# **ANKLE CONTRACTURES IN PEOPLE WITH MULTIPLE SCLEROSIS:** IMPLICATIONS, MEASUREMENT AND TREATMENT

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Submitted by:

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# STATEMENT OF SOURCES

This thesis contains no material published elsewhere or extracted in whole or part from a thesis by which I have qualified for or been awarded another degree or diploma.

No other person's work has been used without due acknowledgement in the main text of the thesis.

This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

All research procedures reported in the thesis received the approval of the Australian Catholic University Human Research Ethics Committee (2018-139H).

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# ABSTRACT

Contractures (loss of passive joint range of motion) are common in people with Multiple Sclerosis (MS) and the ankle joint is the most common site. Ankle contractures are disabling as they impede ankle range of motion (ROM). Full ankle ROM is essential for normal ambulation therefore, ankle contractures play a role in the loss of mobility and physical independence in people with MS. Methods explored in this thesis focused on the implications, measurement and subsequent treatment of ankle contractures in people with MS.

Implications

Reduced ankle ROM was associated with compromised heel-to-toe progression. Compared to healthy controls, people with MS spent less time in contact phase (7.8% vs 25.1%) and more time in the mid stance phase of gait (57.3% vs 33.7%). Significant differences were detected in people with MS between the affected and less-affected limbs for contact (7.8% vs 15.3%) and mid stance (57.3% and 47.1%) phases. Our method of heel-to-toe progression revealed subtle gait impairments that were not detectable using standard spatiotemporal gait parameters.

Reduced ankle ROM was associated with an increase in compensatory head and pelvic movements that influenced gait stability in people with MS. Compared to healthy controls, people with MS had greater asymmetry in head and pelvic movements (Cohen's *d*=1.85 & 1.60) and were less stable (Cohen's *d*=-1.61 to -3.06) even after adjusting for slower walking speeds. Our method of screening for excessive compensatory movements provided clinically-important information that impacted on mobility, symmetry and stability in people with MS.

Measurement

Current measurement techniques lack sensitivity to detect ankle impairments in people with MS. We developed a device (Flexometer) to produce standardised (torque-controlled) and reproducible measurements of passive ankle dorsiflexion. The Flexometer proved to be a valid and reliable method (ICC's 0.94 – 0.99) for assessing ankle ROM in people with MS. The accuracy of this device provides

clinicians and researchers with a tool capable of accurate diagnoses and subsequent treatment of ankle contractures in people with MS.

Treatment

Ankle contractures alter muscle morphology leading to shorter, stiffer muscle fascicles in people with MS. According to our systematic review, there appears to be evidence to support the use of eccentric exercise to improve muscle fascicle length and ankle ROM. Therefore, adaptations from eccentric exercise could potentially target deficits present within muscles affected by contracture in people with MS. We explored the effects of backwards-walking-downhill (eccentric exercise) as a therapeutic modality for the management of ankle joint contractures in people with MS. Results indicated backwards-walking-downhill is a novel, safe and feasible training modality in people with MS with an ankle contracture. Additionally, compared to baseline measurements, MS participants improved by approximately 10 degrees in both passive and active ROM. While clinical outcomes (passive and active ROM) were promising, translation to clinically meaningful changes in walking function require further examination.

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***…Think as wise men do, but speak as common people do."***

Aristotle

First and foremost, I would like to thank my principle supervisor, leader, and mentor Professor David Greene for your unwavering support, encouragement and guidance throughout my entire ACU career. Thank you for putting up with my random ideas, tangents, and extreme procrastinations! Your humility in leadership has taught me to *"think as wise men do, but speak as common people do".* While I am still learning, your guidance goes beyond the walls of ACU and I forever will be a student of your teachings.

***"Well begun is half done"***

Aristotle

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***"The secret to having it all… is knowing you already do."***

Unknown

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friendships, laughs and much needed beers along the way! *“The secret to having it all, is knowing you already do”….* I am one of the lucky ones, it doesn’t get much better.

***“Be as you wish to seem.”***

Socrates

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***“Education is the kindling of a flame, not the filling of a vessel.”***

Socrates

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# LIST OF PUBLICATIONS

**ACCEPTED JOURNAL PUBLICATIONS:**

- ***Psarakis, M.,*** Greene, D., Moresi, M., Baker, M., Stubbs, P., Brodie, M., Lord, S., & Hoang, P. (2017). Impaired heel to toe progression during gait is related to reduced ankle range of motion in people with Multiple Sclerosis. *Clinical Biomechanics*.
- ***Psarakis, M.,*** Greene, D., Cole, M. H., Lord, S. R., Hoang, P., & Brodie, M. A. (2018). Wearable technology reveals gait compensations, unstable walking patterns and fatigue in people with Multiple Sclerosis. *Physiological Measurement*.
- ***Psarakis, M.,*** Greene, D., Lord, S. R., Hoang, P. (2019). Safety, Feasibility and Efficacy or an Eccentric Intervention in People with Multiple Sclerosis with Ankle Contractures. *International Journal of MS Care*
- Brodie, M. A., ***Psarakis, M.,*** & Hoang, P. (2016). Gyroscopic corrections improve wearable sensor data prior to measuring dynamic sway in the gait of people with Multiple Sclerosis. *Computer Methods in biomechanics and biomedical engineering*.
- Ade, V., Schalkwijk, D., ***Psarakis, M.,*** Laporte, M. D., Faras, T. J., Sandoval, R., ... & Stubbs, P. W. (2018). Between session reliability of heel-to-toe progression measurements in the stance phase of gait. PloS one, 13 (7).

**FORTHCOMING PUBLICATIONS:**

- ***Psarakis, M.,*** Greene, D., Hoang, P., Lord, S., Herbert, R., & Gandevia, S. (2019). The validity and reliability of passive ankle dorsiflexion range of motion techniques in people with Multiple Sclerosis.
- ***Psarakis, M.,*** Greene, D., Hoang, P. (2019). Do eccentric exercise interventions improve ankle flexibility? – A Systematic Review
- Hoang, P., ***Psarakis, M.,*** Diong, J., Kwah, L.K., Gandevia, S., Herbert, R. (2019). Passive mechanical properties of the gastrocnemius in people with multiple sclerosis who have developed ankle contractures. Clinical Biomechanics.

**CONFERENCE ABSTRACTS & POSTERS**:

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- Hoang, P., ***Psarakis, M.,*** Greene, D., Lord, S. R. (2018). Safety, Feasibility and Efficacy or an Eccentric Intervention in People with Multiple Sclerosis with Ankle Contractures – Motor Impairment conference, Sydney – Australia.
- Kennedy, D., Mai, S., Ings, L., ***Psarakis, M.,*** Lord, S., Canning, C., & Hoang, P. (2016). Test-Retest Reliability of an Unplanned Volitional Stepping Test (Choice Stepping Reaction Time Test) in People with Multiple Sclerosis - ANS Sensorimotor Control Meeting, Hobart – Australia.
- Mai, S., Kennedy, D., Ings, L., ***Psarakis, M.,*** Lord, S., Canning, C., & Hoang, P. (2016). Reliability of The Physiological Profile Assessment Short Form in People with Multiple Sclerosis - ANS Sensorimotor Control Meeting, Hobart – Australia.
- Kennedy, D.,Mai, S., Ings, L., ***Psarakis, M.,*** Lord, S., Canning, C., & Hoang, P. (2017). Test-retest reliability of two falls specific outcome tools, the PPA and the choice stepping reaction time test in people with Multiple Sclerosis - Progress in MS Research conference, Sydney – Australia.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **MS** | Multiple Sclerosis |
| **CP** | Cerebral Palsy |
| **ROM** | Range of motion |
| **CNS** | Central Nervous System |
| **RRMS** | Relapsing remitting multiple sclerosis |
| **SPMS** | Secondary progressive multiple sclerosis |
| **PPMS** | Primary progressive multiple sclerosis |
| **EDSS** | Expanded disability status scale |
| **MTU** | Muscle-tendon unit |
| **6MWT** | Six-minute walk test |
| **PwMS** | People with MS |
| **ANOVA** | Analysis of variance |
| **ANCOVA** | Analysis of covariance |
| **VT** | Vertical |
| **AP** | Anterior-posterior |
| **ML** | Medial - lateral |
| **NRMSE** | Normalised Root Mean Squared Error |
| **ICC** | Intraclass correlation coefficients |
| **WBLT** | Weight bearing lunge test |
| **SEM** | Standard error of measurement |
| **MDC** | Minimal detectable change |
| **RCT's** | Randomised controlled trials |
| **VAS** | Visual analogue scale |
| **RPE** | Rated Perceived Exertion |
| **HR** | Harmonic Ratios |
| **PF** | Plantarflexion |
| **DF** | Dorsiflexion |
| **DOMS** | Delayed on-set muscle soreness |
| **PACES** | Physical activity enjoyment scale |
| **TA** | Tibialis anterior |

# CHAPTER 1 – INTRODUCTION

## 1.1 GENERAL SYNOPSIS

Multiple Sclerosis (MS) is a chronic neurodegenerative disease that effects over 23,000 people in Australia [1]. People with MS identify gait as the most valuable function of the body, as losing the ability to walk can compromise functional independence [1]. Similar to patients with cerebral palsy (CP) and stroke [4], gait impairments in people with MS may be caused by neurological impairments, muscle weaknesses and reduced range of motion (ROM) [5].

Contractures (loss of ROM) affect nearly 60% of people with MS and the ankle joint is the most common site of occurrence [2]. While the exact definition of a contracture remains unclear it is often associated with significant weakness or marked spasticity, often because both conditions can cause muscles to become immobilised at short lengths. The diagnosis of ankle contractures relies on passive ROM measurements performed in a clinical setting however, recently the validity of diagnostic tests have come under increasing scrutiny [3]. Ankle contractures are particularly disabling as they impede ankle ROM. Inadequate dorsiflexion ROM during gait is problematic as it increases the risk of trips and associated falls due to a reduction in foot clearance [4, 5]. Consequently, contractures result in inefficient compensation strategies [6, 7] and abnormal gait patterns commonly seen in individuals with MS [8].

It is a common assertion in rehabilitation that regular stretching is effective for treating and preventing joint contractures. However, findings from a Cochrane systematic review of 35 randomised controlled trials concluded that interventions involving passive stretching techniques in people with neurological conditions do not elicit any clinically useful immediate, short-term or long-term effects on joint ROM [9]. Therefore, additional research is needed in developing alternative methods for treating and managing contractures in neurological conditions.

## 1.2 THESIS SYNOPSIS

The aim of this thesis was to contribute new knowledge of ankle contractures in people with MS. This thesis contains eight chapters that explore various components of ankle contractures in people with MS (Figure 1.1). Chapters 1 and 2 focus on an overview of the thesis with specific reference to relevant literature. Chapter 3 outlines novel methods used within the thesis. Chapters 4 to 8 comprise five studies that highlight three areas of focus (Implications, Measurement, Treatment) within the thesis. Chapter 9 summarises key findings and discusses the clinical utility of the research.

### 1.21 IMPLICATIONS

Chapters four and five use novel techniques to investigate the implications and consequences associated with ankle contractures. Chapter four focuses on using a pressure sensitive walkway to quantify heel-to-toe progression in people with MS. Heel-to-toe progression refers to foot movement that begins with heel contact and ends with toe off. Effective heel-to-toe progression is essential for efficient and smooth locomotion. Previously, heel-to-toe progression has been measured using force platforms and 3D motion capture systems. However, such analysis may be time consuming and limited to a few steps making it less practical for clinical settings [10]. Pressure sensitive walkways overcome these limitations and have been used to quantify spatiotemporal gait patterns in people with MS [11]. However, no research has used the walkway to calculate heel-to-toe progression. Accurate assessment of heel-to-toe progression in the clinical setting could help inform rehabilitation aimed at improving functional mobility in a variety of neurologically gait impaired populations.

Chapter five focuses on the application of wearable technology to screen for compensatory movements at the head and pelvis that occur in people with MS. People with MS exhibit asymmetries in gait caused by weaknesses and contractures of the lower limbs [2, 12, 13]. Asymmetric spastic paraparesis is the most common gait pattern in people with MS [8] potentially resulting in a variety of impairments effecting trunk and lower limb control. Secondary gait compensations attributed to unilateral ankle contractures in individuals without neuromuscular involvement have revealed compensations occurring at both the hip and knee [7]. Therefore, an ankle contracture could be the primary dysfunction leading to secondary hip

compensations however, it is not known if this is occurring in people with MS. Screening for excessive compensatory movements can provide clinically-important information that impacts on mobility, gait variability and gait stability in people with MS.

