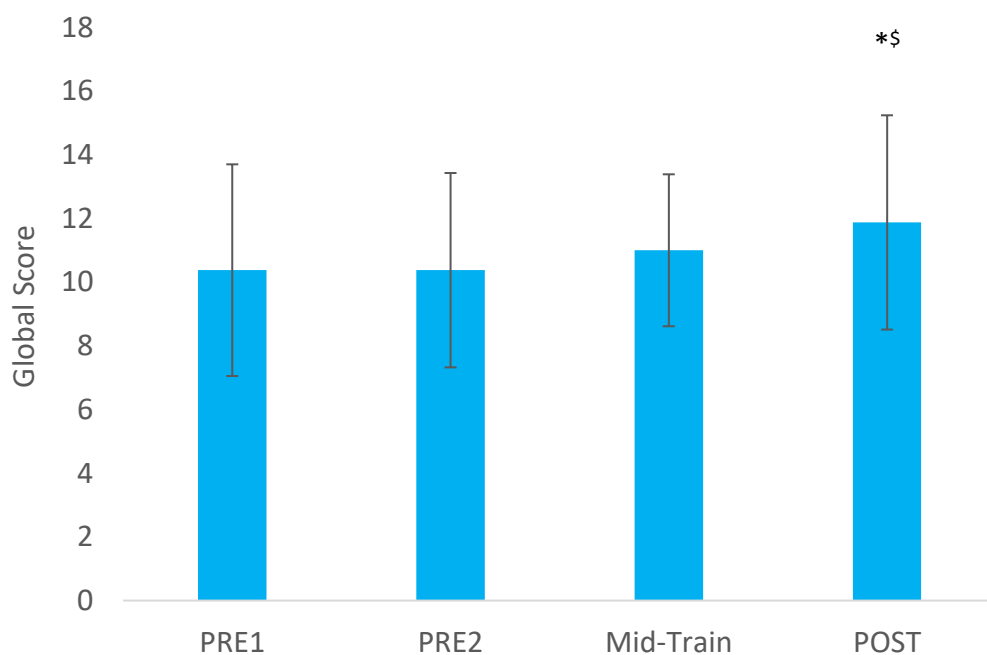


Figure 6.23: Physical self-worth scores in the global domain at PRE1, PRE2, Mid-Train and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation. * represents a significant difference from PRE1 and $\text{\$}$ represents a significant difference from PRE2.

There was no overall main effect of time on sport physical self-perception profile ($p > .05$; Table 6.3).

There was an overall main effect of time on condition physical self-perception profile ($p \leq .001$, $\eta^2 = .43$; Table 6.3), with an observed power of .98. Post hoc

analysis showed that scores did not differ between PRE1 and PRE2 ($p > .05$) but were increased by 20.8% ($p = .004$) from PRE1 to POST and by 22.3% ($p = .001$) from PRE2 to POST.

There was an overall main effect of body physical self-perception profile ($p = .012$; Table 6.3). Post hoc analysis showed that scores did not differ between PRE1 and PRE2 ($p > .05$) or between PRE1 and POST ($p = .073$) but increased by 13.2% ($p = .014$) from PRE2 to POST.

There was no overall main effect of strength physical self-perception profile ($p = .101$; Table 6.3).

There was an overall main effect of time on physical self-perception profile score in the sport importance domain ($p = .004$; Table 6.3). Post hoc analysis showed that scores decreased by 7.2% between PRE1 and PRE2 ($p = .023$), increased by 14.2% between PRE2 and POST ($p = .016$) and did not differ between PRE1 and POST ($p = .102$).

There was no overall main effect of time on physical self-perception profile score in the condition importance domain ($p = .124$, Table 6.3), the body importance domain ($p = .276$, Table 6.3), or the strength importance domain ($p = .629$, Table 6.3).

Table 6.3: Physical self-perception profile scores in the sport, condition, body and strength domains for PRE1, PRE2, Mid-Train and POST. * represents a significant difference from the same variable in PRE1 and [§] represents a significant difference from the same variable in PRE2. S = score, I = Importance.

	Sport		Condition		Body		Strength	
	S	I	S	I	S	I	S	I
PRE1	9.3 ± 3.1	4.1 ± 1.0	11.1 ± 2.8	5.3 ± 1.3	10.6 ± 3.0	4.7 ± 1.1	8.2 ± 2.7	5.2 ± 1.2
PRE2	9.2 ± 2.3	3.9 ± 1.2*	11.0 ± 2.3	5.4 ± 1.2	11.1 ± 2.5	4.4 ± 0.8	8.5 ± 2.6	4.9 ± 1.2
Mid-Train	10.6 ± 2.8	4.1 ± 0.9	12.4 ± 2.1	5.6 ± 1.3	11.8 ± 2.6	4.8 ± 0.7	8.9 ± 2.5	5.4 ± 1.1
POST	10.4 ± 3.1	4.4 ± 1.0 [§]	13.4 ± 2.3* [§]	5.6 ± 1.4	11.9 ± 3.0 [§]	5.0 ± 0.7	9.7 ± 3.0	5.3 ± 1.2

6.3.2.6 Tampa Scale of Kinesiophobia

There was no overall main effect of time on Tampa score ($p = .738$, $\eta p^2 = .04$;

Figure 6.24), with an observed power of .09.

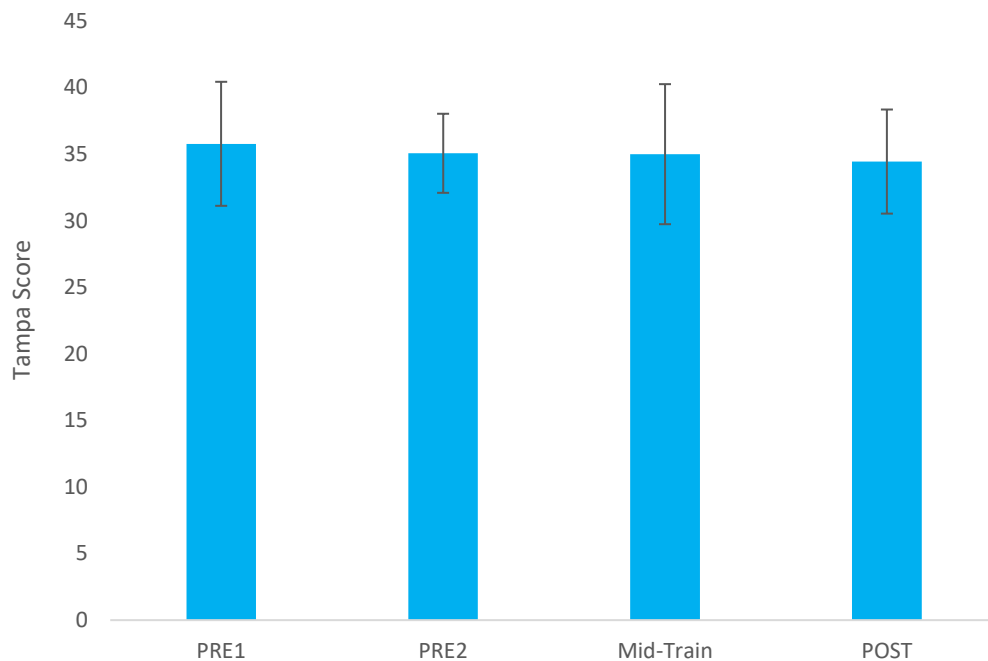


Figure 6.24: Scores from the Tampa Scale of Kinesiophobia at PRE1, PRE2, Mid-Train and POST completion of the RT programme. Bars represent the mean and error bars represent the standard deviation.

6.3.2.7 Participant comments

Throughout the RT programme, numerous participants expressed their feelings towards the RT programme. Such conversations were encouraged by the investigators but never prompted. Participants regularly spoke about how they felt the RT was influencing/had influenced their life. A variety of comments that stood out to the investigators are presented in Appendix 4.8.

6.4 Discussion

6.4.1 Part A – MD versus Controls

Part A of this study examined the mental health and QoL profiles of a group of adults with MD (FSHD, BMD and LGMD), compared to an age-matched control group, along with the severity of kinesiophobia in adults with FSHD and BMD. In addition, relationships between physical activity level, numerous mental health variables and QoL were examined. Overall, various aspects of mental health and wellbeing were poorer in the MD compared to the control group, including physical QoL, the severity of depressive symptoms and physical self-worth, and the severity of kinesiophobia was high in both the FSHD and BMD sub-groups. In addition, clear associations between depressive symptoms and trait anxiety along with self-esteem and physical self-worth were found with QoL in the mental domain.

As expected, QoL in the physical domain was lower in the MD than control group, and QoL in the mental domain was similar between the two groups. This latter result is in accordance with previous studies that also reported no difference in the mental subscale of QoL, between individuals with Duchenne MD and non-dystrophic control populations (Kohler et al., 2005; Pangalila, van den Bos, Bartels, Bergen, Kampelmacher, et al., 2015; Elsenbruch et al., 2013). These results reflect the disability paradox phenomenon (Albrecht and Devlieger, 1999) where, despite the presence of severe disability, perceived QoL in the mental domain is high. This phenomenon has not previously been reported in FSHD, BMD and LGMD. In fact, the opposite (lower QoL than control groups) has previously been established in a group of children and adults with Duchenne MD, BMD and LGMD (Grootenhuis et

al., 2007) and adults with FSHD (Winter et al., 2010; Padua et al., 2009). Based on the previous research, we initially thought that the disability paradox may be exclusive to the Duchenne form of MD, perhaps due to the earlier onset of disease in this form. However, this study demonstrates that ambulatory adults with FSHD, BMD and LGMD also demonstrate a high perceived QoL in the mental domain. In order to understand why some individuals with these types of MD perceive a high QoL in the mental domain whilst others do not, the factors that mediate QoL were also examined in this study.

No association between physical activity, kinesiophobia or any aspect of mental health with QoL in the physical domain was found in this study. Conversely, negative associations between QoL in the mental domain with the severity of depressive symptoms and anxiety, and positive associations between QoL in the mental domain with self-esteem and physical self-worth, were found. Whilst it has previously been established that numerous disease-specific parameters are related to QoL in various forms of MD, such as current age (Uzark et al., 2012), disease severity (Landfeldt et al., 2016; Padua et al., 2009; Otto et al., 2017; Peric et al., 2018) and age at disease onset (Peric et al., 2018), these variables are not open to treatment or intervention. This is the first study to demonstrate an association between QoL and self-esteem, physical self-worth and anxiety in FSHD, BMD and LGMD, and between QoL and the severity of depressive symptoms in FSHD and BMD. Importantly, these variables may be susceptible to change through treatment or interventions such as RT, and they likely contribute towards the contradicting research findings surrounding QoL in the mental domain of individuals with MD.

The severity of trait anxiety did not differ between the study's participant groups, but the severity of depressive symptoms was significantly higher in the MD group than the control group, by 14%. In addition, 36.4% of the MD population exhibited mild depressive symptoms, with 4.5% and 4.5% exhibiting moderate and severe depressive symptoms. The burden of MD itself may cause enough stress to prompt or exacerbate depressive symptoms, or conversely, there may be a joint pathway between the pathogenesis of MD and depressive symptoms. Similarly, higher frequencies of moderate depression have previously been reported in adults with Duchenne MD compared to a control population (18% versus 8%), but to a greater extent than within the current study (Pangalila, van den Bos, Bartels, Bergen, Stam, et al., 2015). This may be due to the more severe presentation of Duchenne MD than FSHD, BMD and LGMD, or there could be a direct link between the pathophysiology of Duchenne MD and symptoms of depression, which is either less pronounced or not present in FSHD, BMD and LGMD.