### 1.22 MEASUREMENT

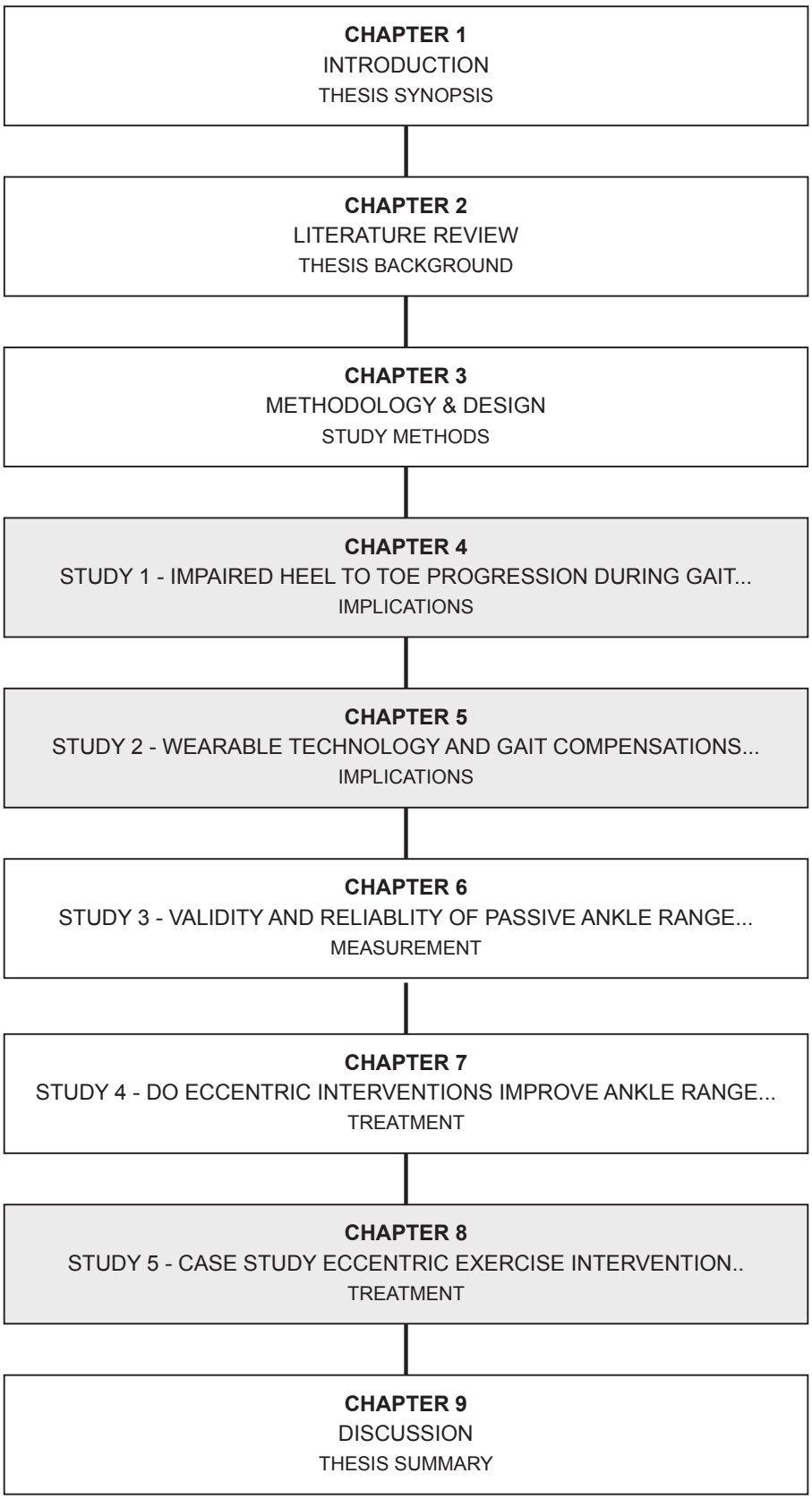
Chapter six compares and contrasts existing techniques using a novel device to measure ankle dorsiflexion ROM in people with MS. Inaccurate measurements of ankle ROM make it difficult to determine if there is an impairment and could lead to incorrect prescription and evaluation of therapy targeted at ankle mobility. This study utilises a novel device that was developed to measure passive ankle ROM in a clinical setting. The validity and reliability of the novel device are explored in order to establish clinical relevance when assessing contractures in people with MS.

### 1.23 TREATMENT

Chapter seven systematically reviews the use of eccentric exercise interventions to improve ankle flexibility. Ankle flexibility is essential for normal ambulation and is important in everyday activities. The focus of this study was to systematically review and evaluate existing knowledge of changes in ankle flexibility following eccentric exercise interventions. This study is intended to inform clinical decision making in the rehabilitation setting.

In response to the systematic review, chapter eight explores the safety and feasibility of a novel exercise intervention (eccentric exercise) to help treat or manage ankle contractures in people with MS. Recent developments in the field of eccentric exercise provide promising results. A number of studies have shown eccentric exercise can increase joint ROM and lengthen muscle fascicles [14-20]. However, to date, no study has examined the safety, feasibility and efficacy of an eccentric exercise intervention in people with MS.

**Figure 1.1** Thesis Overview. Published chapters are shaded in grey.



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# CHAPTER 2 - LITERATURE REVIEW

## 2.1 BACKGROUND OF MULTIPLE SCLEROSIS

### 2.1.1 EPIDEMIOLOGY AND AETIOLOGY

Multiple Sclerosis (MS) is a chronic neurodegenerative disease that affects the central nervous system [1]. MS is a progressive, unpredictable disease that damages the myelin sheath of an axon [2]. Damage to this myelin is called demyelination and is thought to be caused by chronic and recurrent inflammation triggered by the body's own immune system [1]. The term sclerosis is translated from Greek meaning 'hardening of tissue or scars' with scars in MS being referred to as lesions. Lesions impair and interrupt the electrical signals sent from the central nervous system (CNS) and often cause a variety of symptoms that vary in severity, duration and location [3]. The exact cause of MS remains unclear however, it has been suggested that a combination of environmental, genetic and immunological factors play a role in the development of the disease [1].

It is estimated that 2.3 million people globally suffer from MS [4]. MS is twice as common in women as men, with the average onset being 30 years of age [1]. Within Australia, the prevalence of MS is projected to be over 23,000 with females comprising three quarters of all Australians suffering from MS [3]. The most commonly presenting symptoms of MS are sensory and motor deficits [1]. MS often presents in young adults at a time when they are vulnerable both socially and economically [5]. Whilst individuals with MS may experience diverse combinations and severities of MS symptoms, there are three main categories that produce a distinctive pattern relating to the course of the disease. The most commonly accepted categories of MS are (i) relapsing-remitting multiple sclerosis (RRMS), (ii) secondary progressive multiple sclerosis (SPMS), (iii) primary progressive multiple sclerosis (PPMS) and progressive relapsing multiple sclerosis (PRMS).

Every year, 1,000 Australians are diagnosed with MS making it the most common disease of the CNS in young adults [6]. At diagnosis, 85% of people with MS are diagnosed with RRMS10% are diagnosed with PPMS and 5% with PRMS [3]. With time, the majority of people diagnosed with RRMS will eventually

develop SPMS, where disability accumulates progressively without relapses [1]. While there is no cure for MS, current pharmacological therapies can slow disease progression, reduce relapse rate and attenuate the severity and duration of relapses when they occur [7].

### 2.1.2 ECONOMIC COST AND DISEASE BURDEN

In Australia, the total cost of MS per year is approximately $1.038 billion whilst the individual cost per person is $48,945 [3]. Approximately 50 – 80% of people with MS cease full time work within 10 years of diagnosis with the economic burden of MS increasing as the severity of the disease progresses [7]. From an economic and equity perspective, enabling people with MS to retain employment where possible is of paramount importance.

It has been reported that people affected by MS identify restrictions in mobility as the most common and problematic concern [8]. A number of studies demonstrate that gait dysfunction in MS is distinguished by decreased gait speed, walking endurance, step length, cadence and joint motion as well as increased gait variability [9]. The expanded disability status scale (EDSS) is the most commonly used method of quantifying disability in MS and is strongly influenced by a person's walking ability [10]. Walking impairments can be identified early in the MS disease course [10]. However, in both early and late stages of the disease, people with MS perceive gait as the most valuable body function as losing the ability to walk can compromise functional independence.

## 2.2 SKELETAL MUSCLE

### 2.2.1 MUSCLE STRUCTURE AND FUNCTION

Muscles in their most simple function allow for the generation of force to engage in movement. Skeletal muscles have distinct striations caused by the sequential arrangement of their microscopic proteins [11]. Skeletal muscle contractions can be either voluntary mediated by the central nervous system (CNS) or involuntary such as reflexes. Skeletal muscles have four major functional properties; excitability, contractility, extensibility and elasticity. Adequate stimulation from the CNS initiates contractile proteins

within a sarcomere to shorten [11]. Skeletal muscles have the ability to be stretched to a threshold beyond their normal resting length yet also have the ability to recoil and resume their normal length [11].

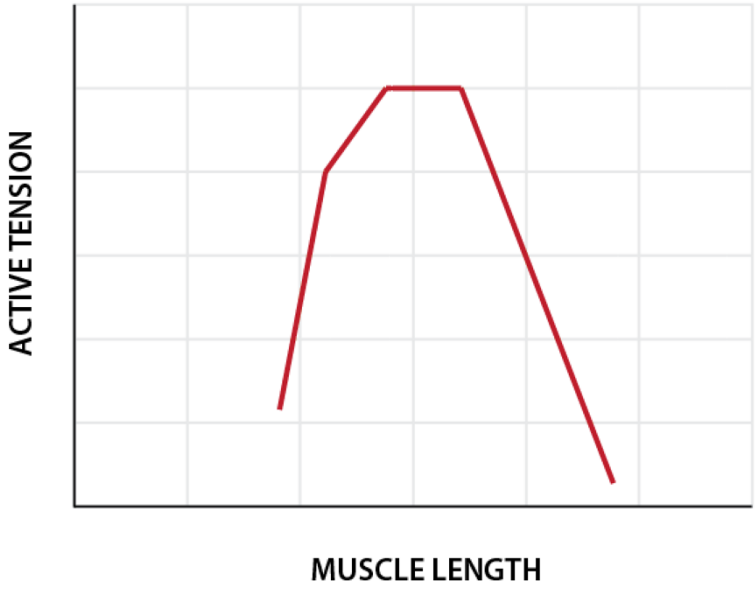
A level of structural muscle hierarchy in order from smallest to largest commences with the myosin and actin filaments. Interlocking myosin and actin filaments form a sarcomere. Sarcomeres, when arranged in series, make up a myofibril that is surrounded by sarcoplasmic reticulum. Myofibrils, arranged in parallel, form a single muscle fibre that is surrounded by endomysium. A bundle of muscle fibres form a fascicle that is surrounded by perimysium. Muscle fibres together create skeletal muscle that is surrounded by epimysium and fascia [12].

### 2.2.2 ACTIVE LENGTH TENSION

Muscle force is initiated when the CNS is sufficiently stimulated. Action potentials travel through the nervous system to motor neurons that innervate muscle fibres [2]. Muscle force is generated when the active protein, myosin, binds to actin and undergoes a slide past the myosin filaments as described by the sliding filament theory [13, 14]. A sarcomere is bordered by two Z discs and when ordered in series create a myofibril. Myosin heads attach to adjoining actin filaments that form a cross bridge [15]. The cross-bridge cycle is repeated with each contraction or shortening of the sarcomere. Although the sarcomere shortens in length, the active proteins do not shorten [11].

As a result of the arrangement between myosin and actin filaments within a sarcomere, the extent of contractile force depends on the number of simultaneously formed cross bridges [11]. The amount of overlap of the filaments within a sarcomere determines the expected force outcome, known as the length tension relationship [16]. Gordon & Huxley [16] demonstrated that an optimal resting length of sarcomeres will enable maximal force production. Either side of this optimal length decreases the number of possible cross bridges, therefore decreasing the amount of active force production (Figure 2.1).

**Figure 2.1** Active length tension curve. Image adapted from [11].




Whilst the optimal resting length of a sarcomere enables maximal force production, further consideration such as the velocity of contraction, play an important role in determining overall muscle output. The inverse relationship between maximal force production and velocity is well established [17, 18]. Muscles contracting at high velocities have reduced availability of cross-bridges [19]. Alternatively, if muscle torque matches load torque, contraction velocity is zero, producing an isometric contraction. Isometric contractions allow for the greatest formation of cross-bridges, thereby producing the most powerful contraction [20]. When load torque continues to increase and exceed muscle torque, a slow lengthening of the muscle occurs, known as an eccentric contraction. Eccentric muscle force is directly proportional to the velocity of its lengthening. However, once the load exceeds threshold, the muscle is forced to lengthen, often uncontrollably [11].

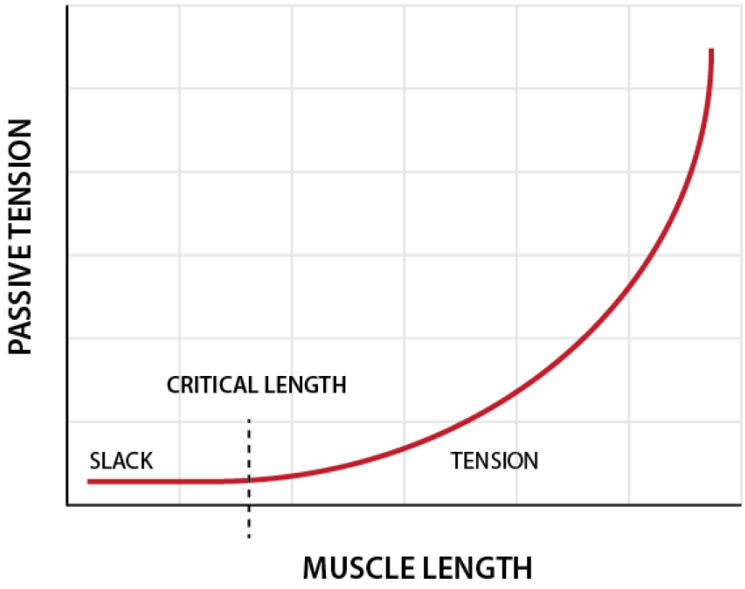
In summary, skeletal muscles can be actively stimulated either voluntarily or involuntarily which allows for the production of force. However, muscles are still capable of producing force without this active response via passive lengthening tension.

### 2.2.3 PASSIVE LENGTH TENSION

Muscle tension can be created via passive stretching of the muscle-tendon unit (MTU). In a relaxed state the increase in resistance does not depend on active protein contractions to generate stiffness; rather passive MTU's act similar to that of an elastic band when being stretched [11].

The passive length tension curve highlights how muscles are compliant and can stretch to a certain threshold without changes in tension (Figure 2.2). This is often referred to as a MTU's "slack length" [11]. After a critical length has been reached and all the slack has been removed, passive forces increase curvilinearly [21]. Simply put, passive muscle stiffness increases as it is lengthened. Beyond a threshold (Figure 2.2 – critical length), muscles become highly resistant to stretch with continued stretching potentially resulting in tissue failure [22].

**Figure 2.2** Passive length tension curve. Image adapted from [11].




The critical length of a muscle has been explored using animal models. Quantifiable evidence of the length-tension relationship was explored by Herbert & Balnave [23] using the soleus muscles of rabbits. Investigators cast-immobilised the soleus muscle in various positions ranging from full plantarflexion to full

dorsiflexion for 10 days. Despite no position-dependent increases in stiffness, when the soleus muscle was fully plantarflexed there was no passive tension in the soleus muscle; meaning it fell completely slack. Furthermore, it was concluded that 10 days of immobilisation produced increased resting stiffness of the MTU. Although an increase in stiffness was established, the source of tension was not isolated in the muscle or tendon. Herbert & Crosbie [24] concluded that tendons play a substantial role in the compliance of the MTU when at rest. As muscles are more compliant than tendons, their contribution to changes in overall length is postulated to be greater.

Despite the previous assumption, ultrasonography measurements taken in vivo on human gastrocnemius muscles verified that on average, muscle fascicles contribute only 27% of the total change in length [25]. Despite being more compliant than tendons, the ratio of tendon-length to muscle fascicle length within the gastrocnemius is 10:1 [25]. Therefore, even small increases in tendon length will contribute to larger increases in total MTU length.