Global self-esteem did not differ between the MD and the control group in the current study. This agrees with Bertrand et al. (2015), who also assessed self-esteem using the Rosenberg Self-esteem Scale in adults with Myotonic MD, and reported no difference compared to normative reference data. However, this finding differs to that of Miladi et al. (1999), who subjectively scored lower levels of self-esteem in children with LGMD compared to a control group, as a consequence of their response to projective cards depicting real life situations. This disparity in findings could be related to the different measures of self-esteem utilised or the difference in participant age between the studies, as both studies that reported no difference between the populations utilised The Rosenberg Self-Esteem Scale and were

conducted in an adult MD population. It is well known that self-esteem typically increases from adolescence to adulthood (Huang, 2010). Therefore, self-esteem may be unaffected in adults with MD, but children with MD may exhibit lower self-esteem compared to control children due to an already vulnerable self-esteem. On the other hand, measures of global self-esteem may not provide sufficient detail into the self-worth of individuals with MD. Self-esteem is a multidimensional construct (Raustorp et al., 2005), said to be influenced by various domain levels of self-worth, such as physical, academic, cognitive and social. Thus, high self-worth in some areas may conceal limitations in the self-worth in other areas.

This is the first study to demonstrate that despite no difference in global self-esteem between the populations, physical self-worth was reduced in individuals with MD compared to an age-matched control group. Specifically, lower physical self-worth was found in the sport competence domain, physical condition domain and physical strength domain, with no differences found in the body attractiveness domain or the importance of any of those domains. Thus, the MD group exhibited lower perceptions of the self in these areas, but they did not place any higher importance on these areas. This information may be useful when designing interventions aimed at improving physical self-worth in this population. Such interventions could focus either on increasing self-perceptions in each physical domain, or on decreasing the level of importance placed on each domain. However, given that the importance placed on each physical domain was no higher than the control group in the current study, it would be far more advantageous to target physical self-perceptions over importance in this population.

Before now, kinesiophobia had not been examined in adults with FSHD, BMD or LGMD, despite evidence that these individuals frequently experience body pain (Jacques et al., 2019), and the knowledge that other chronic pain populations consistently exhibit high levels of kinesiophobia (Ishak et al., 2017; Bränström and Fahlström, 2008; Demirbüken et al., 2015; Svensson et al., 2011). The Tampa Scale of Kinesiophobia revealed that on the whole, kinesiophobia was high in this population (FSHD and BMD), with the mean score topping the cut-off value of 35. In addition, 54% of participants scored equal to or above the cut-off value for a high kinesiophobia score (35). This information is important as high levels of kinesiophobia may have important implications for the management and treatment of MD. For example, fear of movement may influence a person's engagement in physical activity, it may have an effect on adherence to exercise programmes and it may also influence compliance with physiotherapy treatment.

Overall, the severity of depressive symptoms and level of physical self-worth were both afflicted in this population of adults with FSHD, BMD and LGMD. This poor mental health in comparison to non-dystrophic control adults may have important implications for the management of MD and was shown to be directly associated with QoL in this population. These findings add to the pre-existing research that demonstrates higher frequencies of poor mental health in individuals with physical diseases (Moussavi et al., 2007). Taken together, this evidence suggests that mental health treatment pathways tailored specifically for individuals with physical conditions, including MD, would be advantageous. The regular mental health treatment route, alongside individuals with no physical condition, may not be available or specific enough for individuals with MD. It is clear that parameters of

mental health, including the severity of depressive symptoms and anxiety and the level of self-esteem and physical self-worth directly influence perceived QoL in adults with FSHD, BMD and LGMD.

6.4.2 Part B – Effects of RT

Part B of this study examined the influence of a 12-week, twice a week, RT programme on mental health and wellbeing in a group of ambulatory adults with MD (FSHD, BMD and LGMD). Beneficial effects of the RT programme were evident across various areas of mental health and wellbeing, including QoL, the severity of depressive symptoms and trait anxiety and levels of self-esteem and physical self-worth.

The improvement in QoL in both the physical and mental domain following completion of the RT programme, in conjunction with stable values during the 12-week control period, is supportive of RT in adults with MD. This finding is in opposition to Kierkegaard et al. (2011), who reported no change to QoL score post 12-weeks of RT in adults with Myotonic MD. This discrepancy may be due to a number of factors including the type of MD studied. It is well accepted that Myotonic MD differs vastly from the other 8 types of MD because it affects nearly every system in the body (Emery, 2002). Alternatively, the discrepancy may be due to the relatively low level of adherence (75%) reported by Kierkegaard et al. (2011), compared to the high level of adherence achieved in the current study.

In the current study, both depressive and trait anxiety symptoms were significantly improved after completion of RT. The severity of trait anxiety was reduced by 11.2% after the RT programme, in conjunction with stable values during the 12-week

control period. This concurs with previous studies that have demonstrated a beneficial effect of RT on anxiety in other pathological populations, such as older adults, cancer patients and osteoporotic patients (O' Connor et al., 2010).

The severity of depressive symptoms was reduced by 26.2% from PRE1 to POST completion of the RT programme. There was, however, an 8.7% reduction in symptoms of depression within the initial 12-week control period, but it is important to note that an additional 19.2% reduction in depressive symptom severity was evident between PRE2 and POST. Hence, it appears that depressive symptoms were initially reduced purely by being part of the study itself, but depressive symptoms were reduced by a far greater amount after completion of the RT programme. Interestingly, the average depression symptom score immediately prior to the start of the RT programme (PRE2) was 11.3, which, according to the Beck Depression Inventory classification system, sits within the mild depressive symptom category. After completion of the RT programme, the average score was reduced to 9.1, which sits within the normal category reflecting minimal to zero depressive symptoms. The proportion of participants situated in the normal depressive symptom category increased from 47.1% to 64.7% after the RT programme. Overall, it is clear that the RT programme was highly beneficial towards reducing the severity of depressive symptoms in this population. This finding is in line with previous studies that have reported a reduction in the severity of depression with RT in other pathological populations, such as fibromyalgia (Jones et al., 2002; Hakkinen et al., 2001), spinal cord injury (Hicks et al., 2003) and osteoarthritis (O' Reilly et al., 1999) and those studies in older adults that exhibit

adequate adherence to the RT programme (Cassilhas et al., 2007; Timonen et al., 2002; Singh et al., 1997).

Concerning self-esteem and physical self-worth, the RT programme had an overall positive influence on this population, which agrees with previous investigation into the effect of RT on self-esteem and physical self-worth in other clinical populations (Spence et al., 2005; Megakli et al., 2015). In this study, global self-esteem was stable during the initial control period, followed by a 9.6% improvement after completion of the RT programme. Interestingly, physical self-worth, as measured by the global domain of The Physical Self-Perception Profile, was also stable between the initial control period, with a greater increase of 14.5% after completion of the RT programme. This increase stemmed from a 22.3% and 13.2% increase in self-perceptions of physical condition and body attractiveness, respectively. In addition, the importance placed on each of these sub-domains of physical self-worth was unchanged, highlighting that physical self-perceptions in these areas were improved but the relative importance placed on these domains remained the same. This led to an overall improvement in physical self-worth. On the other hand, the importance placed on the sport competence domain increased by 14.2%, with no change to the self-perception of this domain. Thus, perceptions of sport competence were unchanged, but participants perceived this domain with a higher importance after completion of the RT programme. Independently, this finding would negatively influence physical self-worth, but in conjunction with the increases found in self-perceptions of physical condition and body attractiveness, the overall effect of RT on physical self-worth was positive. It not clear why the importance placed on the sport competence domain increased, but it was perhaps

the result of being exposed to an active environment whilst taking part in the RT programme. In any case, the current author does not perceive this increase with negative connotations, as in conjunction with the improvements in physical self-perceptions in the other domains, it may actually contribute to the continuation of RT long-term, given that participants now place more importance on an area related to sport.

There was no overall influence of RT on fear of movement, measured via the severity of kinesiophobia, which is somewhat surprising given the highly positive changes in other areas of mental health and wellbeing found in the current study. The direction of change in kinesiophobia did show a reduction but the observed power for this comparison was exceptionally low (.09) due to analysis of data in a subgroup of the participants only. Therefore, this finding should be regarded circumspectly. This is an important limitation within the current study and future research should seek to investigate the influence of RT on kinesiophobia in a larger sample size with adequate study power.

It is important to note the limitations of the current study. Firstly, the influence of the RT programme was assessed in a mixed group of adults with FSHD, BMD and LGMD, which may have concealed differences between the different types of MD. In addition, there were potential ceiling effects for some of the variables within the present study. For example, although the severity of depressive symptoms were greater than in the control group, only 2 participants were situated in the moderate or severe category for depressive symptoms. Therefore, a different response to RT may occur in a MD population with more severe depressive symptoms. Finally, a

major limitation of the current study is that it provides no insight into whether the improvements in mental health that were found remained following completion of the study. Numerous participants did continue to follow the RT programme upon completion of the study, at least once a week, but as the RT programme was staggered it was logistically not possible to include follow-up tests within the current study.

The current results support the inclusion of a RT programme in the management and treatment of ambulatory adults with FSHD, BMD and LGMD. It is extremely disappointing that RT has previously been discouraged in these populations, as the clinical implications of the current findings are that RT is an innovative and alternative approach to improving mental health and wellbeing in adults with MD. From a holistic perspective, RT is an effective tool to enhance the overall health of adults living with MD. In future, researchers should seek to understand the mechanisms behind such improvements in mental health in these populations. In addition, future research should explore whether the benefits are maintained in the long-term and/or continue to improve with continued training. Furthermore, with examination of a larger sample size it would be advantageous to examine whether certain subtypes of MD differ in their response to RT.

In conclusion, this study highlights that poorer mental health is evident in adults with FSHD, BMD and LGMD, compared to age-matched control adults, shown specifically by higher severity of depressive symptoms and a lower level of physical self-worth. Furthermore, these parameters were directly related to the perceived QoL in these individuals. This is the first study to demonstrate positive effects of a

12-week RT programme on mental health and QoL in a population of adults living with MD (FSHD, LGMD and BMD). These findings highlight that RT is a viable option within the management of MD in adults, particularly where mental health and QoL are low. It is imperative that a change in the outdated perspective, that RT should not be encouraged in individuals with MD, takes place. These findings go some way towards helping to catalyse that change.

Chapter 7

Epilogue

7.1 Summary of Findings

7.1.1 Muscle Strength

The first data chapter (*Chapter 3*) within this thesis aimed to compare lower-limb muscle strength and physical function, between adults with FSHD, BMD and LGMD, to matched control adults. The data showed varying severities of muscle weakness across the MDs in most of the lower-limb muscle groups that were tested. These strength deficits paralleled the pre-existing clinical classifications of weakness distribution patterns in these MD groups, although caution was advised when interpreting the areas of muscle weakness that were highlighted as predominant by clinical classifications. This is because muscle groups that were not categorised as areas of predominant weakness based on the clinical classifications were often still severely weak in comparison to the matched control group.

The second aim of *Chapter 3* was to examine the effect of a 12-week lower-limb RT programme on muscle strength and physical function, in a combined group of adults with MD (FSHD, BMD and LGMD). Importantly, RT improved MVC torque in six of the eight muscle groups that were assessed, and timed performances on the functional tests were improved across the board. In addition, comfortable walking speed increased which was demonstrated by an increase in the distance walked during a 6-minute walk test. Thus, despite previous medical concerns, this RT programme was highly beneficial to muscle strength and physical function in the individuals involved. The success of the RT programme within this study compared to the lack of an effect found in previous investigations is most likely a result of the supervision in our training programme, the complete lower-body nature of our

training programme as opposed to training one or two individual muscle groups in previous studies, and the individualised nature of our RT programme. This study offers the first convincing evidence that RT increases muscle strength in adults with these types of MD.