Tendons are primarily made up of collagen, elastin and proteoglycans that when relaxed, form a wave-like pattern [26]. As tension is applied, a tendon sequentially straightens and is more capable of transmitting and applying tension. The elastic properties of tendons and extracellular tissues were thought to play a major role in passive tension [21, 27]. Magid & Law [28] however, achieved contradictory results and demonstrated (in frog muscles), the main source of tension was within a single myofibril; therefore discounting extracellular structures as a source of tension.

There is growing evidence to suggest that sources of passive tension may be attributed to fibres inside the muscle. A large protein molecule ‘titin’, which spans from a Z disc and wraps itself around the myosin filaments, may be responsible for altering the compliance of passive muscles [29]. Enzymatically-suppressed titin via the use of a mild trypsin treatment resulted in fibres becoming compliant [30]. The molecular spring-like constraint of titin appears to limit the travel of sarcomeres [31]. However, not all studies agree. Prado and colleagues [32] demonstrated that titin-based stiffness was not correlated to overall passive stiffness using adult rabbits. Extracellular structures, particularly collagen, were postulated to be the main components responsible for the passive stiffness.

The cause of passive muscle stiffness is controversial and therefore highly scrutinized. Determining the mechanisms behind the extensibility of muscles and tendons is becoming more applicable in conditions affecting the CNS such as in people with MS. MTU's can become increasingly resistant to stretch allowing a shift in the length tension curve to the left. This shift results in a muscle producing greater stiffness at shorter lengths, thus reducing a MTU's slack length.

### 2.2.4 TENDON AND MUSCLE REMODELLING

Sustained immobilization can alter various structures within joints. Immobilisation of a joint often occurs following injury, surgery or prolonged bed rest [33]. Changes such as an increase in fibro-fatty connective tissue into joint space can increase the force requirements needed for joint movement [34]. Connective tissue changes can begin as early as two weeks as compliance and extensibility are lost. Williams & Goldspink [35] modelled this theory using the soleus muscle of mice. Researchers immobilised the soleus in a shortened position for periods ranging from one day to four weeks. As a result, collagen fibres were organised more acutely to the axis of muscles fibres, thus potentially affecting passive muscle stiffness and compliance. Increases in connective tissue within muscles are common in conditions such as cerebral palsy and are clinically referred to as fibrotic muscles [15, 36]. Collagen is a major factor that is thought to be responsible for much of the extracellular matrix stiffness [37]. Similar findings have been found when muscle fibres become completely denervated such as in paralysis. When muscle fibres become completely denervated they can undergo necrosis [38]. In such cases, a proportional increase in non-contractile elements (such as connective tissue) was found within the muscle to replace the necrotic muscle fibres [39, 40].

During growth, muscles must lengthen at the same time as bone growth. Stretch has shown to be an important signal for longitudinal growth of muscles [41]. When exposed to a high level of stretch, muscle protein synthesis is accelerated to elongate the muscle and restore normal tension [42]. This is achieved via the addition of sarcomeres in series to the end of the myofibrils [27, 43] and is known as longitudinal

sarcomerogenesis. In contrast, the opposite occurs when a muscle is immobilised in a shortened position and deprived of stretch [27, 43].

Immobilising a muscle in a shortened position has shown to negatively impact its passive extensibility [43]. It is believed that a reduction in sarcomere number associated with immobilization would mean fewer sarcomeres in series lengthening and therefore would contribute to shorter fascicle lengths. An influential study by Tabary & Tabary [43] found that immobilisation of the soleus muscle in cats in a lengthened position resulted in a 20% increase in serial sarcomere growth when compared to normal control muscles. In comparison, muscles immobilised in a shortened position had a 40% decrease of sarcomeres in series when compared to normal control muscles. When casts of previously immobilised cats were removed, sarcomere numbers returned to normal within 4 weeks. The established adaptation of sarcomeres in series allows for muscles to adjust and work within their new functional length. Therefore, muscles seem to have the capacity to regulate their optimal sarcomere length tension relationship depending on the demands placed upon them [27, 35, 43].

Immobilising a limb can alter the structure of a muscle however, alternations may not occur in a uniform fashion. Heslinga & Huijing [44] proposed an alternative explanation when experimenting on adult rats. After four to six weeks of immobilisation the number of sarcomeres in series was altered in only the distal fibres without any changes noticed within the proximal fibres. Researchers concluded that slack length was altered due to the atrophy of pennate muscles, particularly within the intramuscular part of the tendon. Heslinga et al. [45] further demonstrated differences in muscle adaptation between the gastrocnemius and soleus. With immobilisation, only the soleus was accompanied by a decrease in sarcomeres (in series) whilst the gastrocnemius only experienced atrophy. Therefore, adaptations in muscles may be selective and respond differently despite being exposed to the same stimulus (immobilisation).

A loss of sarcomeres may not reflect muscle fascicle length [24]. An unexpected result was discovered whilst investigating wrist flexor sarcomeres lengths in people with cerebral palsy [46]. Using laser diffraction technology, researchers found long sarcomere lengths within shortened muscles. It is postulated that a loss of sarcomeres in series can force the remaining sarcomeres to stretch or lengthen [15]. The direct

measurement of sarcomere and fascicle length was explored in a human case report of surgical bone lengthening. The muscle fibre adaptions that occurred due to chronic lengthening proved that the increase in fibre length was due to an increase in sarcomeres and not by an increase or stretching of existing sarcomeres [47]. Whist this study was a case report with one subject, it confirms via direct measurement, sarcomerogenesis occurring in human skeletal muscle secondary to chronic length changes [47]. Despite these results, in clinical populations who have pathologic muscle, sarcomerogenesis may be compromised and not respond as normal muscle. A study in children with cerebral palsy investigated the number of satellite cells within each myofibril. Satellite cells are essential in the regulation of skeletal muscle including synthesis and breakdown. Researchers found that satellite cells per myofibril had decreased by approximately 70% when compared to typically developing children [48]. It has been postulated that satellite cells are essential for sarcomerogenesis and that muscles depleted of satellite cells are unable to fully regain sarcomere number following chronic shortening of the muscle [49]. Therefore, it seems satellite cells play an important role in the ability of muscles to remodel.

In summary, skeletal muscle is highly adaptive and can remodel depending on its functional demands [41]. Stretch has shown to be an important signal for remodelling via longitudinal muscle growth known as sarcomerogenesis [41]. In contrast, when a muscle is deprived of stretch (i.e. immobilised) the opposite can occur [43]. Immobilising a muscle in a shortened position has shown to negatively impact its passive extensibility. Therefore, reducing the amount of available ROM (such as in seen in a contracture) may simulate an immobilised (stretch deprived) muscle that causes shorter, stiffer muscles commonly seen in people with MS.

## 2.3 CONTRACTURES

### 2.3.1 DEFINITION AND DIAGNOSIS OF CONTRACTURE

Unfortunately, there is no standardised definition for contracture therefore it is unclear what consists of a contracture diagnosis. Often, the term contracture and contraction (actively shortening or lengthening a muscle) are mistaken however, these terms are not synonymous. Contractures and spasticity are often confused terms and used as interchangeable terms. Contracture is different from spasticity, which is defined

as a velocity-dependent increase in resistance to stretch [64]. Muscle contracture and spasticity are mediated by different mechanisms but often occur together [50-52]. Despite often presenting together, their mechanisms and clinical presentation are very different [50-52].

While the exact definition of a contracture remains controversial [53], contractures are generally regarded as a reduction in passive joint ROM and an increase in joint stiffness [54-56]. Changes in joint ROM often determine the severity of the contracture, with improvements in ROM associating with less contracture and enhanced functional outcomes [57]. However, this is not consistent within the literature. Contractures are often diagnosed as either being “present” or “absent” without any severity scale [58]. For example, Mehrholz et al. [58] define contractures as a 10% reduction in the full normal passive ROM whereas Blanton et al. [59] defines a contracture as a restriction in ROM that impedes activities of daily living. Singer et al. [60] define an ankle contracture as having less than or equal to zero degrees of passive dorsiflexion ROM. Meaning, a patient is able to achieve plantar grade (90 degrees) or in permanent plantar flexed state. Currently, diagnostic criteria of contractures are often performed statically [61] and it is not known how this translates to function.

Depending on how ankle ROM is reported, 0 degrees (neutral) and 90 degrees (neutral) are synonymous. When 0 degrees is considered neutral, a minimum of 10 degrees (dorsiflexion) is reported to be required for normal ambulation [62]. This would be equivalent to 100 degrees (dorsiflexion) when 90 degrees is considered neutral. In an attempt to standardise a definition within the literature, a working definition of ankle contractures was proposed [55, 56]. As muscles responds differently depending on the amount of torque applied, it has been argued that measurements of joint ROM should be made at a known torque [63]. Therefore, ankle contractures were defined as less than 90 degrees of ankle ROM when 12Nm of torque is applied to the ankle [55, 56]. A clear definition of contracture is needed to help standardise future research however, for the purpose of this thesis, we refer to this working definition of an ankle contracture.

### 2.3.2 CAUSES AND MECHANISM OF CONTRACTURE

The exact cause and mechanism of a contracture remains unknown. Contracture is most commonly seen in people with neurological conditions [65, 66] who have significant weakness or marked spasticity, often

because both conditions can cause muscles to become 'immobilised' at short lengths [67]. A contracture reduces the available ROM that may simulate an immobilised (stretch deprived) muscle causing a reduction in muscle fascicle length. Additionally, immobilising a muscle in a shortened position can negatively impact its passive extensibility [43] common to contracture. Collectively these conditions result in architectural adaptations within the muscle-tendon unit. Despite these common assertions, there is no research that has specifically investigated the mechanism of contracture in people with MS.

### 2.3.3 PREVALENCE OF CONTRACTURE IN MULTIPLE SCLEROSIS

In people with MS, spasticity and muscle weakness are very common [68, 69] and the severity of these problems tend to increase with disease progression. The first MS population-based study of prevalence of joint contracture was conducted in 2013 and outlined in Table 2.1 [54]. Results show that approximately 60% of people with MS have a contracture and approximately 44% of people had developed a contracture in the ankle making ankle contractures the most prevalent issue in people with MS. It was also noted that approximately 30% of people with MS who are still ambulant (with or without an assistive device) have contractures.

**Table 2.1** Prevalence and characteristics of joint contractures of a typical MS cohort [54]

| Prevalence of joint contracture | Percentage (95% CI) |
|---|---|
| in any joint | 56.4 (48.5 – 64.3) |
| **in the ankle** | **43.9 (36.9 – 50.9)** |
| in the knee | 17.0 (11.3 – 22.7) |
| in the hip | 28.8 (22.1– 33.6) |
| in the wrist | 3.8 (0.9 – 6.8) |
| in the elbow | 4.8 (1.6 – 8.0) |
| in the shoulder | (8.3 – 17.9) |

*(n = 156 community - dwelling people with MS)*

### 2.3.4 IMPLICATIONS OF CONTRACTURE

One particularly disabling impairment on gait is a restriction in ankle dorsiflexion ROM which is commonly seen in neurological populations [54]. Normal ankle ROM during gait is essential for efficient, symmetrical

and coordinated gait patterns [70]. Delayed or reduced dorsiflexion ROM during gait can prevent movement of the shank over the foot during the stance phase of gait [71], reduce foot clearance during the swing phase of gait [72] and increase the risk of trips and associated falls [73]. A significant consequence of ankle contractures is the debilitating impact on gait and functional mobility [74].

A recent systematic review comparing secondary gait deviations in patients with various pathologies revealed a range of common gait patterns [75]. Gait patterns such as circumduction, vaulting and steppage gait were attributed to a decline in foot clearance commonly seen in neurological populations. Whilst the review did not include people with MS, impairments such as ankle equinus (restricted ankle ROM) and drop foot result in adaptive strategies that increase pelvic tilt, rotation, elevation and abduction during gait [76, 77]. Adaptive strategies (compensations) leading to asymmetries in individuals without neuromuscular involvement caused by an artificially simulated (unilateral) ankle contracture have shown compensations occurring at both the hip and knee to accommodate for a restriction in ankle ROM [78]. When the simulated constraint was removed, all secondary gait deviations resolved indicating that the ankle may be the cause of compensations occurring higher up the kinetic chain.

In order to maintain function and ambulate, compensatory strategies are necessary to accommodate for a reduced ROM at the ankle. Abnormal gait is a risk factor for both past and future falls with over 50% of people with MS falling at least once over a 3-month period [79]. Therefore, accurate assessment of gait as a screening tool for at-risk individuals is essential in understanding factors contributing to falls in people with MS. Despite this, there is little research that focuses on the implications and consequences of ankle contractures in people with MS.

### 2.3.5 MEASUREMENT OF CONTRACTURE

Unfortunately, there is no standardised method for measuring ankle contractures in neurological populations. Joint ROM is frequently measured in exercise physiology research with over 20 techniques cited within the literature [63]. Many of these techniques are performed routinely in research including goniometry [80], electrogoniometry [81], inclinometry [82], the Lidcombe Template [83, 84] and the weight bearing lunge test [85-87]. However, there is no standardised method making it difficult to compare and

collate results from various studies. Goniometry measurements are commonly used in clinical practice however, measurements are subject to test – re-test reliability issues, dependent on the experience of the tester and do not control for the torque applied across the joint. Similarly, the weight bearing lunge test has a measurement error of approximately 5 - 6 degrees [88] and suffers from uncontrolled torques being applied across the joint that can impact on reliability.

To improve reliability, it has been argued that measurements of joint ROM should be made at a known torque as muscles respond differently depending on the force applied [63]. Reliability is particularly important for intervention-based research that aims to detect changes in joint ROM after an intervention. A number of torque-controlled procedures (such as the Lidcombe Template) have been used in neurological populations to measure ankle joint ROM [55-57]. It is commonly accepted that contractures result in reduced passive joint ROM and therefore warrant investigation. However, contractures also increase joint stiffness [54-56] yet no research has focused on quantifying ankle stiffness in people with MS using passive torque-angle data. Therefore, there is a need to develop a method to measure ankle "stiffness" in combination with ROM that can be used in the subsequent diagnosis criteria of a contracture to better target interventions aimed at improving joint ROM and/or joint stiffness.