7.1.2 Gait

Chapters 4 and 5 of this thesis aimed to compare gait in adults with FSHD, BMD and LGMD with age-matched control adults. *Chapter 4* described the **kinematic** abnormalities of gait in these groups of MD, and *Chapter 5* described the **kinetic** abnormalities of gait in these groups of MD.

Chapter 4 highlighted numerous kinematic abnormalities at the pelvis, hip, knee and ankle joint in each of the MD groups. These abnormalities were evident in the sagittal, coronal and transverse planes. Numerous abnormalities were found in all of the MD groups, including slower gait speed, reduced stride length, reduced cadence, excessive external pelvic rotation and limited ankle dorsiflexion at initial contact and during the swing phase. However, other kinematic abnormalities were isolated to one or two of the individual MD groups, such as a greater anterior pelvic tilt and limited hip extension in stance and at toe-off in the FSHD and BMD groups, and greater hip abduction in swing and a lack of knee flexion or hyperextension of the knee joint in the BMD and LGMD groups. Importantly, the oxygen cost of gait was heightened two-fold in the LGMD group.

Chapter 5 highlighted numerous kinetic abnormalities at the hip, knee and ankle joint along with differences in ground reaction forces in the MD groups compared to controls. Several peak vertical and anterior-posterior ground reaction forces

were smaller in one or all of the MD groups, including peak vertical ground reaction force in loading in all MD groups, peak vertical force in terminal stance in LGMD and peak propulsive force in LGMD. Whereas peak lateral force in terminal stance was greater in the BMD group than controls. Kinetic abnormalities in external joint moments included smaller hip flexor moments during stance in BMD and LGMD, smaller hip extensor moments during late stance in FSHD and LGMD, smaller hip adductor moments during early stance in FSHD and LGMD, reduced knee flexor moments in loading in all MD groups, greater knee extensor moments in mid-stance in FSHD and LGMD and a lack of a plantarflexor moment during loading in all MD groups. Finally, deviations in several joint powers were noted in the MD groups compared to controls, which specifically highlighted a reduced capacity to generate propulsion during late stance in all MD groups. These included a smaller maximum hip flexor generation power in late swing, a smaller maximum knee extensor generation power and a smaller maximum plantarflexion generation power in late stance.

The second aim of *Chapter 4 and Chapter 5* was to examine the effect of a 12-week lower limb RT programme on the kinematics and kinetics of gait in a combined group of adults with MD (FSHD, BMD and LGMD). These studies are the first to assess the effects of RT on gait in a MD population and, importantly, the findings reveal that RT is a highly beneficial technique to improve gait in these individuals.

Kinematic improvements included increased gait speed, stride length and cadence, increased knee flexion at initial contact and during the loading response, increased knee flexion during the swing phase, a reduction in the severity of hyperextension

during the stance phase, increased dorsiflexion at initial contact and during the swing phase and increased ankle inversion at initial contact and eversion at toe-off. Moreover, the improvements found in those individuals with more severe gait abnormalities, including hyperextension of the knee and limited dorsiflexion in the swing phase, were even larger.

Kinetic adaptations showed that RT improved several gait abnormalities and enhanced propulsive capacity in MD, shown specifically by an increase in the maximum external knee flexor moment during stance, a reduction in the excessive external knee extensor moment during stance, an increase in the maximum plantarflexion moment in early stance and an increase in peak plantarflexor power generation during late stance.

The adaptations discussed above contribute towards the faster gait speed and likely contribute towards reduce stress at the joints and reduced fall risk in individuals with MD, all of which are highly desirable towards maintaining ambulation, physical function and physical independence. Although the oxygen cost of gait was not improved in this population post completion of the RT programme, several suggestions were provided that may aid future studies with the aim of improving this aspect of gait.

7.1.3 Mental Health

Chapter 6 of this thesis aimed to compare the mental health and perceived QoL of adults with MD (FSHD, BMD and LGMD). The findings highlight that poorer mental health is evident in adults with MD (FSHD, BMD and LGMD) compared to age-matched control adults. This was shown specifically by a higher severity of

depressive symptoms and a lower level of physical self-worth in the MD compared to the control group. Furthermore, these parameters were directly related to the perceived QoL in these individuals.

This study is novel in the investigation of the effect of a 12-week lower-limb RT programme on variables of mental health and QoL in MD. Positive effects of the RT programme on mental health and QoL were found in a population of adults living with MD (FSHD, LGMD and BMD). Specifically, the severity of depressive symptoms and anxiety were reduced, and self-esteem, physical self-worth and perceived QoL were improved after completion of the RT programme, compared to stable values during the 12-week control period. These findings highlight that RT is a viable option within the management of MD in adults, particularly where mental health and QoL are low.

7.1.4 Global Summary

Muscular, gait and mental health impairments were described in adults with FSHD, BMD and LGMD. Importantly, RT was found to be highly feasible and beneficial towards managing many of these limitations in adults living with MD. Not only did RT positively increase lower limb muscle strength, but the benefits stretched beyond this into areas of gait, mental health and QoL. Previous medical apprehension towards RT in adults living with FSHD, BMD and LGMD are unsubstantiated and in fact, evidence from this thesis strongly contradicts the concerns that RT should be avoided, at least in adults with these types of MD. The key message from these findings is that RT is an innovative means of improving muscle strength, gait and mental health in ambulatory adults with MD. In addition,

supplementary to the quantitative findings of this study, the anecdotal outcomes from this study truly encapsulate the positive impact that the RT programme had on this group of individuals. As demonstrated in *Appendix 4.8*, the unprompted statements from participants surrounding their participation in the RT programme are extremely encouraging, such as *“I feel more confident when I am moving around now”, “I am finding it much easier to kick the ball for my dog”, “It was the highlight of my year”, “I tripped but was able to stop myself from falling over” “I continued training after completing the programme and went on to complete my first disability triathlon”* and *“It has given me that boost that I needed to be more physically active”*.

7.2 Clinical Implications

The findings from this thesis contribute towards the understanding of muscle strength deficits, gait abnormalities and mental health in adults with FSHD, BMD and LGMD. In addition, the findings enhance understanding of the effects of RT in adults with FSHD, BMD and LGMD. As a result, a number of key clinical implications were identified.

Deficits in lower-body muscle strength and physical function compared to a non-dystrophic age-matched control group were quantified in adults with FSHD, BMD and LGMD. These data contribute to the currently under-reported, but clinically described, physiological and functional understanding of FSHD, BMD and LGMD, and provide some support for the pre-existing clinical classifications of muscle weakness distribution in these populations. Importantly though, these data provide greater detail of muscle weakness than the pre-existing clinical descriptions of

weakness distribution, through the assessment of individual muscle groups. The findings demonstrate that clinicians should interpret clinical descriptions of weakness distribution in FSHD, BMD and LGMD cautiously, as muscles not categorised as regions of predominant weakness in clinical descriptions were often still severely weak compared to control adults.

Kinematic and kinetic abnormalities of gait compared to control adults were identified in FSHD, BMD and LGMD. The clinical implications of these abnormalities are extensive, including increased risk of pain, excessive forces at the joints, increased fall and injury risk, increased fatigue and psychological implications. For example, the excessive anterior pelvic tilt that was identified may result in low back pain through greater stresses and loads placed on the spine, hyperextension of the knee likely leads to pain and damage through excessive compressive forces at the structures of the knee joint and the presence of foot drop in the swing phase likely heightens the risk of falls in these MD groups. Notably, all of these primary implications have the potential to cause additional abnormalities and a domino effect. Thus, participation in strength training and a specialised programme of physiotherapy should be a crucial element within the management of these MD conditions. Furthermore, in advanced abnormalities such as severe foot drop, the use of orthotic devices may be appropriate to provide further support towards the maintenance of safe ambulation in MD.

The examination of psychological variables in adults with MD highlight poor mental health compared to age-matched control adults. The severity of depressive symptoms and level of physical self-worth were both afflicted in this population of

adults with MD and were directly associated with perceived quality of life. These findings have direct implications for the care of, and service delivery to adults living with MD. Mental health treatment should form a key aspect of the management of MD and mental health pathways tailored specifically for adults living with MD would be advantageous. The regular mental health treatment route, alongside individuals with no physical condition, may not be suitable for individuals with physical disabilities such as MD.

The findings within this thesis demonstrate highly beneficial effects of a 12-week lower-body RT programme in a combined group of adults with FSHD, BMD and LGMD. RT is an effective tool that increased lower-limb muscle strength and physical function, improved walking ability through an increase in gait speed and a reduction in various kinematic and kinetic abnormalities, and improved mental health and quality of life through a reduction in the severity of depressive symptoms and anxiety and an increase in self-esteem, physical self-worth and perceived quality of life. The clinical implications of these findings are that RT is an innovative approach to maintaining or improving physical and mental independence in individuals with MD, and should therefore be considered within the management of MD. From a holistic perspective, RT is a practical treatment that can enhance the overall health of adults living with MD.

Historically, health care professions were apprehensive about RT in individuals with MD. Some individuals were strongly advised not to participate in RT and other activities that may physically exert their muscles, whilst others were discouraged from doing so but were not categorically directed not to participate in such

activities. To date, although physical activity is now generally accepted as beneficial in MD, whether RT is harmful, null or beneficial in individuals with MD remains ambiguous. However, the findings within this thesis provide evidence that RT is beneficial in adults with MD and the clinical implications of this are that supervised RT should be actively promoted in individuals with MD.

Further to the benefits of RT to participants themselves, the RT programme completed within this thesis had implications for the physiotherapy department at the Neuromuscular Centre in terms of time and resources. All participants who underwent the 12-week RT programme became knowledgeable about their training programme overtime and eventually became capable of continuing their training in a semi-supervised manner, once their participation in this study came to an end. For the physiotherapy department this brought about a welcomed easement, freeing up valuable time and resources to be expended elsewhere in the department. For participants, they gained greater autonomy in managing their condition.

7.3 Limitations

Inevitably, this thesis has some key limitations that should be considered. The individual studies have some limitations that are specific to that study, but the key limitations of this thesis are shared between each study.

The heterogeneous nature of the MD conditions, particularly LGMD, is visible within the data by the often-large standard deviation. This large standard deviation likely contributed towards the low power in some of the kinetic variables within *Chapter 6*, and therefore may have concealed additional differences between the groups or as a function of the RT programme. However, variance within the MD groups is

typical of the nature of these conditions and therefore the groups within this study represent these MDs well.

A second important limitation of this thesis is that three different types, although functionally similar, of MD were combined to examine the effect of the RT programme. The consequence of this is that the effect of RT cannot be separated between the different types of MD. For example, differences in the magnitude of effects may exist between the MDs. However, combining the participant groups provided sufficient power for the majority of dependant variables. Ideally, a greater sample size would have been utilised to enable analysis of the effect of RT on FSHD, BMD and LGMD individually, but this was not logistically feasible. The importance of establishing the potential role of RT in ambulatory adults with MD outweighed this limitation. Thus, it was deemed appropriate to combine the participants groups in order to do so.

A third key limitation of this thesis was that no follow-up analysis was completed. The implication of this is that no knowledge of whether the training effects remained, continued or diminished post completion of the RT programme was captured. It may have been insightful to incorporate some long-term follow up of the participants within these studies, particularly as approximately ten of the 17 participants that completed the RT programme continue to undertake RT at least once a week. However, a long-term follow-up to these studies was not feasible within the time frame.

7.4 Future Research Directions

The outcomes of this thesis have prompted several future research directions that would further add to the understanding of physical and mental challenges in MD, and to the role of RT in individuals with MD.

A clear outcome from this thesis is a greater knowledge of both the physical and mental benefits of RT in adults living with FSHD, BMD and LGMD. This thesis provides the first convincing evidence that RT increases muscle strength in adults with these conditions. Future studies should aim to establish the influence of RT programme frequency and intensity. It would be advantageous to determine the optimal frequency and intensity of RT in FSHD, BMD and LGMD, as understandably, this may differ to that of non-dystrophic individuals. Although this thesis provides evidence of a positive effect of RT in MD, an important question remains; how much RT is too much in these MD conditions? To enable health professionals to give detailed advice regarding the frequency and intensity of RT to individuals with MD, future research should seek to establish thresholds between which RT is beneficial.

A second future research direction that emanated from the outcomes of this thesis is the association between the identified gait abnormalities and muscle strength. Such associations were not directly assessed within this thesis, but they were proposed numerous times. Of course, it is possible that other factors contributed towards, or were responsible for the gait adaptations found within *Chapters 5 and 6*. Therefore, it would be advantageous for future studies to examine these potential associations, as this would provide greater direction for the design of future RT programmes in MD.

Numerous gait adaptations from the RT programme were found in this thesis, but no change in the oxygen cost of gait was found. This result prompted an exciting future research direction. Studies should continue to investigate the influence of RT programmes on gait in MD, with the addition of a gait re-training element. This is suggested as although numerous gait adaptations were found, gait re-training alongside RT may produce greater or even additional adaptations. Importantly, the inclusion of a gait re-training element may enable researchers to prompt gait adaptations that lead to a lower cost of gait in MD.

An important finding within this thesis was the greater severity of depressive symptoms and lower levels of physical self-worth within adults with MD, compared to the age-matched control adults. Research studies that utilise qualitative methods would enable a greater, more in-depth analysis of mental health and wellbeing in MD. In addition, qualitative investigation into the effects of RT in individuals with MD may provide a reference or insight into the mechanisms behind the improved mental health that was found within this thesis.

Finally, the positive impact of RT in adults with MD that is demonstrated by this thesis promotes RT as an evolving area of research in MD. The findings incite a plethora of research questions, such as how the proximity between participation in RT and the onset of the condition influences the overall effect. In addition, the knowledge that RT does improve muscle strength in FSHD, BMD and LGMD opens up new avenues that involve enabling individuals with MD to partake in RT programmes more easily. One avenue to do this involves eliminating some of the barriers to RT that are experienced by individuals with MD. For example, the design

of accessible RT equipment that provides the user with adjustable levels of support and/or assistance whilst completing exercises, such as the squat bed that was designed and used in this thesis.

7.5 Global Conclusion

It is overwhelmingly evident that individuals with FSHD, BMD and LGMD display strength deficits of varying severity and distributions in the lower-limb muscles. In addition, gait is slower, and a multiplicity of kinematic and kinetic abnormalities exist throughout the gait cycle. Furthermore, mental health and wellbeing is compromised in adults with MD, particularly in the areas of depressive symptoms and physical self-worth. The findings from this thesis reveal persuasively the effectiveness of RT as an intervention, to both improve and manage the debilitating physical and mental limitations experienced daily in adults living with MD. RT is shown to be highly beneficial; it is economical; it is most certainly value for money in terms of time and resources, and it is an innovative treatment option. That is, it enables adults with MD to actively partake in improving their physical and mental health and is of itself therapeutic and beneficial towards maintaining independence. It is therefore imperative that the outdated view, that RT should not be encouraged in individuals with MD, is changed. The findings of this thesis go some way towards helping to inform and catalyse that change.

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Appendices

Appendix 1

Publications

**European Society of Movement Analysis in Children and Adults Annual Meeting
2018, Prague 24-29 September 2018**

Abstract Submission

Gait & Posture, Volume 65, Supplement 1 (2018) pp. 166-167

Is progressive resistance training an effective intervention in adults with Muscular Dystrophy?

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Introduction

Muscular dystrophies (MD) are inherited disorders with condition specific manifestations, yet they are all characterised by progressive muscle deterioration. This deterioration results in weakness, pain and impaired walking or potentially a loss of ability to walk and with it, independence. Those who remain ambulatory walk slower and experience debilitating and painful gait characteristics (D'Angelo et al., 2009), one of the most apparent is knee hyperextension. Resistance training (RT) has previously been shown to increase six-minute walk (6MW) distance in adults with Myotonic MD (Gianola et al., 2013). However, the detailed gait improvements that may accompany the increase in walking speed with RT are yet to be reported.

Research Question

Does RT improve walking capacity and gait kinematics, specifically knee hyperextension, in adults with Limb-girdle and Facioscapulohumeral MD?

Methods

Seven adults with MD (2 with Facioscapulohumeral and 5 with Limb-girdle MD; 44.7 ± 13.1 yrs.) completed testing immediately before (PRE1) and after (PRE2) a 12-week control period, then after completion of a 12-week (two sessions per week) supervised RT programme (POST). Gait analysis was performed at a self-selected pace, using a 3D motion capture system (VICON) with AMTI force plates, from which spatial and temporal parameters and sagittal plane knee joint kinematics were extracted. Additionally, the 6MW test was completed. For comparison, knee angle data are presented from four age-matched controls without MD.

Results

Walking speed and 6MW distance significantly increased from PRE1 and PRE2 to POST, and stride length from PRE1 to POST (Table 1). A significant reduction in minimum knee angle during the stance phase (PRE1: $-8.8 \pm 11.3^\circ$, PRE2: $-10.4 \pm 12.3^\circ$, POST: $-5.4 \pm 8.8^\circ$), swing phase (PRE1: $-1.6 \pm 3.8^\circ$, PRE2: $-3.5 \pm 4.2^\circ$, POST: $1.3 \pm 3.7^\circ$) and at heel strike (PRE1: $-1.4 \pm 4.6^\circ$, PRE2: $-2.5 \pm 5.7^\circ$, POST: $.98 \pm 2.9^\circ$) was found, POST RE compared to PRE1 and PRE2 (Figure 1).

Discussion

These results offer support for RT as a treatment approach in adults with Limb-girdle and Facioscapulohumeral MD. RT improved walking performance and the severity of knee hyperextension whilst walking. This reduction in excessive motion at the knee

may reduce the risk of damage to the knee joint and surrounding ligamentous structures. Future work will consider additional gait deviations to help promote the benefits of RT in MD. The clinical implications of these findings are that RT is an innovative approach to maintaining or improving physical independence in individuals with MD.

Table 1: Mean \pm SD spatial and temporal walking parameters for MD participants at PRE1, PRE2 and POST completion of the RT programme. Significant differences from PRE1 and PRE2 are denoted by * and #, respectively.

	PRE1	PRE2	POST	% Change (PRE2-POST)
Walking speed (m/s)	0.81 \pm 0.2	0.81 \pm 0.2	0.87 \pm 0.2*#	+7.4
Stride length (m)	1.17 \pm 0.1	1.20 \pm 0.1	1.27 \pm 0.1*	+5.8
Stride width (m)	0.16 \pm 0.04	0.14 \pm 0.02	0.14 \pm 0.02	0
Cadence (s/m)	83 \pm 16.5	81 \pm 16.0	83 \pm 15.5	+2.5
6MWD (m)	261 \pm 88	271 \pm 75	292 \pm 70*#	+7.7

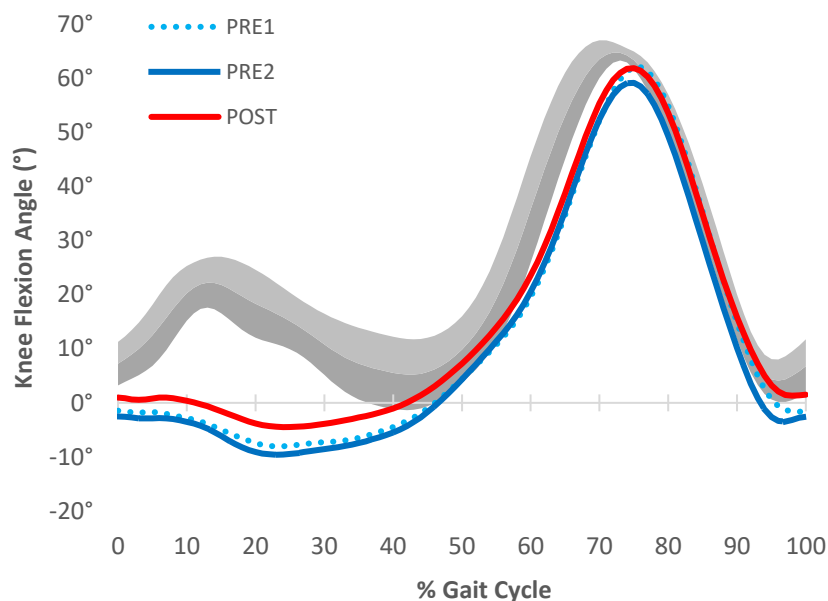


Figure 1: Mean knee flexion (+) and extension (-) angle during the gait cycle in individuals with MD at PRE1 (dotted line), PRE2 (dashed line) and POST (line) completion of RT. The grey band (\pm 1 standard deviation) represents control group data. On the x-axis, 0% represents heel strike and 100% the following ipsilateral heel strike.

Appendix 2

**Plug in Gait model
&
Resistance Training
Programme**

A 2.1 Vicon Plug in Gait marker set and descriptions

Figure A2.1 and Figure A2.2 (Vicon, 2010) provide a visual example of the position of the 39 markers according to the Vicon plug in gait marker set. Table A2.1 provides written descriptions of the marker positions on the body, in accordance with the Vicon plug in gait model (Vicon, 2010).

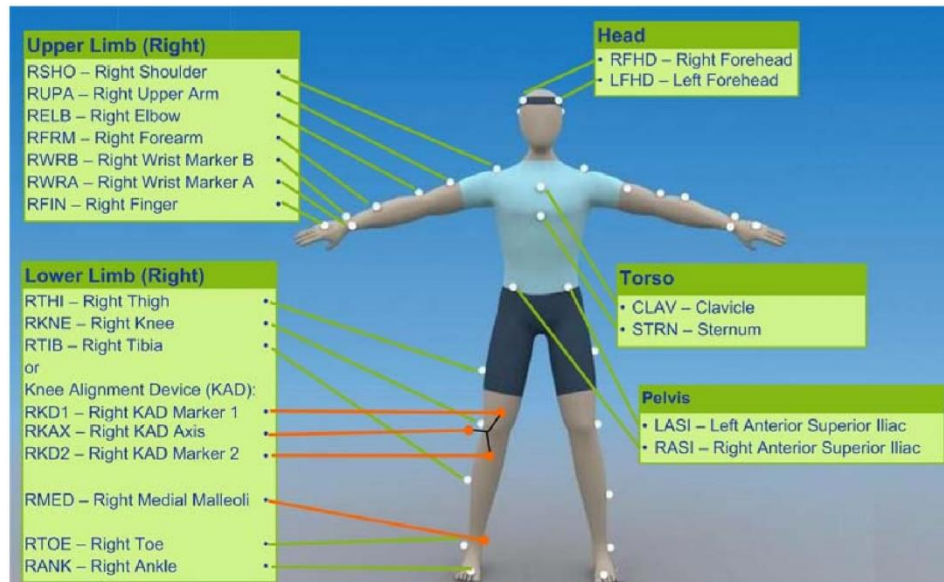


Figure A2.1: Anterior view of the Vicon plug in gait marker set, taken from Vicon (2010).