### 2.3.6 TREATMENT OF CONTRACTURE

Primary intervention for the prevention and treatment of muscle contracture involves the application of various types of muscle stretching. It is a common assertion in rehabilitation that regular stretching is effective for treating and preventing contractures [89]. Types of interventions include passive stretching, splinting, serial casting and manual stretching. The duration of stretches varies depending on its application. Manual stretches when administered by a professional can be applied for several minutes while stretch interventions such as splinting or casting can be applied for days or weeks at a time [89].

Evidence from animal studies suggests that contractures can be improved via passive stretching [27, 33, 43, 90]. Stretching has shown to induce sarcomerogenesis in previously immobilized soleus muscles of cats by 20% [43]. More recently, Coutinho, Gomes [33] verified that 40 minutes of stretching three times a week can increase the number of sarcomeres in the soleus muscle of rats. Whilst findings in animal models

have been well documented, evidence in humans is lacking. However, due to ethical issues, it is difficult to observe changes in human skeletal muscle subjected to stretch [90]. Stretching used as a conservative treatment in advanced contractures has shown little effect on outcomes [74].

A Cochrane systematic review of 35 randomised trials examined the effects of stretching for the prevention and treatment of contracture and concluded that there is moderate-to-high quality evidence that stretching does not have clinically useful immediate, short-term or long-term benefits on joint range of motion [91]. These findings challenge the common assertions in rehabilitation about contracture management and stretching interventions for neurological conditions. Stretching programs administered by rehabilitation professionals do not appear to trigger the required remodelling of muscles [89].

More invasive interventions to manage severe contractures include surgical interventions such as tendon and muscle releases. However, the long-term effects of surgical interventions for contractures have not been investigated in randomised controlled trials.

Muscle contractures are common in multiple sclerosis that result in an impairment of motor performance. In light of current findings, there is a need for a review of current clinical practice guidelines for the treatment and management of contractures.

### 2.3.7 ECCENTRIC EXERCISE

A muscle contracts eccentrically when it is stretched while actively generating force [11]. Unaccustomed eccentric exercise causes muscle damage, which often results in delayed onset muscle soreness in the days following exercise [92]. However, repeated exposure to eccentric exercise produces less muscle soreness and less muscle damage [93]. This is known as the repeat bout effect [94]. Muscle damage associated with unaccustomed eccentric exercise is thought to be due to disruption of overstretched sarcomeres [95]. Experimental data from both animal and human studies [96] suggest that diminishing levels of soreness associated with repeated bouts of exercise occurs because eccentric training induces longitudinal sarcomerogenesis - an increase in the number of sarcomeres arranged in series within muscle fibres. Longitudinal sarcomerogenesis subsequently reduces the strain on sarcomeres.

A number of studies [97-102], and a recent systematic review [103], have examined whether a program of eccentric exercise can produce increases in joint ROM or increases in resting muscle fascicle length. Longer fascicle lengths have been shown to correlate with increased ROM at the joint where muscle fibres cross, whereas shorter lengths have been shown in reduced ROM, as evidenced previously in muscle contracture [104]. Characteristics of those studies and their findings are summarised in the Table 2.2. All studies involved people without contracture, although one study was conducted on adolescents who had "tight hamstrings" [102]. All of the studies claimed eccentric training increased joint ROM or muscle fascicle length, with the exception of the study by Foure et al. [105]. Collectively these studies provide some evidence, but not convincing evidence, that eccentric exercise can stimulate muscle remodelling which can increase the length and extensibility of a muscle. Further to this, eccentric exercise has shown to increase satellite cell number lasting up to 8 days following a single bout of eccentric training, which is likely to contribute to the addition of sarcomeres [106]. It should be noted however, that several studies have significant methodological issues. For example, studies measured fascicle lengths at an unknown passive tension which makes comparisons between trained subjects and controls difficult to interpret. Additionally, not all studies measured outcomes beyond a few hours after the last exercise session – therefore it is unclear if the apparent effects were transient or sustained.

In summary, eccentric exercise may stimulate the longitudinal growth of muscle fibres that may contribute to increases in ROM. If successful, eccentric exercise has the potential to be used as a treatment for contracture in people with MS. To our knowledge, no study has examined the use of eccentric exercise to treat contracture in people with MS.

**Table 2.2** Randomised trials investigating effects of eccentric training programs on joint range of motion or passive properties of muscles

| Ref. | Design | Main finding |
|---|---|---|
| Nelson & Brandy [102] | 69 adolescent males with tight hamstring muscles randomly allocated to eccentric hamstring training (6 submaximal contractions × 3/week × 6 weeks), static stretch or control. Un-blinded and subjective assessment. Per protocol analysis. | Two days after the last stretch, the eccentric group had a mean of **11˚ more knee extension** (95% CI 8 to 14˚) than controls. |
| Blazevich et al. [98] | 33 young adults randomly allocated to eccentric knee extensor training (24-36 maximal efforts, 30˚/s × 3/week × 10 weeks), concentric training or control. | Four days after the last training session, vastus lateralis **fascicle length (hip and knee at 0˚) increased 4.5%** (95% CI 3 to 6%) more than in controls. |
| Mahieu et al. [99] | 74 adults randomised to eccentric training (15 heel drops daily for 6 weeks) or control. Goniometric assessment was blinded but it was not clear if the assessment was after the last day of training. | After the training period the eccentric training group had **-3˚ (95% CI 0 to 6) more ankle dorsiflexion** range with knee extended than controls. |
| Duclay et al. [97] | 18 men were assigned to eccentric calf muscle training (36 contractions at 120% concentric MVC in 18 sessions over 7 weeks) or control. It was not clear if allocation was random. | Three to four days after the last training session, medial gastrocnemius fascicle length was measured at rest in the neutral ankle position. **No effect** size data were reported. |
| Potier at al. [100] | 22 adults randomly assigned to eccentric hamstring muscle training (24 repetitions with a 1RM load, ×3/week for 8 weeks) or control. It was not clear if the assessment was after the last day of training. Fascicle length measure involved dubious extrapolation. Range of motion measures are probably invalid. | After the training period the eccentric training group had **muscle fascicles (measured at rest with knee extended) that were 12 mm longer** (95% CI 9 to 15 mm) than controls. |
| Reeves et al. [101] | 19 older adults (mean 70 years) "randomly" allocated to groups that trained the knee extensors eccentrically (20 repetitions of 80% of the 5RM load, ×3/week for 14 weeks) or concentrically. A large imbalance in age suggests allocation may not have been random. It was not clear if the assessment was after the last day of training. | After the training period the eccentric training group had **muscle fascicles (measured at rest with knee in 10˚ flexion) that were 17 mm longer** (95% CI 6 to 28 mm) than controls. |
| Foure et al. [105] | 24 adults randomly allocated to train the ankle plantarflexors eccentrically (heel lowering and stepping down for 1 hour × 34 sessions over 14 weeks) or control. | 1 week after the training period, the eccentric ankle **dorsiflexion range of motion was 2˚ more** (95% CI 2 to 8˚), **slack length of the gastrocnemius was 7 mm longer** (-20 to 30 mm) and gastrocnemius muscle-tendon stiffness was higher (5 /m, 95% CI -7 to 18 /m) in the training group than in the control group. |

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# CHAPTER 3 - METHODOLOGY

## 3.1 PREFACE

As per university guidelines, the methods and study designs utilised within each study of this thesis are described in their entirety below. Methods presented in chapters 4,5,6,7 and 8 are in accordance with specific journal requirements that have either been published (Chapters 4 & 5), currently under review (Chapter 8) or prepared for submission (Chapters 6 & 7).

## 3.2 STUDY 1 - IMPAIRED HEEL TO TOE PROGRESSION DURING GAIT IS RELATED TO REDUCED ANKLE RANGE OF MOTION IN PEOPLE WITH MULTIPLE SCLEROSIS

### 3.2.1 STUDY DESIGN

This study was a cross-sectional study design comparing heel-to-toe progression in people with MS (PwMS) with age and gender matched controls.

### 3.2.2 PARTICIPANTS

Twelve healthy participants (four males and eight females) and twelve participants with MS (three males and nine females) took part in the study. Healthy participants were matched where possible for age, sex, height and body mass. Inclusion criteria for eligible participants in the MS group included; i) a confirmed diagnosis of MS by a neurologist; ii) An Expanded Disability Status Scale (EDSS) of $\leq 6$ and able to walk independently; iii) no relapses within the past 12 weeks; iv) free from any other disease, injury or illness preventing them from participating in a 6MWT. Participants were excluded from the study if they required the use of a foot-ankle orthosis as such devices interferer with normal heel-toe sequencing. All healthy controls were free from disease, injury or illness that affected gait. The study was approved by the Human Studies Ethics Committee at the University of New South Wales (2013 312N). Informed consent was obtained from all participants prior to participation.

### 3.2.3 ANKLE RANGE OF MOTION ASSESSMENT

Adequate ROM is essential for normal, efficient locomotion. As ankle ROM can influence heel-to-toe progression [1], passive ROM was measured on the more affected side in PwMS to assess the overall ROM available at the ankle joint. Joint contractures are often assessed in the clinic using passive ankle RoM [2, 3]. Briefly, 100N of pulling force was applied to the heads of the metatarsals, parallel to the shank and the ankle angle was measured using an inclinometer (Rippstein - Plurimeter).

### 3.2.4 GAIT ASSESSMENTS

Participants completed a 6-minute walk test (6MWT) wearing comfortable footwear at a self-selected fast walking speed on a twenty-metre walking pathway. A standard protocol was used. Participants were instructed “to walk as far as possible for 6 minutes”. Participants were reminded that they would be walking for 6 minutes and could stop and rest if needed. Participants were given standardised encouragement after each minute. A six-metre long GAITRite$^{TM}$ mat was positioned four metres from the start of the walking pathway to ensure normal gait patterns had resumed after each turn. Spatiotemporal measures were collected along with footprint data of each step and exported for subsequent analysis. Multiple passes over the measurement area were combined for each participant.

### 3.2.5 HEEL-TO-TOE PROGRESSION

Only complete foot prints were used in the analyses. Each footprint was divided into three equal areas that defined the heel, mid-foot and forefoot sensors. Sensor activation and deactivation data for each were then used to calculate the Contact, Mid Stance and Propulsive phases of gait. Contact phase began with heel strike and terminated with forefoot loading and contact duration was calculated by subtracting the ‘heel on’ time from the ‘toe on’ time. Mid stance phase began with forefoot loading and terminated at heel lift and duration was calculated by subtracting ‘toe on’ time from ‘heel off’ time. The propulsive phase began with heel lift and terminated at toe off and was calculated by subtracting ‘heel off’ time from ‘toe off’ time. The phase durations were then normalised by dividing by total foot contact time and gait phases were reported as a percentage for the subsequent statistical analysis.

### 3.2.6 STATISTICAL ANALYSIS

Analyses were performed with SPSS statistical package (version 23). Analysis of variance (ANOVA) was used to assess group differences in heel-to-toe progression and mobility measures for people with and without MS and between affected and non-affected sides for PwMS. Post-hoc t-tests and effect sizes, Cohen's *d* [4] were calculated to assess between group differences. Because a large effect for gait velocity was observed (*d*=-1.82,), analysis of covariance (ANCOVA) was further undertaken to determine if the group differences remained significant after adjusting for walking speed. Pearson's correlations were used to investigate any associations between heel-to-toe progression and participant demographics. Significance was set at $p < 0.05$ for all comparisons. A post-hoc power analysis (two tailed, $p$ =.05) was conducted with the program *G*Power [5]* to ascertain if our study was sufficiently powered to detect the group differences in 6MWT performances.

## **3.3 STUDY 2 -** WEARABLE TECHNOLOGY REVEALS GAIT COMPENSATIONS, UNSTABLE WALKING PATTERNS AND FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS

### 3.3.1 STUDY DESIGN

This study was a cross-sectional study design comparing gait symmetry, stability and compensations in people with MS (PwMS) with age and gender matched controls.

### 3.3.2 SUBJECTS

Twelve participants with MS (three males and nine females) and twelve healthy participants (four males and eight females) participated in the study. Healthy participants were matched where possible for age, sex, height and body mass. Inclusion criteria for eligible participants in the MS group included; i) a confirmed diagnosis of MS by a neurologist; ii) an Expanded Disability Status Scale (EDSS) of $\leq 6$ (indicating the ability to walk at least 100 meters with or without a walking aid); iii) the ability to walk independently; iv) no relapses within the past 12 weeks; v) free from any other disease, injury or illness preventing them from completing 6MWT. All healthy controls were free from any diseases, injuries or illnesses that may have affected their gait at the time of testing. Informed consent was obtained from all participants prior to

participation and the study was approved by the Human Studies Ethics Committee at the University of New South Wales (2013 312N).

### 3.3.3 CLINICAL DISABILITY ASSESSMENT

Range of motion (ROM) at the ankle joint was measured on both sides and uses as the basis to determine the more affected leg in PwMS. Matching sides were assessed for control participants. The method for quantifying passive ankle ROM has been described previously [2, 3]. Briefly, 100N of pulling force was applied to the heads of the metatarsals, parallel to the shank and the ankle angle was measured using an inclinometer (or Plurimeter). Similarly, active ROM was measured using an inclinometer with participants actively dorsiflexing their ankle without assistance from the examiner.

Functional mobility was assessed using the 6MWT, which required participants to walk back and forth along a 20-metre walkway at a self-selected fast walking pace. Participants were given standard instructions to "walk as far as possible for six minutes" with standardized encouragement given at 1, 3 and 5 minutes [6]. The distance walked in the six-minute walk period was recorded.

### 3.3.4 EXPERIMENTAL PROTOCOL

Compensatory head and pelvis movement patterns were measured during the 6MWT using two tri-axial accelerometers (Opal™ by APDM, sampling frequency 128Hz). The sensors were fixed to the participant's head and pelvis as detailed in previous studies [7]. Briefly, the first tri-axial accelerometer was incorporated into a light plastic helmet liner (total mass 67g) and secured to the participant's head. The second tri-axial accelerometer was rigidly attached to the participant's pelvis between the posterior superior iliac spines using double-sided tape and a thick Velcro belt to reduce soft tissue artefact. During the 6MWT, data were reported according to a global vertical, body-centred heading, coordinate system [8]. As such, movements of the head and pelvis in the vertical (VT) direction were independent of body position or sensor orientation and were expressed relative to the global vertical. The anterior / posterior (AP) axis of the tri-axial accelerometers pointed forwards and parallel to the floor, while the medial / lateral (ML) axes were directed right (-ve) to left (+ve) perpendicular to the direction of travel.