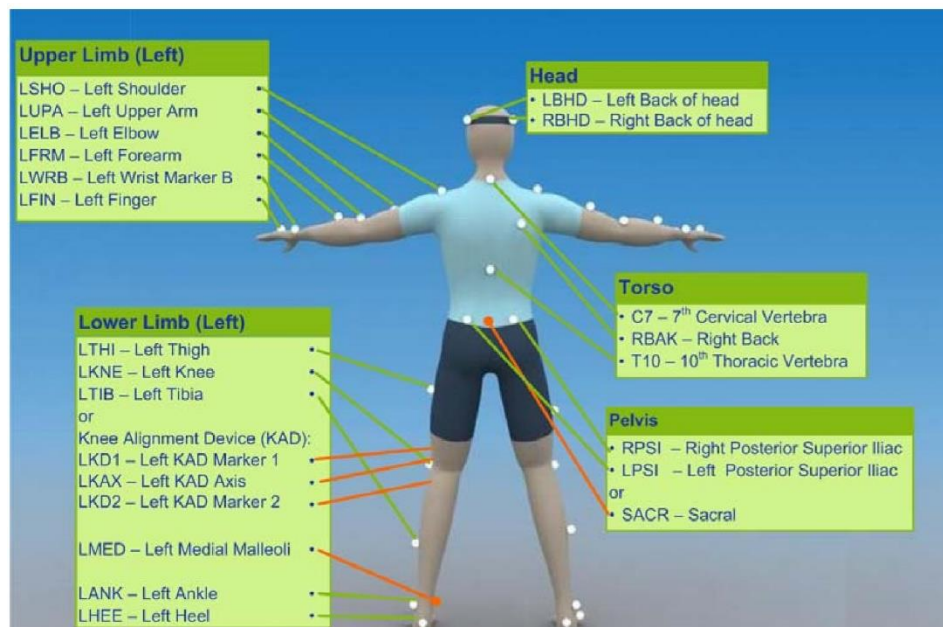


Figure A2.2: Posterior view of the Vicon plug in gait marker set, taken from Vicon (2010).

A 2.2 - Consistent Resistance Exercises

Table A.2.2 describes the six consistent elements of the exercise programme for all participants. Equipment used for the cardiovascular warm-up was interchangeable depending on preference and a mixture of the Wi-Fit balance games were completed for between 5-10 minutes. The step-up exercise was completed at various progressive heights, ranging between 3 cm, 6 cm, 9 cm, 12 cm and 15 cm above the ground. One variation of the squat, knee flexion and knee extension exercise was completed based on the strength and physical function of the participant.

Table A.2.2: Description of the six exercises that were consistently included in all training programmes, along with the specific variations of each exercise and the progressive variations in training load.

Exercise	Variations	Description	Training Load Progression
Aerobic Warm-up			
	Cycle Ergometer Rowing Machine Seated cross-trainer	Five minutes of cardiovascular exercise was performed at a moderate intensity	<ul style="list-style-type: none"> Level between 12-14 on the Borg Rating of Perceived Exertion Scale
Wi-Fit Balance Games			
	Table Tilt	With the feet placed on a balance board, participants were required to move their centre of mass in order to tilt marbles on top of a moving platform into holes. Parallel bars were placed either side of the participant for safety but they were encouraged not to use them unless required.	<ul style="list-style-type: none"> Beginner Advanced

Downhill Skiing	With the feet placed on a balance board, participants were required to move their centre of mass between the gates of a skiing slalom course.
Football Heading	With the feet placed on a balance board, participants were required to move their centre of mass in order to head footballs coming from different directions.

Step-up



Exercise Block With the feet positioned hip distance apart, participants stepped up onto an exercise block with one leg. Keeping the heel planted on the box and the torso erect, participants lifted their body up and placed the opposite foot onto the platform. Participants then stepped down with one foot and followed with the back leg.

- Body weight
- Body weight + dumbbells
- Body weight + dumbbells + increased step height

Step height was selected based on ability to perform the movement with the correct posture throughout the exercise. Parallel bars were placed either side of the participant for safety, but they were encouraged not to use them unless required.

Squat



Free Standing

Participants flexed their hips, knees and ankle whilst maintaining a flat or slightly lordosis back position and kept their heels on the floor. Participants continued the descent until their thighs were parallel with the ground, after which they extended their hips and knees into a standing position. Participants extended their arms out in front to aid balance if required.

- Body weight
- Body weight + plate weights/kettlebells

If participants were unable to complete the movement or unable to balance, an alternative exercise variation was utilised.



Standing with Swiss Ball

Participants stood with a Swiss exercise ball between their lower back and a wall. They flexed their hips, knees and ankle whilst continually pushing back into the ball and kept their heels on the floor. Participants continued the descent until their thighs were parallel with the ground after which they extended their hips and knees into a standing position.

- Body weight
- Body weight + plate weights/kettlebells

If participants were unable to complete the movement due to muscle weakness, an alternative exercise variation was utilised.



Squat Bed

Participants lay supine on the squat bed plinth with their hips and knees at 90 ° and the feet secured to the footplate. Participants extended their hips, knees and ankle whilst keeping their heels on the footplate until they reached full extension, or slightly before, of the knees and hips. Participants then flexed at the hip knee and ankle until their knees returned to at a 90° angle.

- Plinth angle



If participants were unable to keep their heels flat on the footplate, a wedge was secured under the heels.

Knee Flexion



Leg Curl

Participants were seated on a leg curl and extension machine (Pro Heavy Duty, XS Sports). The seat was adjusted so the latera epicondyle of the knee joint was in line with the axis of rotation and the back was firmly against the back pad. The lower legs were placed on top of the padded lever so that the legs were at 90° to the torso. Participants bent their knees to curl their heels downwards through a 90° range of motion. Participants then straightened their knees to return to a starting position.

- Weight of lever arm
- Plate weights

If participants were unable to complete the movement due to the additional weight of the lever, the exercise was completed in a gravity neutral position.



Side-Lying

Participants lay on their side with their knees extended on a physiotherapy bed. They flexed their top knee to bring their heel to their buttocks.

- Gravity neutral
- Resistive rubber bands
- Progress to leg curl machine



Knee Extension



Knee Extension

Participants were seated on a knee extension machine (Pro Heavy Duty, XS Sports). The seat was adjusted so the lateral epicondyle of the knee joint was in line with the axis of rotation and the back was firmly against the back pad. The anterior aspect of the lower legs was placed behind the padded lever, which was positioned at 90 ° to the horizontal. Participants extended their lower legs to full extension and then lowered the legs back down to the starting position.

- Weight of lever arm
- Plate weights

If participants were unable to complete the movement due to the additional weight of the lever, the exercise was completed in a gravity neutral position.



Side-lying


Participants lay on their side on a physiotherapy bed with their bottom knee extended and their top knee flexed at 90°. They extended their top knee until the leg was parallel with their bottom leg.

- Gravity neutral
- Resistive rubber bands
- Progress to knee extension machine

2.3 – Individual Resistance Exercises

Table A.2.3 describes the variations of exercises and progressive training loads that were available for each muscle group (dorsi-flexor, plantar-flexor, hip flexor, hip extensor, hip abductor, hip adductor, hip internal rotator, hip external rotator, abdominal and lower back muscles). The specific exercise that was selected for each muscle group was dependent upon the functional ability and initial strength of the participant. The training load was progressive but in cases of severe weakness the load was initially reversed, so that the exercise was either assisted or completed in a gravity neutral or gravity assisted position.

Table A.2.3: Description of individual exercises and training load progressions for each muscle group.

Muscle Group	Variations	Description	Training Load
Ankle Dorsi-Flexors			
	Lay Supine	<p>Participants lay supine on a physiotherapy bed with their knees slightly flexed and a foam roller underneath. Participants lay with their ankle (2 cm proximal to their medial malleolus) hanging over the end of the bed to allow movement of the calcaneus. Participants dorsi-flexed their ankle through a full range of motion and then extended back to a neutral ankle position. Resistive bands were secured around the forefoot and attached to a wall hook. Ankle weights were fastened around the forefoot.</p>	<ul style="list-style-type: none"> • Assistive rubber bands • Limb weight • Ankle weights • Resistive rubber bands • Cable machine

Ankle Plantar-Flexors

Standing



Participants stood with both feet placed on the edge of an exercise block, ensuring that the balls of their feet were firmly planted on the step and their heels were lowered. Participants raised up onto their toes, through a full range of motion and then lowered back down into the starting position.

If balance was particularly poor or hyperextension occurred at the knees, a seated or lay alternative was utilised.

- Body weight
- Body weight + dumbbells/plate weights

Seated



Participants were seated on a chair with their ankles, knees and hips at a 90° angle. Starting with both feet placed flat on the ground, participants raised their heels through a full range of motion and then lowered their heels back to the starting position. Plate weights were placed on the thighs and secured in place by participants during the lift.

- Limb weight
- Limb weight + plate weight



Lay Supine

Participants lay supine on a physiotherapy bed with their knees slightly flexed and a foam roller placed underneath both knees. Participants lay with their ankle (from 2 cm proximal to their medial malleolus) hanging freely over the end of the bed, to allow free movement of the calcaneus. Participants plantar-flexed their ankle through a full range of motion and then relaxed back to a dorsi-flexed ankle position. Resistive bands were secured around the forefoot and a hook on the wall.

- Gravity assistance
- Resistive rubber bands
- Cable machine

Hip Flexors



Standing

Participants stood up straight with the cable lever or rubber bands attached around their ankle (if in use), posterior to their body. They stood a distance away to ensure that there was tension in the resistance, with their hip in a slightly extended position. Participants paced their body weight onto one leg and on the opposite side, they flexed their hip joint with a bent knee, to lift their knee up and bring the thigh parallel with the floor. Participants then extended their knee and hip to return the leg back to the starting position.

- Limb weight
- Ankle Weights
- Resistive rubber bands
- Cable machine

If excessive movement was evident at the torso due to muscle weakness or single leg stance could not be achieved, an alternative exercise position was utilised.



Lay Supine

Participants lay supine on a physiotherapy bed with their knees fully extended. They flexed at the hip joint with their knee bent to bring one knee towards their chest and then they extended their hip and knee to place the leg flat on the bed again.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable machine

If participants were unable to keep their back flat on the bed and instead arched their back during the lift due to muscle weakness of their core and/or lower back, a side-lying position was utilised instead.



Side-lying

Participants lay on their side in a straight line with their pelvis and shoulders in vertical alignment. The top leg was lifted up (abducted), until it was at the same height as the pelvis. From this position, participants flexed at the hip to bring the knee towards the chest.

- Gravity neutral
- Resistive rubber bands
- Ankle weights
- Cable machine

If participant were unable to keep the pelvis still, the exercise was completed against a wall for support.

Hip Extensors (Gluteus Maximus)



Standing

Participants stood up straight with the cable lever or rubber bands attached around their ankle (if in use), anterior to their body. They stood a distance away to ensure that there was tension in the resistance, with their hip in a slightly flexed position. Keeping the torso upright and the working leg straight, participants extended their hip to take the leg back to maximum hip extension and then returned back to the starting position.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable machine

If participants were unable to keep the back flat and instead arched at the back or hyperextension at the stance knee occurred, an alternative exercise position was used.



Kneeling
Prone
(Glute
Kickback)

Participants were in a knelt position on a physiotherapy bed, with their arms extended in front of them (perpendicular to the torso), in a kneeling push up position. The knees were bent at 90° to the thigh. Participants lifted one leg so that the heel moved towards the ceiling and the knee remained bent at 90°, until the thigh was level with the back. Participants then lowered the leg back to the starting position.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable machine

If participants were unable to hold bodyweight through their upper body, an alternative exercise was chosen.



Lay supine
(Glute
Bridge)

Participants lay supine on a physiotherapy bed, with their knees bent, their feet flat and their arms down by the sides. Participants raised their pelvis towards the ceiling using the glute muscles, keeping the back flat with no arching of the back. Participants then lowered their pelvis back down onto the bed.

- Body weight
- Weighted barbell

If participants were unable to keep the back flat and instead arched their back during the movement, an alternative exercise was selected.



Side-lying

Participants lay on their side in a straight line, with their pelvis and shoulders in vertical alignment. The top leg was lifted up (abducted) until it was at the same height as the pelvis. From this position, participants extended at the hip to bring the leg backwards.

If significant weakness in the abductors was present, manual assistance was given to keep the leg abducted.

- Gravity neutral
- Ankle weights
- Resistive rubber bands
- Cable machine

Hip Abduction (Glute Medius)

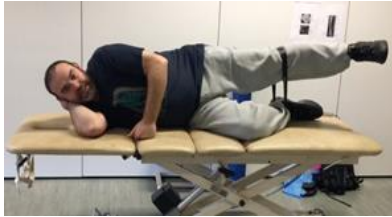


Standing

Participants stood with one foot on a step to give clearance to the working leg. Keeping the toes upwards, participants moved their leg laterally away from their body, keeping the knee straight. Participants then lowered the leg back to the starting position. Participants held onto a wall or the cable machine for stability.

If participants were unable to complete the exercise without leaning the upper body into the opposite direction of movement or single limb stance was not achievable, an alternative exercise was utilised.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable machine



Side-lying

Participants lay on their side on a physiotherapy bed in a straight line, with their pelvis and shoulders in vertical alignment. The top leg was lifted, keeping the knees straight and ensuring that no rotation occurred at the pelvis. Participants then lowered the leg back down to the starting position.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable machine

If participants were unable to complete the movement due to the weight of their leg or without rotating the pelvis backwards, an alternative exercise was chosen.



Side-lying
(clamshell)

Participants lay on their side on a physiotherapy bed with their shoulders and pelvis in vertical alignment, with the knees bent, hips flexed and heels together. Keeping the heels together and the upper body and pelvis still, participants rotated the hip to raise the knee of the top leg until it was parallel with the hip. Participants then lowered the knee back to the starting position.

- Limb weight
- Resistance bands

If participants were unable to complete the exercise without rolling the pelvis backwards, it was completed against a wall for support or a gravity neutral exercise was utilised.



Lay Supine

Participants lay supine on a physiotherapy bed with their knees fully extended and feet hip distance apart. Participants lifted the leg off the surface of the bed by flexing the hip slightly and then abducted the hip to move the leg away from the body, keeping the knees straight and the foot vertical.

- Gravity neutral
- Ankle weight
- Resistive rubber bands
- Cable machine

A slide board was placed under the foot if participants were unable to lift the leg from the surface of the bed due to hip flexor weakness.

Hip Adduction



Standing

Participants stood up straight with their feet shoulder width apart and holding onto bars or the cable machine for support, they placed all their weight onto one leg. They lifted the opposite leg of the floor and keeping the ankle dorsi-flexed, they pulled their leg towards the midline of their body and continued until the ankle passed the stance leg. They then returned the leg to the starting position.

If participants were unable to keep their back flat without arching it, or were unable to stand on one leg, an alternative was chosen.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable Machine



Lay Supine

Participants lay supine on a physiotherapy bed, with their arms down by their sides, their knees bent, and feet flat on the bed. A ball was placed between their knees and they were instructed to squeeze the ball to compress its shape and then release back to the starting position.

- Softball
- Progress to exercise above

Once participants were able to deform the shape of the softball they progressed to the exercise above.



Lay Supine

Participants lay supine on a physiotherapy bed with their knees fully extended and one leg abducted out at 30°. Participants lifted the leg of the surface of the bed slightly and then adducted the hip to move the leg towards the midline of the body, until the legs were hip distance apart, keeping the knees straight and the foot vertical. Participants then returned the leg back to the starting position.

- Gravity neutral
- Ankle weights
- Resistive rubber bands
- Cable machine

A slide board was placed under the foot, if participants were unable to lift the leg from the surface of the bed

Hip External Rotators

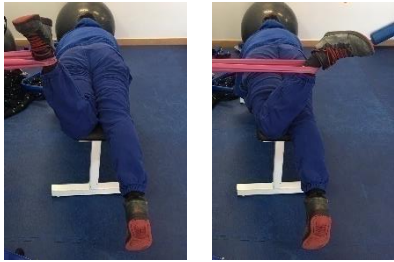


Seated

Participants were seated on a chair or bench with their non-involved foot placed slightly in front. Keeping the knee bent at 90° and the ankle dorsi-flexed to give clearance from the ground, participants pulled their lower leg under the thigh of the non-involved leg, by externally rotating the hip. Participants then returned the leg to the starting position.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable Machine

If participants were unable to externally rotate the hip due to the weight of their lower leg, the alternative exercise was utilised.



Lay Prone

Participants lay prone on a physiotherapy bed with their legs hip distance apart, one knee fully extended and the working knee bent at 90°. Keeping the knee bent, participants pulled their foot towards the thigh of the opposite leg by externally rotating at the hip. Participants then returned to the starting position.

- Gravity assisted
- Resistive rubber bands
- Cable machine

Hip Internal Rotators



Seated

Participants were seated on a chair or bench with their non-involved foot placed slightly in front. Keeping the knee bent at 90° and the ankle dorsi-flexed to give clearance from the ground, the participant pushed their lower leg away from the non-involved leg, by internally rotating the hip. Participants then returned the leg to the starting position.

- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable Machine

If participants were unable to internally rotate the hip in this position, the alternative exercise was utilised.



Lay Supine

Participants lay supine on a physiotherapy bed with their knees fully extended and their legs hip distance apart. Their hips were relaxed and externally rotated so that the participant's feet were not vertical. Participants rotated the entire leg medially, so that their feet moved past a vertical position into an internally rotated hip position and then returned to the starting position.

- Assistive rubber bands
- Limb weight
- Ankle weights
- Resistive rubber bands
- Cable machine

Abdominals



Seated

Participants were seated on a bench with their feet hip distance apart and planted on the ground and their back against the back support. The back support of the bench could be inclined at numerous angles to the seat. The angles were 90°, 101°, 113°, 124°, 135°, 146°, 158°, 169° and 180°, which enabled the range of movement of the exercise to be decreased in circumstances of severe weakness. The back angle was set at 135°, unless participants were unable to complete the movement, in which case it was reduced. Participants pulled their torso forwards, flexing at the hips so that the shoulders moved towards the thighs and then returned to the starting position. Participants crossed their arms across their chest and, if applicable, held the resistance bands/cable stirrups in both hands.

- Reduced back angle
- Body weight
- Resistive rubber bands
- Cable machine

If the bench was too low for participants to sit down onto and/or stand up from, an alternative exercise was utilised.



Lay Supine

Participants lay supine on a physiotherapy bed with their knees bent and feet flat. Participants flexed to raise their upper torso from the bed as high as possible whilst keeping the lower back in contact with the bed. Participants then returned to the starting position.

- Body weight
- Plate weight

Lower-Back



Lap Prone on Swiss ball

Participants lay prone on a Swiss ball, with their feet hip distance apart on the floor or against the base of a wall for support. They crossed their arms across their chest and raised their torso off the ball to extend the back. Participants then returned to the starting position.

If participants were unable to steady the ball, an alternative exercise was utilised.

- Assistive rubber bands
- Body weight
- Plate weights



Lay Prone

Participants lay prone on a physiotherapy bed, with their legs extended and their arms extended out in front of them. Participants raised their upper body and arms off the surface of the bed and then returned to the starting position.

- Assistive rubber bands
- Body weight
- Plate weights

Appendix 3

Gait Kinematics

A3.1 Trendeleberg gait and compensated Trendeleberg gait

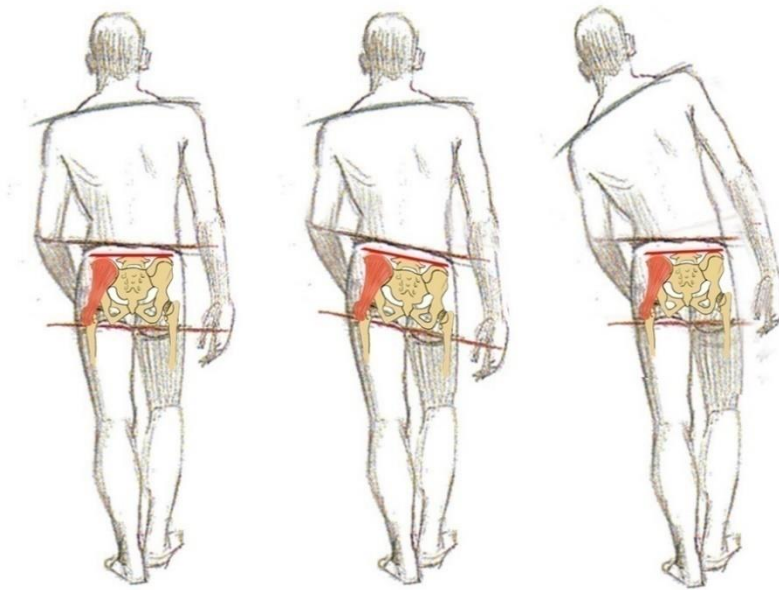


Figure A3.1: Visual representation of a normal pelvic position during gait (left image), a positive Trendeleberg pelvic position during gait (middle image) and a compensated Trendeleberg pelvic position during gait (right image).

A3.2: Lateral trunk lean examples



Figure A3.2: Examples of compensatory lateral trunk lean towards the support side during the gait cycle in this study.

A3.3 Lack of Knee Flexion in stance/hyperextension examples



Figure A3.3: Examples of the lack of knee flexion during the loading response in the stance phase and hyperextension in the stance phase found in our study.

A3.4 Effects of RT on Fall Frequency

Table A3.4: Mean \pm standard deviation of self reported fall frequency in the previous 12 weeks, measured at PRE1, PRE2 and POST completion of the RT programme.

PRE1	PRE2	POST
9.9 \pm 33.7	10.4 \pm 34.7	5.5 \pm 20.5

A3.5 Effects of RT on Knee Hyperextension



Figure A3.5: Example of the reduction in the severity of hyperextension at mid-stance from before completion of the RT programme (left image) to afterwards (right image).