Data were recorded continuously for the 6WMT duration. Participants completed laps of a 20-metre walkway. The walkway was marked with 1-metre incremented scale fixed to the floor. Data collection was run through custom built graphic user interface in MATLAB. Gait parameters were calculated using the middle 18-metres of each lap. The start and end of each 18-meter segment were annotated using push buttons each time the participants passed the 1-meter and 19-metre markers. At the completion of the test an alarm sounded, participants were instructed to stop and the distance the last part-lap input into the research software by the clinician using the 1-metre walkway scale. Distance walked was calculated by multiplying the number of laps by 20-meters plus the last part-lap distance.

The middle 18-metres of each lap were used in order to limit the effect of end turns and changes in walking speed on our planned analysis of straight line and 'steady state' walking. For the primary aims of unfatigued walking gait parameters were calculated using the first 18-metre lap segment to minimise the effect fatigue has on gait in PwMS [9]. The secondary analysis of inter-lap reliability used data from the first and second laps and the analysis of fatigue used the first and last laps.

### 3.3.5 DATA ANALYSIS

Custom software was developed in MATLAB to record and analyse the data. Our software used APDM's development protocols to communicate directly with the devices and maintain synchronization with external events. Walks by participants were synchronized with video footage in case confirmation of any aspect of their performance was required.

Measures of mobility included speed ($m.s^{-1}$), cadence ($steps.min^{-1}$), and step length (cm). Measures of gait variability and asymmetry included, stride time variability (ms), step time asymmetry (%), pelvic and head sway variability (cm). Measures of gait compensations included pelvis sway area ($cm^2$), head sway area ($cm^2$), pelvis asymmetry (%) and head asymmetry (%). Gait stability measures included harmonic ratios of both the head and pelvis in the vertical, anterior-posterior and medial-lateral axes.

For each lap, walking speed was calculated as the distance travelled (i.e. 18-metres) divided by the time taken to complete the distance. Heel strikes were measured by detecting the peak AP acceleration of the pelvis sensor each step cycle [10]. Cadence, stride time variability, and step time asymmetry (between left and right steps) were then calculated from the measured heel strikes [11]. Step length was calculated from the distance travelled divided by the number of steps. Stride time variability was reported as the standard deviation of stride times (two consecutive steps equals one stride). Stride time variability was reported in milliseconds as this is a well-established risk factor for falls [12]. Step time asymmetry was calculated as the percentage difference between the mean left and right step times (Equation 1). Step time asymmetry was reported as an absolute value to prevent group means being erroneously close zero in the subsequent statistical analyses [11].

**Equation 1:** Step time asymmetry was calculated as the absolute percentage difference each lap

$$StepTimeAsymmetry = abs\left(\frac{mean(StepTime_{left}) - mean(StepTime_{right})}{\min\left(mean(StepTime_{left}),\ mean(StepTime_{left})\right)}\right) * 100\%$$

Left and right steps were determined from the ML movements of the head sensor over consecutive strides. During each swing phase the participants head was observed to reside primarily over the stance foot. Therefore, (over multiple strides) if the mean ML position of the head sensor during odd steps was greater than the mean ML position of the head during even steps, then the first step of the walk segment was a left step. For steady state straight line walking the step assignment algorithm was confirmed by video to be 100% accurate for people with and without MS.

The head and pelvic excursions during each gait cycle were measured by twice integrating (using MATLAB's cumulative sum function) the corrected linear accelerations from the first lap of the 6MWT and high-pass filtered (using filter thresholds scaled to 0.25 and 0.5 of the step frequency) to obtain an accurate measurement of the stride to stride movements [8]. Measurements were based on previously validated methods with low Normalized Root Mean Squared Errors (NRMSE ≤4%) reported between the gold standard VICON motion capture data and the wearable device data [8]. Movement patterns from multiple

gait cycles were overlaid in 3D space, which allowed a mean trajectory for the both the head and pelvis to be calculated separately and three new gait parameters were calculated (Equations 2-4).

**Equation 2:** Sway area was the product of the AP and ML 95% sway ranges in the transverse plane.

$$SwayArea = 95\%rangeML * 95\%rangeAP$$

**Equation 3:** Vertical asymmetry was the absolute difference between left and right mean vertical trajectory ranges divided by the minimum vertical trajectory range and expressed as a percentage.

$$AsymmetryVT = abs\left(\frac{rangeVT_{left} - rangeVT_{right}}{\min(rangeVT_{left}, rangeVT_{right})}\right) * 100\%$$

**Equation 4:** Sway variability (variance) was the standard deviation of trajectory spread in 3D space. Each gait cycle (stride) was partitioned into 100 points. At each point, the variance of trajectories for all gait cycles about the mean for that point was calculated and the standard deviations of all axes combined.

$$SwayVariance = \sqrt{\sum_{100}^{n=1} \frac{var(SwayAP_n) + var(SwayML_n) + var(SwayVT_n)}{100}}$$

Gait stability was measured using Harmonic ratios. Harmonic ratios along each axis were calculated as a validated measure of dynamic stability. Lower values indicate more out of phase disturbances during the gait cycle, reduced stability and increased risk of falling [13, 14]. Briefly, data from each stride (two steps as defined by heel strikes) were transformed into the frequency domain using a Fast Fourier Transformation. Harmonic ratios for each lap were then calculated using the first 20 harmonics. For the AP and VT axes the in phase ‘stabilizing’ accelerations repeat in multiples of two each stride and therefore the sum of the even harmonic amplitudes were divided by the sum of the odd harmonic amplitudes. For the ML axis this ratio was inverted to account for the different movement period [13].

### 3.3.6 STATISTICAL ANALYSIS

***Primary analyses***

For the primary analysis of unfatigued walking; analysis of variance (ANOVA) was used to assess the differences in gait, demographics and clinical scores for people with and without MS. A Chi-Square test was used to assess for differences in gender distribution. Because the PwMS walked significantly slower than the healthy age-matched controls, the effects of walking speed on the other gait parameters were assessed using analysis of covariance (ANCOVA). Because of the small sample size, in PwMS conservative Spearman's rank correlations were used to assess how the participant demographics and clinical scores related to the gait compensations. Values (≥+0.7 or ≤-0.7) indicated a strong correlation; (≥+0.5 or ≤-0.5) a moderate correlation; and (≥+0.3 or ≤-0.3) a weak correlation. Spearman's correlations were also used to investigate how gait compensations in PwMS related to their mobility, gait variability, gait asymmetry and gait stability. Significance was set at $p \leq 0.05$ for all statistical tests.

Sample size calculations were based on reported walking speeds for PwMS of 86cm.s$^{-1}$ (standard deviation 27cm.s$^{-1}$) and healthy controls of 139cm.s$^{-1}$ (standard deviation 21cm.s$^{-1}$) [15]. A power of 0.99 to detect the expected between group differences with a two-tailed significance of $\alpha=0.05$ was used to inform the size of the study comprising PwMS (n=12) and healthy controls (n=12).

***Secondary analyses***

Intraclass correlation coefficients (ICC) were used to assess the inter-lap agreement between the first and second laps of the 6MWT. These ICCs were used for the secondary evaluation of reliability. Criterion referenced reliability ICC (2,1) was used and 95% confidence intervals reported. ICC values greater than 0.70 indicate good agreement and gait parameters that are suitable for group comparisons. ICC values greater than 0.90 indicate excellent agreement and gait parameters that are suitable to inform individual patient care [16]. A two-way ANOVA with repeated measures in one factor (lap number) was used for the secondary evaluation of fatigue during the 6MWT. The gait parameters for the first and last laps from each participant were used. For each gait parameter, the main effects for group (PwMS vs healthy controls) and time (first lap vs last lap) and the group by time interaction were calculated. Significance was set at $p \leq 0.05$ for all statistical tests.

## **3.4 STUDY 3 -** THE VALIDITY AND RELIABILITY OF PASSIVE ANKLE DORSIFLEXION RANGE OF MOTION TECHNIQUES IN PEOPLE WITH MULTIPLE SCLEROSIS

### 3.4.1 STUDY DESIGN

This study was a cross-sectional study design comparing the validity and reliability of two methods for measuring ankle ROM in young adults, in people with MS and with age and gender matched controls.

### 3.4.2 PARTICIPANTS

In total, 60 participants took part in the validation component of the study (n = 60). Twenty participants with MS (4 males and 16 females), twenty healthy age- and gender-matched controls (4 males and 16 females) and twenty healthy young adults, defined as being between the ages of 18 – 34 (10 males and 10 females). MS participants were recruited from an out-patient MS rehabilitation setting (Sydney, Australia). Inclusion criteria for eligible participants in the MS group included a confirmed diagnosis of MS by a neurologist. Participants were excluded if there was a presence of co-existent conditions, including pain secondary to the diagnosis of MS that would limit ankle range of motion (i.e. ankle surgery or fractures). Control participants were excluded if they had any history of surgical interventions effecting the ankle or pain secondary to an ankle injury. The study was approved by the Human Studies Ethics Committee at the Australian Catholic University (2018-139H). Informed consent was obtained from all participants prior to participation.

### 3.4.3 OVERVIEW

Day 1 testing data (n = 60) were used to assess the concurrent validity between the Weight bearing lunge test (WBLT) and the Flexometer. The relationship (Pearson's Correlation) and agreement (Bland Atman) between the 2 methods was used to determine concurrent validity. However, the WBLT was not suitable for all patients with MS (4/20), therefore their data was excluded from validity analysis (n = 56, 16 MS, 20 healthy age- and gender-matched controls, 20 healthy young adults).

A sub-group (n = 33, 11 MS, 11 healthy age- and gender-matched controls, 11 healthy young adults) participated in a reliability measure 7 days after their first test (i.e. Day 1 vs Day 2). Day 1 vs Day 2 testing data were used to assess the intra-rater reliability of the 2 methods. Reliability measures were taken 7 days apart to mimic clinical practice (i.e. weekly booking with a physiotherapist or exercise physiologist) and minimise assessor re-call of previous scores. Testing was performed on both ankles (left and right) in 2 positions (knee-flexed and knee-extended). Ankle dorsiflexion, when measured in a position of knee extension, is an accepted measure of gastrocnemius length [17]. In comparison, ankle dorsiflexion measured in a position of knee flexion minimises the influence of the gastrocnemius and can reflect factors influenced by soleus muscle length and compliance of the talocrural (ankle) joint complex. All tests were performed 3 times and an average was used in subsequent analysis as previously suggested [18]. All participants were tested following a warm up that included continuous walking along a walking track (5 x 20m laps). Prior to data acquisition, all participants (ankles) were pre-conditioned (6 stretch cycles / repetitions). All tests were performed in a randomised order.

### 3.4.4 INSTRUMENTATION & PROCEDURES

Flexometer

The 'Flexometer' is a revised version of the original Lidcombe Template [19] and provides instantaneous resultant ankle angles. The battery-operated device contains a microcontroller (Arduino-Uno) that powers two digital inclinometers (Inertial Measurement Unit - LSM6DS33) and a push-type load cell (micro parallel beam type load cell – TAL220). One inclinometer is contained within the base plate whilst the second is contained within a small case that is positioned on the shin at a distance of 15cm distal to the tibial tuberosity (providing shank angle relative to the foot). Small LED lights within the shank case allow for the visualisation of pre-determined torque cut offs. The base plate contains 2 velcro straps that cross over the dorsal surface of the foot and secure it in place without impeding ankle joint dorsiflexion. A laser is light located on the top/centre of the base plate to allow for consistent measures. Participants were placed in a long sitting position using a chair and foot stool and a foam roll (10cm diameter) was placed under the knee to flex at 90 degrees (Figure 1B). For the knee extended version, the roller was removed, and the stool moved further out to allow for full knee extension. To minimise effects of thixotrophy on muscle, the ankle was moved through 6 cycles before data was collected. The tester pushed on the load cell until a pre-determined torque

cut off was reached and ROM was recorded. Torque cut off was set at 12Nm as previously outlined [20, 21].

Weight Bearing Lunge Test

The WBLT has previously been shown the have excellent reliability (ICC = 0.97 – 0.98) for measuring ankle dorsiflexion range [22]. An inclinometer (Rippstein - Plurimeter) was used during the lunge test and shank angle was measured for both testing variations (knee-flexed and knee-extended). A vertically taped line was placed perpendicular to the wall to help control subtalar joint movement as previously suggested within the literature [22, 23]. In addition, a taped line on the floor was used for participants to position their 2$^{nd}$ toe and centre of their heel to minimize subtalar pronation. Participants were instructed to place both hands on the wall in front of them and lunge forward to touch the wall with their knee (on the tape) while keeping the heel of their foot in contact with the ground. For the knee extended position, participants were instructed to first extend their knee fully and then lean forward while keeping their heel in contact with the ground (Figure 1A). The inclinometer was placed on the anterior border of the tibia (15cm from the tibial tuberosity) for data collection. Participants performed 6 pre conditioning 'lunge attempts' to find the maximum amount of ankle range whilst maintain full heel contact. To compare data, scores from the WBLT were added by 90 degrees to use the same reference system as the Flexometer. A larger number was indicative of a greater amount of dorsiflexion ROM. MS patients who required a 4-point walker were excluded from all WBLTs.

### 3.4.5 STATISTICAL ANALYSIS

A statistician blinded to assessor and measurement method undertook the analyses and confirmed normal distribution of data. To assess validity, a Pearson's correlation was calculated to assess the relationship between the WBLT and the Flexometer using day 1 data. Interpretation of Pearson correlation (r values) were as follow; < 0.5 low; 0.5 - 0.7 moderate; 0.7 - 0.9 high; > 0.9 very high [24]. The level of significance was set at $p < 0.05$ for correlation tests. An additional analysis using a Bland Altman test [25] was used to assess the degree of agreement between the methods. To assess reliability, data was tested for normal distribution and intraclass correlation coefficient (ICC) was performed on 33 samples at two different time

points by a single rater. A two-way mixed-effects model based on average rating ($k$ = 3) and absolute agreement was used to assess intra-rater reliability. Mean estimations and 95% confidence intervals were reported using SPSS statistical package version 24 (SPSS Inc, Chicago, IL). Interpretation of ICCs were as follows; <0.5 poor; between 0.5 and 0.75 moderate; between 0.75 and 0.9 good; and >0.9 excellent [26]. Standard error of measurement (SEM) and minimal detectable change (MDC) were calculated using methods described by Weir et al. [27]. SEM was calculated using the following equation; √mean square error taken from a 2-way repeated measures ANOVA. MDC was calculated using the following equation; SEM x 1.96 x √2. Smaller SEM and MDC indicate better reliability and sensitivity of the measures respectively.