Appendix 4

Questionnaires and Participant Comments

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3
- c Lifting or carrying groceries 1 2 3
- d Climbing several flights of stairs 1 2 3
- e Climbing one flight of stairs 1 2 3
- f Bending, kneeling, or stooping 1 2 3
- g Walking more than a mile 1 2 3
- h Walking several hundred yards 1 2 3
- i Walking one hundred yards 1 2 3
- j Bathing or dressing yourself 1 2 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Cut down on the amount of time you spent on work or other activities 1 2 3 4 5
- b Accomplished less than you would like 1 2 3 4 5
- c Were limited in the kind of work or other activities 1 2 3 4 5
- d Had difficulty performing the work or other activities (for example, it took extra effort) 1 2 3 4 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Cut down on the amount of time you spent on work or other activities 1 2 3 4 5
- b Accomplished less than you would like 1 2 3 4 5
- c Did work or other activities less carefully than usual 1 2 3 4 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a Did you feel full of life? 1 2 3 4 5
- b Have you been very nervous? 1 2 3 4 5
- c Have you felt so down in the dumps that nothing could cheer you up? 1 2 3 4 5
- d Have you felt calm and peaceful? 1 2 3 4 5
- e Did you have a lot of energy? 1 2 3 4 5
- f Have you felt downhearted and low? 1 2 3 4 5
- g Did you feel worn out? 1 2 3 4 5
- h Have you been happy? 1 2 3 4 5
- i Did you feel tired? 1 2 3 4 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c I expect my health to get worse.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

A 4.2 Beck Depression Inventory

11. 0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.
12. 0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.
13. 0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.
14. 0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.
15. 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.
16. 0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.
17. 0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.
18. 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.
19. 0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

- 20.
- 0 I am no more worried about my health than usual.
 - 1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
 - 2 I am very worried about physical problems and it's hard to think of much else.
 - 3 I am so worried about my physical problems that I cannot think of anything else.
- 21.
- 0 I have not noticed any recent change in my interest in sex.
 - 1 I am less interested in sex than I used to be.
 - 2 I have almost no interest in sex.
 - 3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score _____ Levels of Depression

1-10	_____	These ups and downs are considered normal
11-16	_____	Mild mood disturbance
17-20	_____	Borderline clinical depression
21-30	_____	Moderate depression
31-40	_____	Severe depression
over 40	_____	Extreme depression

A 4.3 State-Trait Anxiety Inventory for Adults

State-Trait Anxiety Inventory for Adults

Self-Evaluation Questionnaire

STAI Form Y-1 and Form Y-2

Developed by Charles D. Spielberger

in collaboration with R.L. Gorsuch, R. Lushene, P.R. Vagg, and G.A. Jacobs

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SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1

Please provide the following information:

Name _____ Date _____ S _____
 Age _____ Gender (Circle) **M** **F** T _____

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right now*, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

VERY MUCH SO
 MODERATELY SO
 SOMEWHAT
 NOT AT ALL

- | | | | | |
|--|---|---|---|---|
| 1. I feel calm..... | 1 | 2 | 3 | 4 |
| 2. I feel secure | 1 | 2 | 3 | 4 |
| 3. I am tense | 1 | 2 | 3 | 4 |
| 4. I feel strained | 1 | 2 | 3 | 4 |
| 5. I feel at ease | 1 | 2 | 3 | 4 |
| 6. I feel upset | 1 | 2 | 3 | 4 |
| 7. I am presently worrying over possible misfortunes | 1 | 2 | 3 | 4 |
| 8. I feel satisfied | 1 | 2 | 3 | 4 |
| 9. I feel frightened | 1 | 2 | 3 | 4 |
| 10. I feel comfortable | 1 | 2 | 3 | 4 |
| 11. I feel self-confident..... | 1 | 2 | 3 | 4 |
| 12. I feel nervous | 1 | 2 | 3 | 4 |
| 13. I am jittery | 1 | 2 | 3 | 4 |
| 14. I feel indecisive..... | 1 | 2 | 3 | 4 |
| 15. I am relaxed | 1 | 2 | 3 | 4 |
| 16. I feel content | 1 | 2 | 3 | 4 |
| 17. I am worried | 1 | 2 | 3 | 4 |
| 18. I feel confused..... | 1 | 2 | 3 | 4 |
| 19. I feel steady..... | 1 | 2 | 3 | 4 |
| 20. I feel pleasant..... | 1 | 2 | 3 | 4 |

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

Name _____ Date _____

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

ALMOST NEVER
SOMETIMES
OFTEN
ALMOST ALWAYS

- | | | | | |
|--|---|---|---|---|
| 21. I feel pleasant..... | 1 | 2 | 3 | 4 |
| 22. I feel nervous and restless | 1 | 2 | 3 | 4 |
| 23. I feel satisfied with myself..... | 1 | 2 | 3 | 4 |
| 24. I wish I could be as happy as others seem to be | 1 | 2 | 3 | 4 |
| 25. I feel like a failure | 1 | 2 | 3 | 4 |
| 26. I feel rested | 1 | 2 | 3 | 4 |
| 27. I am "calm, cool, and collected" | 1 | 2 | 3 | 4 |
| 28. I feel that difficulties are piling up so that I cannot overcome them..... | 1 | 2 | 3 | 4 |
| 29. I worry too much over something that really doesn't matter..... | 1 | 2 | 3 | 4 |
| 30. I am happy | 1 | 2 | 3 | 4 |
| 31. I have disturbing thoughts | 1 | 2 | 3 | 4 |
| 32. I lack self-confidence..... | 1 | 2 | 3 | 4 |
| 33. I feel secure | 1 | 2 | 3 | 4 |
| 34. I make decisions easily | 1 | 2 | 3 | 4 |
| 35. I feel inadequate..... | 1 | 2 | 3 | 4 |
| 36. I am content | 1 | 2 | 3 | 4 |
| 37. Some unimportant thought runs through my mind and bothers me | 1 | 2 | 3 | 4 |
| 38. I take disappointments so keenly that I can't put them out of my mind..... | 1 | 2 | 3 | 4 |
| 39. I am a steady person..... | 1 | 2 | 3 | 4 |
| 40. I get in a state of tension or turmoil as I think over my recent concerns
and interests | 1 | 2 | 3 | 4 |

A 4.4 Rosenberg Self-Esteem Scale

NICHD SECCYD—Wisconsin

ROSENBERG SELF-ESTEEM SCALE

The next questions ask about your current feelings about yourself. For each of the following, please circle the number that corresponds with the answer that best describes how strongly you agree or disagree with the statement about yourself now.

	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree
1. I feel that I am a person of worth, or at least on an equal plane with others.	1	2	3	4
2. I feel that I have a number of good qualities.	1	2	3	4
3. All in all, I'm inclined to feel that I am a failure.	1	2	3	4
4. I am able to do things as well as most other people.	1	2	3	4
5. I feel I do not have much to be proud of.	1	2	3	4
6. I take a positive attitude toward myself.	1	2	3	4
7. On the whole, I am satisfied with myself.	1	2	3	4
8. I certainly feel useless at times.	1	2	3	4
9. I wish I could have more respect for myself.	1	2	3	4
10. At times, I think I am no good at all.	1	2	3	4

A 4.5 Physical Self-Perception Profile

THE PHYSICAL SELF PERCEPTION PROFILE (PSPP)

WHAT AM I LIKE?

These are statements which allow people to describe themselves.
There are no right or wrong answers since people differ a lot.

First, decide which one of the two statements best describes you.

Then, go to that side of the statement and check if it is just “sort of true” or “really true” FOR YOU.

Really True for Me	Sort of True for Me	EXAMPLE	Sort of True for Me	Really True for Me
<input type="checkbox"/>	<input type="checkbox"/>	Some people are very competitive	<input checked="" type="checkbox"/>	<input type="checkbox"/>

REMEMBER to check only ONE of the four circles

1	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are not very good when it comes to playing sports.	BUT	Others feel that they are <u>really good</u> at just about every sport	<input type="checkbox"/>	<input type="checkbox"/>
2	<input type="checkbox"/>	<input type="checkbox"/>	Some people are not very confident about their level of physical conditioning and fitness	BUT	Others always feel confident that they maintain excellent conditioning and fitness	<input type="checkbox"/>	<input type="checkbox"/>
3	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that compared to most, they have an attractive body	BUT	Others feel that compared to most, their body is not quite so attractive	<input type="checkbox"/>	<input type="checkbox"/>
4	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are physically stronger than most people of their sex	BUT	Others feel that they lack physical strength compared to most others of their sex	<input type="checkbox"/>	<input type="checkbox"/>
5	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel extremely proud of who they are and what they can do physically	BUT	Others are sometimes not quite so proud of who they are physically	<input type="checkbox"/>	<input type="checkbox"/>

	Really True for Me	Sort of True for Me				Sort of True for Me	Really True for Me
6	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are among the best when it comes to athletic ability	BUT	Others feel that they are not among the most able when it comes to athletics	<input type="checkbox"/>	<input type="checkbox"/>
7	<input type="checkbox"/>	<input type="checkbox"/>	Some people make certain they take part in some form of regular vigorous physical exercise	BUT	Others don't often manage to keep up regular vigorous physical exercise	<input type="checkbox"/>	<input type="checkbox"/>
8	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they have difficulty maintaining an attractive body	BUT	Others feel that they are easily able to keep their bodies looking attractive	<input type="checkbox"/>	<input type="checkbox"/>
9	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that their muscles are much stronger than most others of their sex	BUT	Others feel that <u>on the whole</u> their muscles are not quite so strong as most others of their sex	<input type="checkbox"/>	<input type="checkbox"/>
10	<input type="checkbox"/>	<input type="checkbox"/>	Some people are sometimes not so happy with the way they are or what they can do physically	BUT	Others always feel happy about the kind of person they are physically	<input type="checkbox"/>	<input type="checkbox"/>
11	<input type="checkbox"/>	<input type="checkbox"/>	Some people are not quite so confident when it comes to taking part in sports activities	BUT	Others are among the most confident when it comes to taking part in sports activities	<input type="checkbox"/>	<input type="checkbox"/>
12	<input type="checkbox"/>	<input type="checkbox"/>	Some people do not usually have a high level of stamina and fitness	BUT	Others always maintain a high level of stamina and fitness	<input type="checkbox"/>	<input type="checkbox"/>
13	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel embarrassed by their bodies when it comes to wearing few clothes	BUT	Others do not feel embarrassed by their bodies when it comes to wearing few clothes	<input type="checkbox"/>	<input type="checkbox"/>
14	<input type="checkbox"/>	<input type="checkbox"/>	When it comes to situations requiring strength some people are one of the first to step forward	BUT	When it comes to situations requiring strength some people are one of the last to step forward	<input type="checkbox"/>	<input type="checkbox"/>

	Really True for Me	Sort of True for Me			Sort of True for Me	Really True for Me	
15	<input type="checkbox"/>	<input type="checkbox"/>	When it comes to the physical side of themselves some people do not feel very confident	BUT	Others seem to have a real sense of confidence in the physical side of themselves	<input type="checkbox"/>	<input type="checkbox"/>
16	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are always one of the best when it comes to joining in sports activities	BUT	Others feel that they are not one of the best when it comes to joining in sports activities	<input type="checkbox"/>	<input type="checkbox"/>
17	<input type="checkbox"/>	<input type="checkbox"/>	Some people tend to feel a little uneasy in fitness and exercise settings	BUT	Others feel confident and at ease at all times in fitness and exercise settings	<input type="checkbox"/>	<input type="checkbox"/>
18	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are often admired because their physique or figure is considered attractive	BUT	Others rarely feel that they receive admiration for the way their body looks	<input type="checkbox"/>	<input type="checkbox"/>
19	<input type="checkbox"/>	<input type="checkbox"/>	Some people tend to lack confidence when it comes to their strength	BUT	Others are extremely confident when it comes to their physical strength	<input type="checkbox"/>	<input type="checkbox"/>
20	<input type="checkbox"/>	<input type="checkbox"/>	Some people always have a real positive feeling about the physical side of themselves	BUT	Others sometimes do not feel positive about the physical side of themselves	<input type="checkbox"/>	<input type="checkbox"/>
21	<input type="checkbox"/>	<input type="checkbox"/>	Some people are sometimes a little slower than most when it comes to learning new skills in a sports situation	BUT	Others have always seemed to be among the quickest when it comes to learning new sports skills	<input type="checkbox"/>	<input type="checkbox"/>
22	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel extremely confident about their ability to maintain regular exercise and physical condition	BUT	Others don't feel quite so confident about their ability to maintain regular exercise and physical condition	<input type="checkbox"/>	<input type="checkbox"/>