## **3.5 STUDY 4 -** DO ECCENTRIC EXERCISE INTERVENTIONS IMPROVE ANKLE FLEXIBILITY? – A SYSTEMATIC REVIEW

### 3.5.1 STUDY DESIGN

This study was a systematic review on the effect of eccentric interventions on ankle ROM. This study was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [28].

### 3.5.2 SEARCH STRATEGY

The following electronic databases were searched: Cochrane Central Register of Controlled Trials (Cochrane Library): SportDiscus with Full Text (EbscoHost), The Allied and Complementary Medicine Database (AMED), Web of Science & Medline. Database searches were conducted between 20 and 24 March 2019. Terms used in search strategy include: Eccentric, “negative work”, “Active stretching”, “Range of motion”, ROM, fascicle*, “joint flexib*”, PROM, “muscle length”, Stiffness, “muscle?tendon”, dorsiflexion, Ankle, gastrocnemius, Soleus, “triceps surae”, achilles, “calf muscle”, “plantar flexor”. Truncation, phrase searching and controlled language (MESH and Subject Headings) were used with concepts being searched across subject fields and ‘entire records’ for each database (table 1). After the initial search, all titles and abstracts were screened for eligibility by two authors and disagreements were solved by consensus using a third independent reviewer.

### 3.5.3 STUDY SELECTION CRITERIA

Study eligibility criteria were developed prior to searching to minimise bias. All peer-reviewed articles were examined for suitability with no restrictions placed on publication date. Studies were not limited to randomized controlled trials (RCT's). No limitations were placed on populations however, studies were limited to human experiments only. Conference proceedings, qualitative studies, sources pertaining to nursing, medicine, social work and other allied health professionals were excluded. Studies were excluded if; (i) the 'intervention' (eccentric exercise protocol) was less than 4 weeks in duration; (ii) a combination of eccentric and concentric exercise was used a primary intervention (i.e. Interventions must have been pure eccentric protocols); (iii) there was no direct measurement of muscle length (e.g. fascicle length) or passive ROM measurements were not reported. As longer fascicle lengths correlate with increased ROM [29], both ROM and fascicle length measures were included in this systematic review which collectively represent ankle flexibility.

### 3.5.4 QUALITY ASSESSMENT

A modified checklist by Downs and Black [30] was used to assess the risk-of-bias and methodological quality in the included studies. This checklist accounts for both randomized controlled trial and non-randomized studies included in this systematic review and was performed independently by two authors. The modified version has a maximum score of 28 with study quality classified as "excellent" (24-28 points), "good" (19-23 points), "fair" (14-18 points) or "poor" (<14 points).

### 3.5.5 DATA SYNTHESIS

As the outcome measures in this review were diverse, pooled data (meta-analysis) could not be completed. Data were presented as mean changes (improvements / decrements) in ROM or muscle fascicle lengths. Additionally, authors of included studies were contacted to confirm data reported if not presented in their respective studies.

## **3.6 STUDY 5 -** SAFETY, FEASIBILITY AND EFFICACY OF AN ECCENTRIC EXERCISE INTERVENTION IN PEOPLE WITH MULTIPLE SCLEROSIS WITH ANKLE CONTRACTURES – A CASE SERIES

### 3.6.1 STUDY DESIGN

This study was an exploratory research designed to examine the safety and feasibility of an eccentric exercise program (walking backward and downhill on an inclined treadmill) in people with MS who had ankle joint contractures.

### 3.6.2 PARTICIPANTS

Five consecutive participants with MS (2 male, 3 female), recruited from an out-patient MS rehabilitation setting (Sydney, Australia). Inclusion criteria were: a confirmed diagnosis of MS by neurologists, an Expanded Disability Status Scale (EDSS) of $\leq 6$ (EDSS was calculated using Toronto EDSS Calculator® developed by NeuroApps Toronto), passive ankle dorsiflexion ROM less than 90 degrees when a dorsiflexion torque of 10Nm was applied to the forefoot of the relaxed ankle, no relapses in the preceding 12 weeks and free from any other disease, injury or illness preventing participant from exercising. People who were not mobile or had fixed contractures in the ankle were excluded. The study was approved by the Human Studies Ethics Committee at the University of New South Wales (2013 312N). Informed consent was obtained from all participants prior to participation.

### 3.6.3 ASSESSMENTS

Baseline assessment was conducted seven days before the first training session. Re-assessments were conducted within three days after their last training session.

*i. Safety and Feasibility*

Safety was calculated by the number of adverse events reported by patients both during and after the intervention. Some aspects of the feasibility of the intervention was assessed by recruitment rate, acceptability (based on adherence rate and enjoyment levels), implementation and practicality [31]. Recruitment rates were calculated by dividing the number of participants included in the study by the number of participants who were assessed for eligibility. Enjoyment levels were calculated using the

physical activity enjoyment scale (PACES) questionnaire at the conclusion of the study [32]. Participants were asked to report on their overall 'enjoyment' of the intervention, a higher score reflects a greater level of enjoyment. Participants were asked to report on their DOMS (delayed onset of muscle soreness) using visual analogue scale (VAS) from 0 (no pain) to 10 (unbearable pain) after each session and over a 72hr period. Peak DOMS was recorded for the 24 sessions. The perceived difficulty of each session was monitored using Rated Perceived Exertion (RPE) scale where participants rated how difficult they perceived the training was. Participants were asked to give an RPE every 10 minutes during training and after resting for 10 minutes from 0 (nothing all) to 10 (very heavy) [33].

*ii) Ankle Range of Motion*

Passive and active ROM were measured on the more affected ankle of potential participants with MS. To measure passive ROM, 100N of pulling force (~ 10 kg on a force gauge) was applied to the heads of the metatarsals of the affected ankle and pulled toward the knee, parallel to the shank and the ankle angle was measured using an inclinometer [3]. To measure active ROM, participants were required to actively dorsiflex the ankle as far as they could and again ankle angle was measured using an inclinometer.

*iii) Functional Mobility Assessment*

Participants completed a 6-minute walk test at self-selected walking speeds on a 20m marked walking pathway. Participants were given standard instructions to "as fast and as far as possible without rest for six minutes" with standardised encouragement given at 1, 3 and 5 minutes [6]. The distance walked in the six-minute walk period was recorded. 6-minute walk test was chosen to evaluate if the improvement in the ankle ROM following eccentric exercise helped improve functional mobility.

### 3.6.4 INTERVENTION

Eccentric exercise training (twice a week for 12 weeks = 24 sessions) was conducted under the supervision of an accredited Exercise Physiologist. Participants performed eccentric exercise by walking backwards downhill on an inclined treadmill (h/p/cosmos – model: pulsar 3p) using a previously published protocol [34] with the inclination was between 10 and 14 degrees. Each training session included a 5-minute warm-up

consisting of slow forward walking on a treadmill followed by 10 concentric/eccentric contractions of the plantar flexor muscles (calf raises/lower) of the leg with ankle joint contracture (participants were instructed to hold on the bars of the treadmill for safety). After 5-minute warm up, the belt of the treadmill was turned on reverse direction. Participants were then instructed to step as far backward as possible with the affected leg in a toe-to-heel pattern while keeping the knee straight (to maximise the stretch on the gastrocnemius). After each step with the affected leg, the unaffected leg stepped backwards in a normal pattern. Participants were instructed to use hand rails for support only if needed. The first two (2) sessions were considered as training period. Participants were trained between 10 and 20 minutes at the speed as tolerated. After training sessions, participants were encouraged to walk backwards, at the speed they were comfortable with, as long as they could tolerate with the maximal time being 60 minutes [35] (the highest exercise period time achieved was 50 minutes. No participant could walk backwards for 60 minutes). An overhead body weight support harness was offered as an additional level of support (supplementary video shows a participant with MS performing the intervention).

### 3.6.5 DATA ANALYSIS

This study aimed to explore the effectiveness of an eccentric exercise training program on reduced ankle ROM (secondary aim). Therefore, here we only reported the magnitude of the differences before and after intervention and 95% confidence intervals. No further statistical analysis was performed.

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# **CHAPTER 4 -** IMPAIRED HEEL TO TOE PROGRESSION DURING GAIT IS RELATED TO REDUCED ANKLE RANGE OF MOTION IN PEOPLE WITH MULTIPLE SCLEROSIS

## 4.1 PREFACE

The aim of this study was to determine the associations between gait impairment, heel-to-toe progression and ankle range of motion in people with MS. A novel method was developed to calculate heel-to-toe progression in people with and without MS. This study was the first to explore heel-to-toe progression in the clinical setting and may provide clinicians with a functional measure to assess ankle function in a dynamic setting that may help better inform rehabilitation interventions.

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The work presented in this chapter has been published and cited as;

***Psarakis, M.,*** *Greene, D., Moresi, M., Baker, M., Stubbs, P., Brodie, M., Lord, S., & Hoang, P. (2017). Impaired heel to toe progression during gait is related to reduced ankle range of motion in people with Multiple Sclerosis. Clinical Biomechanics.*

Associated work related to this chapter has been published and cited as;

*Ade, V., Schalkwijk, D.,* ***Psarakis, M.,*** *Laporte, M. D., Faras, T. J., Sandoval, R., ... & Stubbs, P. W. (2018). Between session reliability of heel-to-toe progression measurements in the stance phase of gait. PloS one, 13 (7).*

## 4.2 ABSTRACT

**Background:** Gait impairment in people with Multiple Sclerosis results from neurological impairment, muscle weakness and reduced range of motion. Restrictions in passive ankle range of motion can result in abnormal heel-to-toe progression (weight transfer) and inefficient gait patterns in people with Multiple Sclerosis. The purpose of this study was to determine the associations between gait impairment, heel-to-toe progression and ankle range of motion in people with Multiple Sclerosis.

**Methods:** Twelve participants with Multiple Sclerosis and twelve healthy age-matched participants were assessed. Spatiotemporal parameters of gait and individual footprint data were used to investigate group differences. A pressure sensitive walkway was used to divide each footprint into three phases (contact, mid-stance, propulsive) and calculate the heel-to-toe progression during the stance phase of gait.

**Findings:** Compared to healthy controls, people with Multiple Sclerosis spent relatively less time in contact phase (7.8% vs 25.1%) and more time in the mid stance phase of gait (57.3% vs 33.7%). Inter-limb differences were observed in people with Multiple Sclerosis between the affected and non-affected sides for contact (7.8% vs 15.3%) and mid stance (57.3% and 47.1%) phases. Differences in heel-to-toe progression remained significant after adjusting for walking speed and were correlated with walking distance and ankle range of motion.

**Interpretation:** Impaired heel-to-toe progression was related to poor ankle range of motion in people with Multiple Sclerosis. Heel-to-toe progression provided a sensitive measure for assessing gait impairments that were not detectable using standard spatiotemporal gait parameters.

***Keywords:*** Heel – Toe sequence, Footprint, Ankle Rocker, Electronic walkway, Gait Impairment

## 4.3 INTRODUCTION

Multiple Sclerosis (MS) is a chronic neurodegenerative disease that effects over 23,000 people in Australia [1]. People with Multiple Sclerosis (PwMS) identify restrictions in gait as their most common and problematic concern [2, 3]. Similar to patients with cerebral palsy (CP) and stroke [4], gait impairments in PwMS may result from neurological impairments, muscle weaknesses and reduced ankle range of motion (RoM), often referred to as "joint contractures" [5]. Ankle joint contractures are common in PwMS and are associated with impaired walking ability.

Healthy gait is defined by regular heel-to-toe progression (weight transfer) that facilitates efficient locomotion. Heel-to-toe progression refers to foot movement that begins with heel contact and ends with toe off. Effective heel-to-toe progression is essential in preserving momentum during the stance phase of gait and is influenced by functional ankle and foot rockers [6]. Ankle rocking during the stance phase of gait acts as a pivot point to allow for tibial progression. Adequate passive ankle dorsiflexion is needed to allow for forward progression of the tibia over the foot [6]. Normal heel-to-toe progression is compromised by ankle contractures [7] and can result in inefficient compensation strategies (such as knee hyperextension) often evident in people with neurological conditions [4].

Heel-to-toe progression can be measured using force platforms and 3D motion capture systems. However, such analysis may be time consuming and limited to a few steps making it less practical for clinical settings [8]. In lieu, gait impairments are often assessed using observational rating scales, which may lack sensitivity to detect subtle changes in gait patterns [9]. Portable electronic walkways overcome these limitations and have been used to quantify spatiotemporal gait patterns (e.g. step length, step time and stepping variability) in PwMS [10] and for footprint analysis in healthy people [11].

The purpose of this study was to determine the associations between gait impairment, heel-to-toe progression and ankle RoM in PwMS. A novel method of footprint analysis was used to provide information about how abnormal heel-to-toe progression may affect mobility in people with and without MS during a six-minute walk test (6MWT). Accurate assessment of heel-to-toe progression in the clinical setting could

help inform rehabilitation aimed at improving functional mobility in a variety of neurologically gait impaired populations.

## 4.4 METHODS

### 4.4.1 PARTICIPANTS

Twelve healthy participants (four males and eight females) and twelve participants with MS (three males and nine females) took part in the study. Healthy participants were matched where possible for age, sex, height and body mass (Table 4.1). Inclusion criteria for eligible participants in the MS group included; i) a confirmed diagnosis of MS by a neurologist; ii) An Expanded Disability Status Scale (EDSS) of $\leq 6$ and able to walk independently; iii) no relapses within the past 12 weeks; iv) free from any other disease, injury or illness preventing them from participating in a 6MWT. Participants were excluded from the study if they required the use of a foot-ankle orthosis as such devices interferer with normal heel-toe sequencing. All healthy controls were free from disease, injury or illness that affected gait. The study was approved by the Human Studies Ethics Committee at the University of New South Wales (2013 312N). Informed consent was obtained from all participants prior to participation.

### 4.4.2 ANKLE RANGE OF MOTION ASSESSMENT

Adequate RoM is essential for normal, efficient locomotion. As ankle RoM can influence heel-to-toe progression [7], passive RoM was measured on the more affected side in PwMS to assess the overall RoM available at the ankle joint. Joint contractures are often assessed in the clinic using passive ankle RoM [12, 13]. Briefly, 100N of pulling force was applied to the heads of the metatarsals, parallel to the shank and the ankle angle was measured using an inclinometer (Rippstein - Plurimeter).

### 4.4.3 GAIT ASSESSMENTS

Participants completed a 6MWT wearing comfortable footwear at a self-selected fast walking speed on a twenty-metre walking pathway. A standard protocol was used. Participants were instructed “to walk as far as possible for 6 minutes”. Participants were reminded that they would be walking for 6 minutes and could stop and rest if needed. Participants were given standardised encouragement after each minute. A six-

metre long GAITRite™ mat was positioned four metres from the start of the walking pathway to ensure normal gait patterns had resumed after each turn. Spatiotemporal measures were collected along with the footprint data of each step and exported for subsequent analysis. Multiple passes over the measurement area were combined for each participant.

### 4.4.4 HEEL-TO-TOE PROGRESSION

Only complete foot prints were used in the analyses. Each footprint was divided into three equal areas that defined the heel, mid-foot and forefoot sensors (Figure 4.1). Sensor activation and deactivation data for each were then used to calculate the Contact, Mid Stance and Propulsive phases of gait (Figure 4.1). Contact phase began with heel strike and terminated with forefoot loading and contact duration was calculated by subtracting the 'heel on' time from the 'toe on' time. Mid stance phase began with forefoot loading and terminated at heel lift and duration was calculated by subtracting 'toe on' time from 'heel off' time. The propulsive phase began with heel lift and terminated at toe off and was calculated by subtracting 'heel off' time from 'toe off' time. The phase durations were then normalised by dividing by total foot contact time and gait phases were reported as a percentage for the subsequent statistical analysis.

### 4.4.5 STATISTICAL ANALYSIS

Analyses were performed with SPSS statistical package (version 23). Analysis of variance (ANOVA) was used to assess group differences in heel-to-toe progression and mobility measures for people with and without MS and between affected and non-affected sides for PwMS. Post-hoc t-tests and effect sizes, Cohen's *d* [14] were calculated to assess between group differences. Because a large effect for gait velocity was observed (*d*=-1.82, Table 4.1), analysis of covariance (ANCOVA) was further undertaken to determine if the group differences remained significant after adjusting for walking speed. Pearson's correlations were used to investigate any associations between heel-to-toe progression and participant demographics. Significance was set at $p < 0.05$ for all comparisons. A post-hoc power analysis (two tailed, $p = .05$) was conducted with the program *G*Power [15]* to ascertain if our study was sufficiently powered to detect the group differences in 6MWT performances.

## 4.5 RESULTS

PwMS had similar demographics to the healthy controls (Table 4.1) but had significantly reduced passive ankle RoM (87.9º vs 96.6º) and shorter six-minute walk distances (330m vs 506m). The average EDSS of PwMS was 4.1 (SD=1.2) representing a moderate level of disability.

With respect to the spatiotemporal assessments, PwMS walked significantly slower ($1.02ms^{-1}$ vs $1.57ms^{-1}$, *d*=-1.82) with lower cadence (98.8steps/min vs 121.2 steps/min, *d*=-1.49), shorter step lengths (61.5cm vs 77.5cm, *d*=-1.71) and longer stance times (0.08s vs 0.61s, *d*=1.43) than the healthy controls. However, the differences in cadence, step length and stance time did not remain significant after adjusting for using ANCOVA (Table 4.2).

With respect to quantifying heel-to-toe progression, PwMS spent a lower proportion of stance time in the contact phase (7.8% vs 25.1%, *d*=-3.21) and a greater proportion of time in the mid stance phase (57.3% vs 33.7%, *d*=2.61) than the heathy controls. The large effects [14] of MS on heel-to-toe progression remained significant after adjusting for walking speed using ANCOVA (Table 4.2). Furthermore, in PwMS, significant differences between the affected and non-affected side were only observed in the assessment of heel-to-toe progression (Figure 4.2 & 4.3). Compared to the non-affected side, on the affected side PwMS spent a lower proportion of stance time in contact phase (7.8% vs 15.3%, *d*=-1.33) and a greater proportion in mid stance phase (57.3% vs 47.1%, *d*=0.91).

The post hoc power analysis was based on the observed differences in 6MWT distances (176m, Table 4.1), pooled standard deviation (99m) and the mean performance of the healthy controls (506m). The effect of MS on walking distance (*d*=-1.78) was large [14]. The power to detect an effect of this size in the present study comprising PwMS (n=12) and healthy controls (n=12) was high (>98%). This indicates the study was sufficiently powered to investigate gait differences between people with and without MS.

With respect to the participant demographics and background clinical assessments (Table 4.1) poor heel-to-toe progression was associated with reduced ankle passive RoM and shorter 6MWTs but not with

differences in sex, age, height, weight or BMI. A reduction in the contact phase of gait was significantly ($p \leq 0.05$) correlated with decreased 6MWT distances ($r^2 = 0.42$) and decreased passive range of ankle motion ($r^2 = 0.18$). An increase in the mid-stance phase of gait was significantly ($p \leq 0.05$) correlated with decreased 6MWT distances ($r^2 = 0.64$) and decreased range of ankle motion ($r^2 = 0.17$).

## 4.6 DISCUSSION

People with Multiple Sclerosis develop restrictions in ankle RoM that results in abnormal gait patterns. This study aimed to identify the associations between gait impairment, heel-to-toe progression and ankle RoM in PwMS. Results demonstrated that heel-to-toe progression is impaired in PwMS. Compared to healthy controls, PwMS spent relatively less time in the contact phase and more time in the mid-stance phase of gait. The large effect sizes observed for both the contact phase ($d$=-3.21) and the mid-stance phase of gait ($d$=2.61) indicates the potential clinical utility of assessing heel-to-toe progression objectively. In our study, the impaired heel-to-toe progression in PwMS was correlated with reductions in both passive ankle RoM and 6MWT distance ($r^2 = 0.17$ to $0.64$), highlighting a plausible functional pathway between clinically assessed contracture (reduced passive ankle RoM), inefficient gait patterns and reduced mobility in PwMS.

Consistent with previous research, PwMS completed a significantly shorter 6MWT distance, walked slower with lower cadences, took shorter steps and spent more time in the stance phase of gait [10, 16]. Asymmetric spastic para-paresis is a common gait pattern in PwMS [17] and side to side variability is often reported [18]. However, in the current study, significant differences between the affected and non-affected sides were only observed in measures of heel-to-toe progression; percentage contact time and percentage mid stance, but not in measures of step length or stance time as previously suggested to be common in neurological populations such as MS [18] and Stroke [19].

The objective assessment of heel-to-toe progression had two main advantages over the traditional spatiotemporal parameters of cadence, step length and stance time. Firstly, differences were detected between the affected and non-affected limbs and secondly, differences remained significant after adjusting for walking speed. Together this suggests that the quantification of heel-to-toe progression may reveal subtle gait abnormalities related to gait symmetry that assessment of step lengths and stance times may

not detect.

It has previously been reported that ankle joint contractures can influence gait patterns [5], and that abnormal heel-to-toe progression can result from reduced RoM at the ankle joint [7]. Consistent with these findings, we found PwMS had significantly reduced passive RoM at the ankle when compared to healthy controls. Reduced passive ankle RoM was moderately correlated with both the reduction in the contact phase of gait ($r^2$= 0.18) and the increase in the mid-stance phase of gait ($r^2$= 0.17). Furthermore, we found decreased 6MWT performances were strongly correlated with both the reduction in the contact phase of gait ($r^2$= 0.42) and the increase in the mid-stance phase of gait ($r^2$= 0.64). Impaired heel-to-toe progression potentially provides a functional link between ankle joint contractures and mobility limitations in PwMS and therefore may offer a new target for rehabilitation.

Effective heel-to-toe progression is essential for maintaining momentum and efficiency during gait [6]. Contact support period in our analysis was terminated with forefoot loading. The rapidity of this loading or plantarflexion at initial contact (IC) is regulated by the pretibial muscles including the tibialis anterior, extensor hallucis longus and extensor digitorium longus. Our results also demonstrated a significant difference between affected (7.8%) and non-affected (15.3%) limbs throughout the contact phase of stance which was potentially caused by a combination of weakness associated with the pretibial muscles and restrictions in ankle RoM commonly observed in PwMS [5, 6].

The reduction of time spent in the contact phase was inversely associated with greater time spent in the mid-stance phase. The significant increases detected between the affected (57.3%) and non-affected (47.1%) limbs during the mid-stance phase of gait can alter forward progression and result in compensation strategies such as knee hyperextension to aid with locomotion [4]. The propulsive phase of gait demonstrated no significant differences between PwMS and healthy controls suggesting PwMS may employ a variety of compensatory gait strategies such as vaulting which could influence the amount of time spent in this period leading up to toe off.

We acknowledge certain study limitations. First, our cohort included participants with an average EDSS score of 4.1 (SD=1.2) representing a moderate level of disability within the MS population. Therefore, care must be taken with generalising our findings to MS populations with higher EDSS scores because the severity of the disease can influence gait patterns and may affect heel-to-toe progression. Second, our small sample size (n=24) was relatively small. However, the post-hoc power analysis revealed our study was sufficiently powered to investigate group differences because the effects of MS on walking ability were large. Further investigation is now required to better understand the mechanism causing the inter-limb differences in heel-to-toe progression. Specifically, it was a limitation that only passive ankle RoM was assessed and future research should also investigate the relationship between active ankle RoM during walking and heel-to-toe progression. Future research could also investigate the sensitivity of heel-to-toe progression to changes in gait associated with other neurological conditions such as Stroke and Parkinson's disease and determine if targeted interventions can modify heel-to-toe progression and therefore improve mobility.

## 4.7 CONCLUSIONS

In summary, the study findings demonstrate that objective assessment of heel-to-toe progression during a six-minute walk test identified functionally and clinically important differences in the gait of people with multiple sclerosis and potentially provides a new target for improving mobility in PwMS.

## Acknowledgements

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**Table 4.1** Participant characteristics, passive ankle range of motion and six-minute walking distance for people with MS and health controls

| | People with MS | | Healthy Controls | | ANOVA |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value |
| **Sex (male=1)** | 1.75 | 0.45 | 1.67 | 0.49 | 0.67 |
| **Age [years]** | 52.0 | 9.1 | 55.8 | 12.23 | 0.40 |
| **Height [m]** | 1.69 | 0.06 | 1.65 | 0.09 | 0.21 |
| **Mass [kg]** | 71.5 | 17.9 | 72.3 | 9.91 | 0.89 |
| **BMI [kg/m2]** | 25.1 | 5.7 | 26.8 | 3.34 | 0.39 |
| **Passive Ankle RoM [º]** | 87.9 | 7.8 | 96.6 | 5.92 | **0.006** |
| **6MWT [m]** | 330 | 112 | 506 | 82.64 | **<0.001** |

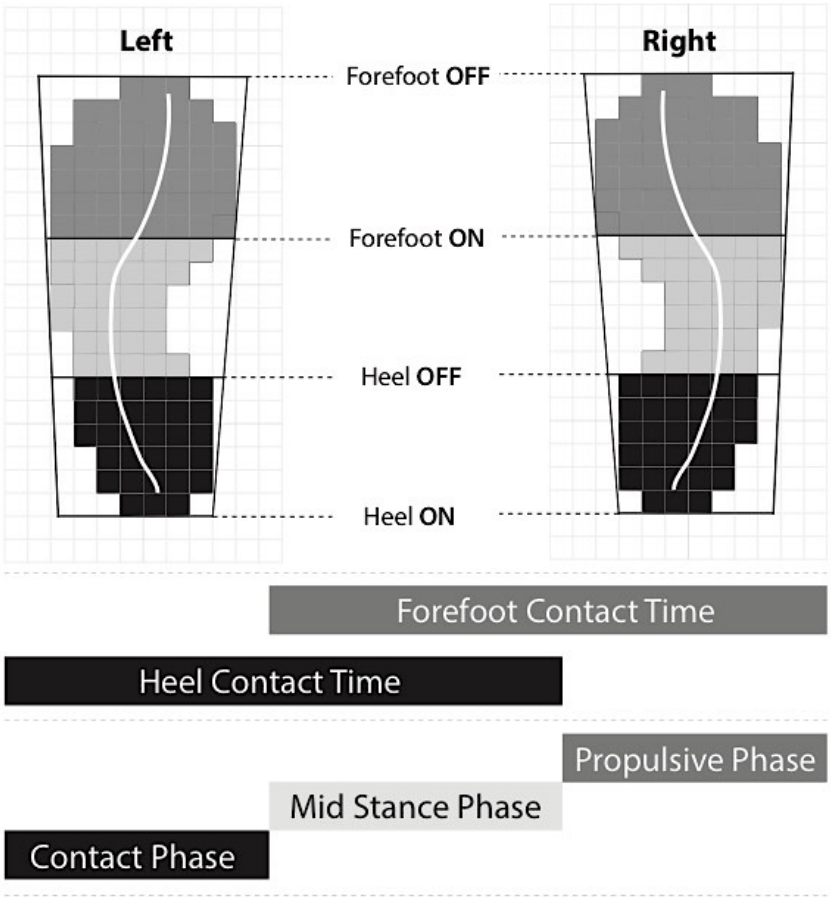
**Table 4.2** Heel-to-toe progression, spatiotemporal and mobility measures assessed during the six-minute walk test for people with MS and healthy controls.

| | MS | | Healthy Control | | ANOVA | ANCOVA | Effect sizes Cohen's d |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value | p-value | |
| **Mobility measures** | | | | | | | |
| *Velocity [m/s]* | 1.02 | 0.35 | 1.57 | 0.24 | **< 0.001** | N/A | -1.82 |
| *Cadence [steps/min]* | 98.8 | 20.1 | 121.2 | 6.8 | **0.001** | 0.83 | -1.49 |

| | 1. MS Affected | | 2. MS Non Affected | | 3. Healthy Controls | | ANOVA | ANCOVA | Post-hoc t-tests & Effect sizes Cohen's d | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | p-value | p-value | 1 vs 2 | d | 1 vs 3 | d | 2 vs 3 | d |
| **Heel-to-Toe progression** | | | | | | | | | | | | | | |
| *% Contact** | 7.8 | 5.1 | 15.3 | 6.1 | 25.1 | 5.8 | **<0.001** | **<0.001** | **0.004** | **-1.33** | **<0.001** | **-3.21** | **0.001** | **-1.63** |
| *% Mid Stance*** | 57.3 | 12.6 | 47.1 | 9.4 | 33.7 | 8.8 | **<0.001** | **0.005** | **0.03** | **0.91** | **<0.001** | **2.16** | **0.002** | **1.47** |
| *% Propulsion**** | 34.9 | 10.8 | 37.6 | 7.6 | 41.2 | 6.6 | 0.21 | 0.69 | 0.48 | -0.29 | 0.10 | -0.70 | 0.23 | -0.50 |
| **Spatiotemporal measures** | | | | | | | | | | | | | | |
| *Step Length [cm]* | 61.5 | 9.5 | 60.5 | 11.3 | 77.5 | 9.2 | **<0.001** | 0.78 | 0.83 | 0.09 | **<0.001** | -1.71 | **0.001** | -1.64 |
| *Toe Out [º]* | 10.3 | 6.4 | 6.6 | 10.0 | 4.4 | 5.4 | 0.17 | 0.42 | 0.29 | 0.45 | 0.02 | 0.99 | 0.52 | 0.27 |
| *Stance Time [s]* | 0.80 | 0.17 | 0.88 | 0.23 | 0.61 | 0.05 | **0.002** | 0.11 | 0.36 | -0.38 | **0.002** | 1.43 | **0.001** | 1.56 |