	Really True for Me	Sort of True for Me			Sort of True for Me	Really True for Me	
23	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that compared to most, their bodies do not look in the best of shape	BUT	Others feel that compared to most their bodies always look in excellent physical shape	<input type="checkbox"/>	<input type="checkbox"/>
24	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are very strong and have well developed muscles compared to most people	BUT	Others fell that they are not so <u>strong</u> and their muscles are not very well developed	<input type="checkbox"/>	<input type="checkbox"/>
25	<input type="checkbox"/>	<input type="checkbox"/>	Some people wish that they could have more respect for their physical selves	BUT	Others always have great respect for their physical selves	<input type="checkbox"/>	<input type="checkbox"/>
26	<input type="checkbox"/>	<input type="checkbox"/>	Given the chance, some people are always one of the first to join in sports activities	BUT	Other people sometimes hold back and are not usually among the first to join in sports	<input type="checkbox"/>	<input type="checkbox"/>
27	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that compared to most they always maintain a high level of physical conditioning	BUT	Others feel that compared to most their level of physical conditioning is not usually so high	<input type="checkbox"/>	<input type="checkbox"/>
28	<input type="checkbox"/>	<input type="checkbox"/>	Some people are extremely confident about the appearance of their body	BUT	Others are a little self-conscious about the appearance of their bodies	<input type="checkbox"/>	<input type="checkbox"/>
29	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that they are not as good as most at dealing with situations requiring physical strength	BUT	Others feel that they are among the best at dealing with situations which require physical strength	<input type="checkbox"/>	<input type="checkbox"/>
30	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel extremely satisfied with the kind of person they are physically	BUT	Others sometimes feel a little dissatisfied with their physical selves	<input type="checkbox"/>	<input type="checkbox"/>

HOW IMPORTANT ARE THINGS TO YOU? (PIP)

	Really True for Me	Sort of True for Me				Sort of True for Me	Really True for Me
1	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that being good at sports is vitally important to them	BUT	Others feel that being good at sports is not so important to them	<input type="checkbox"/>	<input type="checkbox"/>
2	<input type="checkbox"/>	<input type="checkbox"/>	Some people do not feel that maintaining a high level of physical conditioning is very important to them	BUT	Others feel that maintaining a high level of physical conditioning is extremely important to them	<input type="checkbox"/>	<input type="checkbox"/>
3	<input type="checkbox"/>	<input type="checkbox"/>	Some people believe that having an attractive physique or figure is vitally important to them	BUT	Others believe that having an attractive physique or figure is not all that important in their lives	<input type="checkbox"/>	<input type="checkbox"/>
4	<input type="checkbox"/>	<input type="checkbox"/>	Some people believe that being physically strong is not so important to them	BUT	Others feel that it is extremely important to them to be physically strong	<input type="checkbox"/>	<input type="checkbox"/>
5	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that having very good sports ability and skill is not so important to them	BUT	Others feel that having a high level of sports ability is really important to them	<input type="checkbox"/>	<input type="checkbox"/>
6	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that maintaining regular vigorous exercise is vitally important to them	BUT	Others feel that keeping up regular vigorous exercise is not of prime importance to them	<input type="checkbox"/>	<input type="checkbox"/>
7	<input type="checkbox"/>	<input type="checkbox"/>	Some people do not feel it so important to them to spend a lot of time and effort maintaining an attractive body	BUT	Others think that it is vitally important to spend time and effort maintaining an attractive body	<input type="checkbox"/>	<input type="checkbox"/>
8	<input type="checkbox"/>	<input type="checkbox"/>	Some people feel that being strong and having well developed/toned muscles is vitally important to them	BUT	Others feel that being strong and having well developed/toned muscles is not so important to them	<input type="checkbox"/>	<input type="checkbox"/>

A 4.6 Tampa Scale of Kinesiophobia

Tampa Scale for Kinesiophobia (Miller , Kori and Todd 1991)

- 1 = strongly disagree
 2 = disagree
 3 = agree
 4 = strongly agree

1. I'm afraid that I might injure myself if I exercise	1	2	3	4
2. If I were to try to overcome it, my pain would increase	1	2	3	4
3. My body is telling me I have something dangerously wrong	1	2	3	4
4. My pain would probably be relieved if I were to exercise	1	2	3	4
5. People aren't taking my medical condition seriously enough	1	2	3	4
6. My accident has put my body at risk for the rest of my life	1	2	3	4
7. Pain always means I have injured my body	1	2	3	4
8. Just because something aggravates my pain does not mean it is dangerous	1	2	3	4
9. I am afraid that I might injure myself accidentally	1	2	3	4
10. Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening	1	2	3	4
11. I wouldn't have this much pain if there weren't something potentially dangerous going on in my body	1	2	3	4
12. Although my condition is painful, I would be better off if I were physically active	1	2	3	4
13. Pain lets me know when to stop exercising so that I don't injure myself	1	2	3	4
14. It's really not safe for a person with a condition like mine to be physically active	1	2	3	4
15. I can't do all the things normal people do because it's too easy for me to get injured	1	2	3	4
16. Even though something is causing me a lot of pain, I don't think it's actually dangerous	1	2	3	4
17. No one should have to exercise when he/she is in pain	1	2	3	4

Reprinted from:

Pain, Fear of movement/(re) injury in chronic low back pain and its relation to behavioral performance, 62, Vlaeyen, J., Kole-Snijders A., Boeren R., van Eek H., 371.

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A 4.7 Physical Activity Scale for Individuals with Physical Disability

Physical Activity Scale for Individuals with Physical Disability (PASIPD)

Participant I.D.: _____

Date: _____

Item: <i>Note: d = days, hr= hours, score recorded should be the corresponding answer choice for average number of hours per day spent on the activity (1-4)</i>	Score	Score x Item multiplier
<i>Leisure Time Activity:</i>		
<p>1. During the past 7 days how often did you engage in stationary activities such as reading, watching TV, computer games, or doing handcrafts?</p> <p>1. Never (Go to question #2) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d)</p> <p>What were these activities? On average, how many hours per day did you spend in these stationary activities?</p> <p>1. Less than 1hr^[SEP] 2. 1 but less than 2hr 3. 2-4hr^[SEP] 4. More than 4hr</p>		
<p>2. During the past 7 days, how often did you walk, wheel, push outside your home other than specifically for exercise. For example, getting to work or class, walking the dog shopping, or other errands?</p> <p>1. Never (Go to question #3) 2. Seldom (1-2d)^[SEP] 3. Sometimes (3-4d)^[SEP] 4. Often (5-7d)</p> <p>On average, how many hours per day did you spend wheeling or pushing outside your home?</p> <p>1. Less than 1hr^[SEP] 2. 1 but less than 2hr^[SEP] 3. 2-4hr 4. More than 4hr</p>		
<p>^[SEP]3. During the past 7 days, how often did you engage in light sport or recreational activities such as bowling, golf with a cart, hunting or fishing, darts, billiards or pool, therapeutic exercise (physical or occupational therapy, stretching, use of a standing frame) or other similar activities?</p>		

<p>1. Never (Go to question #4) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d) What were these activities? On average, how many <u>hour</u> per day did you spend in these <i>light sport or recreational</i> activities? 1. Less than 1hr^[SEP] 2. 1 but less than 2hr 3. 2-4hr^[SEP] 4. More than 4hr</p>		
<p>4. During the past 7 days, how often did you engage in <i>moderate sport and recreational</i> activities such as doubles tennis, softball, golf without a cart, ballroom dancing, wheeling or pushing for pleasure or other similar activities? 1. Never (Go to question #5) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d) ^[SEP] What were these activities? On average, how many hours per day did you spend in these <i>moderate sport and recreational</i> activities? 1. Less than 1hr^[SEP] 2. 1 but less than 2hr 3. 2-4hr^[SEP] 4. More than 4hr</p>		
<p>5. During the past 7 days, how often did you engage in <i>strenuous sport and recreational</i> activities such as jogging, wheelchair racing (training), off-road pushing, swimming, aerobic dance, arm cranking, cycling (hand or leg), singles tennis, rugby, basketball, walking with crutches and braces, or other similar activities 1. Never (Go to question #6) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d) ^[SEP]What were these activities? On average, how many hours per day did you spend in these <i>strenuous sport or recreational</i> activities? 1. Less than 1hr^[SEP] 2. 1 but less than 2hr 3. 2-4hr^[SEP] 4. More than 4hr</p>		
<p>6. During the past 7 days, how often did you do any exercise <i>specifically</i> to increase muscle strength and endurance such as lifting weights, push-ups, pull-ups, dips, or wheelchair push-ups, etc? 1. Never (Go to question #7) 2. Seldom (1-2d) 3. Sometimes (3-4d)</p>		

<p>4. Often (5-7d) What were these activities? On average, how many hours per day did you spend in these exercises to increase muscle strength and endurance? 1. Less than 1hr 2. 1 but less than 2hr 3. 2-4hr 4. More than 4hr</p>		
Household Activity		
<p>7. During the past 7 days, how often have you done any <i>light housework</i>, such as dusting, sweeping floors or washing dishes? 1. Never (Go to question #8) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d) On average, how many hours per day did you spend doing light housework? 1. Less than 1hr 2. 1 but less than 2hr 3. 2-4hr 4. More than 4hr</p>		
<p>8. During the past 7 days, how often have you done any <i>heavy housework or chores</i> such as vacuuming, scrubbing floors, washing windows, or walls, etc? 1. Never (Go to question #9) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d) On average, how many hours per day did you spend doing heavy housework or chores? 1. Less than 1hr 2. 1 but less than 2hr 3. 2-4hr 4. More than 4hr</p>		
<p>9. During the past 7 days, how often you done <i>home repairs</i> like carpentry, painting, furniture refinishing, electrical work, etc? 1. Never (Go to question #10) 2. Seldom (1-2d) 3. Sometimes (3-4d) 4. Often (5-7d) On average, how many hours per day did you spend doing home repairs? 1. Less than 1hr 2. 1 but less than 2hr 3. 2-4hr 4. More than 4hr</p>		

<p>10. During the past 7 days how often have you done <i>lawn work or yard care</i> including mowing, leaf or snow removal, tree or bush trimming, or wood chopping, etc?</p> <ol style="list-style-type: none"> 1. Never (Go to question #11) 2. Seldom (1-2d)^[SEP] 3. Sometimes (3-4d)^[SEP] 4. Often (5-7d) <p>On average, how many hours per day did you spend doing lawn work?^[SEP]</p> <ol style="list-style-type: none"> 1. Less than 1hr^[SEP] 2. 1 but less than 2hr 3. 2-4hr^[SEP] 4. More than 4hr 		
<p>11. During the past 7 days, how often have you done <i>outdoor gardening</i>?</p> <ol style="list-style-type: none"> 1. Never (Go to question #12) 2. Seldom (1-2d)^[SEP] 3. Sometimes (3-4d)^[SEP] 4. Often (5-7d) <p>On average, how many hours per day did you spend doing outdoor gardening?</p> <ol style="list-style-type: none"> 1. Less than 1hr^[SEP] 2. 1 but less than 2 hr 3. 2-4hr^[SEP] 4. More than 4hr 		
<p>12. During the past 7 days, how often did you <i>care for another person</i>, such as children, a dependent spouse, or another adult?</p> <ol style="list-style-type: none"> 1. Never (Go to question #13) 2. Seldom (1-2d)^[SEP] 3. Sometimes (3-4d)^[SEP] 4. Often (5-7d) <p>On average, how many hours per day did you spend caring for another person?</p> <ol style="list-style-type: none"> 1. Less than 1hr^[SEP] 2. 1 but less than 2hr 3. 2-4hr 4. More than 4hr 		
<p>Work-related Activity</p>		
<p>13. During the past 7 days, how often did you <i>work for pay or as a volunteer</i>? (Exclude work that mainly involved sitting with slight arm movement such as light office work, computer work, light assembly line work, driving bus or van, etc.)</p> <ol style="list-style-type: none"> 1. Never (Go to END) 2. Seldom (1-2d)^[SEP] 3. Sometimes (3-4d) 4. Often (5-7d) <p>On average, how many hours per day did you spend work-</p>		

ing for pay or as a volunteer?

- 1. Less than 1hr
- 2. 1 but less than 4hr
- 3. 5 but less than 8hr
- 4. 8hr or more

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PASIPD Score (Sum of items x item multiplier): _____

A 4.8 Participant Comments