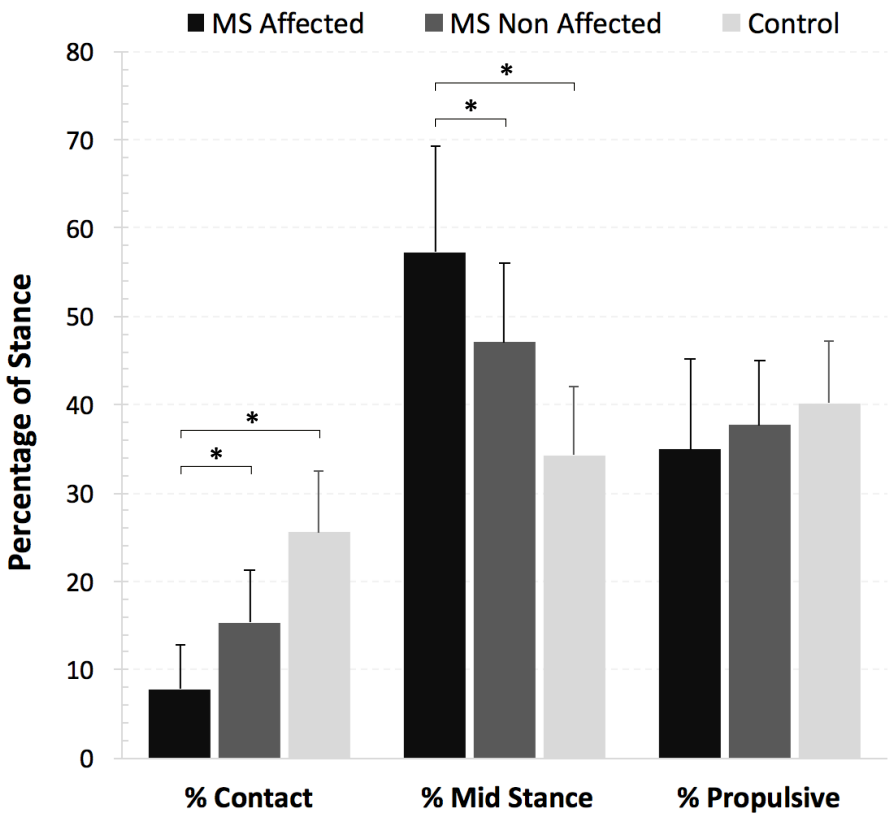
**ANCOVA –** Analysis of covariance adjusting for walking speed.
***% Contact** - Time between heel loading and forefoot loading (Toe On – Heel On / Total Time)
****% Mid Stance** - Time between forefoot loading and heel lift (Heel Off – Toe On / Total Time)
*****% Propulsion** - Time between heel lift and toe off (Toe Off – Heel Off / Total Time)

**Figure 4.1** GAITRite™ Footprint Analysis



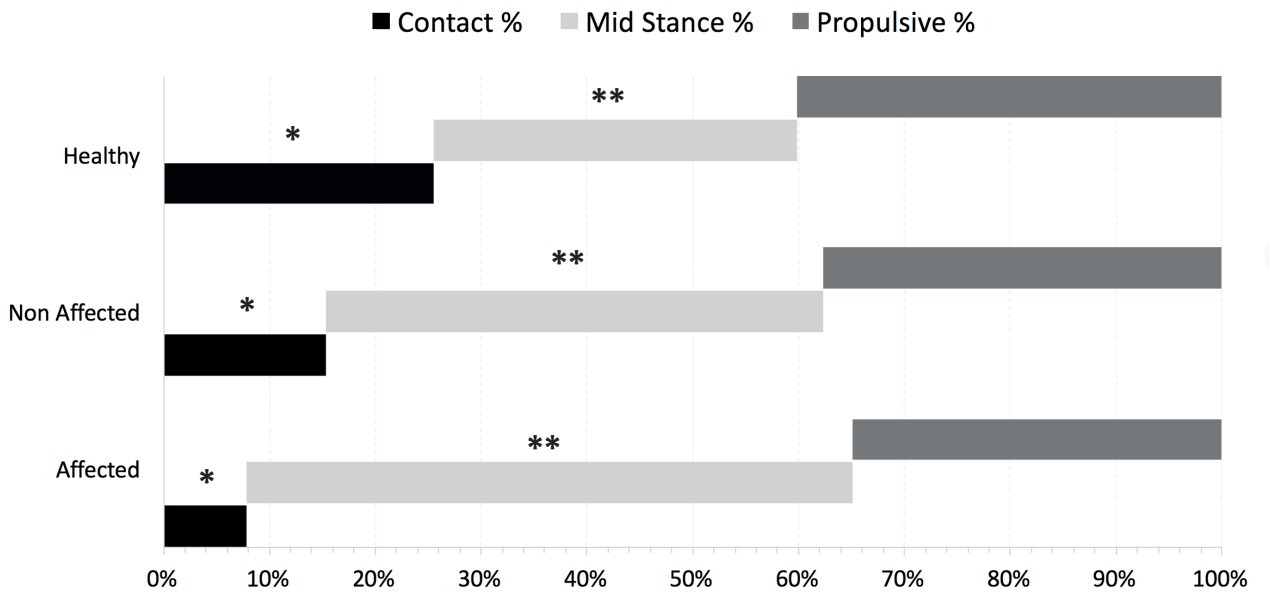

The contact phase begins with heel ON and is terminated with forefoot ON. The mid stance phase begins with forefoot ON and is terminated at heel OFF. The propulsive phase begins with heel OFF and is terminated at forefoot OFF.

**Figure 4.2** Stance phase percentages




*Significant difference in % Contact and % Mid stance between affected, non-affected and healthy groups.

**Figure 4.3** Heel-to-toe progression during stance




*Significant difference in Contact % between affected, non-affected and healthy groups.
**Significant difference in Mid Stance % between affected, non-affected and healthy groups.

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# **CHAPTER 5 -** WEARABLE TECHNOLOGY REVEALS GAIT COMPENSATIONS, UNSTABLE WALKING PATTERNS AND FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS

## 5.1 PREFACE

The aim of this study was to quantify head and pelvis movement patterns that occur in people with multiple sclerosis with ankle contractures and determine how secondary gait compensations impact gait stability. This was achieved by using wearable technology (accelerometers) and applying methods previously published. Wearable device technology provided an efficient and reliable way to screen for excessive compensatory movements often present in people with multiple sclerosis and provides clinically-important information that impacts mobility, stride time variability and gait stability.

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The work presented in this chapter has been published and cited as;

***Psarakis, M.,*** *Greene, D., Cole, M. H., Lord, S. R., Hoang, P., & Brodie, M. A. (2018). Wearable technology reveals gait compensations, unstable walking patterns and fatigue in people with Multiple Sclerosis. Physiological Measurement.*

Associated work related to this chapter has been published and cited as;

*Brodie, M. A.,* ***Psarakis, M.,*** *& Hoang, P. (2016). Gyroscopic corrections improve wearable sensor data prior to measuring dynamic sway in the gait of people with Multiple Sclerosis. Computer Methods in biomechanics and biomedical engineering.*

## 5.2 ABSTRACT

People with Multiple Sclerosis (PwMS) often experience a decline in gait performance, which can compromise their independence and increase falls. Ankle joint contractures in PwMS are common and often result in compensatory gait patterns to accommodate reduced ankle range of motion (ROM). Using advances in wearable technology, the aim of this study was to quantify head and pelvis movement patterns that occur in PwMS with disability and determine how these secondary gait compensations impact on gait stability.

Twelve healthy participants and twelve PwMS participated in the study. Head and pelvis movements were measured using two tri-axial accelerometers. Measures of gait compensation, mobility, variability, asymmetry, stability and fatigue were assessed during a six-minute walking test.

Compared to healthy controls, PwMS had greater vertical asymmetry in their head and pelvic movements (Cohen's $d$=1.85 & 1.60). Lower harmonic ratios indicated that PwMS were more unstable than controls (Cohen's $d$=-1.61 to -3.06), even after adjusting for their slower walking speeds. In the PwMS, increased compensatory movements were correlated with reduced ankle active ROM ($r$=-0.71), higher disability (EDSS) scores ($r$=0.58), unstable gait ($r$=-0.76), reduced mobility ($r$=-0.76) and increased variability ($r$=0.83).

Wearable device technology provides an efficient and reliable way to screen for excessive compensatory movements often present in PwMS and provides clinically-important information that impacts on mobility, stride time variability and gait stability. This information may help clinicians identify PwMS at high risk of falling and develop better rehabilitation interventions that, in addition to improving mobility, may help target the underlying causes of unstable gait.

***Keywords:*** Harmonic Ratio, Accelerometer, Dynamic Stability, Compensations, Gait Screening

## 5.3 INTRODUCTION

Multiple sclerosis (MS) is a chronic neurodegenerative disease affecting over 2.3 million people worldwide [1]. People with Multiple Sclerosis (PwMS) often develop gait impairments that affect functional mobility, physical independence and quality of life [2, 3]. Gait impairments in PwMS are multifactorial in nature and often caused by a range of factors including; spasticity, sensory loss, fatigue, muscle weakness and joint contractures [4-6]. Joint contractures affect approximately 57% of those with MS and the ankle joint is the most common site for contractures [5]. Ankle contractures result in a significant reduction of dorsiflexion range of motion (ROM) and often require compensatory movements of the knee and hip to accommodate restricted ankle ROM [7, 8]. Compensatory gait patterns such as circumduction and vaulting assist with the reduced toe clearance during the swing phase of gait [9], while compensations such as knee hyperextension may be caused by the lack of passive dorsiflexion during the stance phase of gait [10]. Abnormal gait is a significant risk factor for falls with over 50% of PwMS falling at least once over a 3-month period [11].

Clinical gait analysis is often used to monitor disability and disease progression in neurological populations [12]. Gait impairments are commonly assessed using functional measures, such as the timed-up-and-go or the six-minute walk test (6MWT) to assess mobility, but these tests lack sensitivity to detect changes in gait quality [13]. Gait quality may be assessed by observational rating scales, however, the accuracy of this method is highly dependent on the observer's experience [14]. Optical motion capture laboratories can provide accurate assessments of compensatory movements that occur during gait [7, 8], but such resources are impractical in many clinical settings [13]. Therefore, an accurate and clinically-feasible method to assess compensatory movements and their effect on gait stability in PwMS would assist clinicians during rehabilitation to target the underlying causes of poor mobility and unstable gait.

Asymmetric spastic paraparesis is a common gait pattern in PwMS that results in uncoordinated movements of the lower limbs that affects trunk movements [6, 15]. Recent advances using wearable devices have enabled accurate assessments of pelvic, trunk and head movement patterns while walking in both healthy and neurological populations [9, 13, 16, 17]. Accelerometers have been used to assess dynamic gait stability using harmonic ratios (HR) for stroke survivors [18], people with cerebral

palsy [19], individuals with Parkinson's disease [20-22] and recently in PwMS [23] without disability. Previous research using wearable technology has shown PwMS have an increase in trunk variability [24], an increase in lateral trunk motion [13], poorer lower limb ROM [25], and have poorer gait smoothness [23].

Head and pelvis stabilisation play an important role in maintaining balance and postural stability during gait [26] yet few studies have focused on using wearable devices to quantify the compensatory movements that occur at both the head and the pelvis in PwMS with disability.

Extending this body of literature, the primary aim of this study is to (i) quantify the head and the pelvis movement patterns in people with and without MS and (ii) determine how these secondary gait compensations may impact on mobility and gait stability, symmetry and variability during unfatigued walking. Secondary analyses include fatigue and inter-lap reliability. New methods to assess these compensatory movements that occur in PwMS with disability are presented.

## 5.4 METHODS

### 5.4.1 SUBJECTS

Twelve participants with Multiple Sclerosis (three males and nine females) and twelve healthy participants (four males and eight females) participated in the study. Healthy participants were matched where possible for age, sex, height and body mass (Table 5.1). Characteristics of MS group are presented in Table 1. Inclusion criteria for eligible participants in the MS group included; i) a confirmed diagnosis of MS by a neurologist; ii) an Expanded Disability Status Scale (EDSS) of $\leq 6$ (indicating the ability to walk at least 100 meters with or without a walking aid); iii) the ability to walk independently; iv) no relapses within the past 12 weeks; v) free from any other disease, injury or illness preventing them from completing 6MWT. All healthy controls were free from any diseases, injuries or illnesses that may have affected their gait at the time of testing. Informed consent was obtained from all participants prior to participation and the study was approved by the Human Studies Ethics Committee at the University of New South Wales (2013 312N).

### 5.4.2 CLINICAL DISABILITY ASSESSMENT

Range of motion (ROM) at the ankle joint was measured on both sides and uses as the basis to determine the more affected leg in PwMS. Matching sides were assessed for control participants. The method for quantifying passive ankle ROM has been described previously [27, 28]. Briefly, 100N of pulling force was applied to the heads of the metatarsals, parallel to the shank and the ankle angle was measured using an inclinometer (or Plurimeter). Similarly, active ROM was measured using an inclinometer with participants actively dorsiflexing their ankle without assistance from the examiner.

Functional mobility was assessed using the 6MWT, which required participants to walk back and forth along a 20-meter walkway at a self-selected fast walking pace. Participants were given standard instructions to “walk as far as possible for six minutes” with standardized encouragement given at 1, 3 and 5 minutes [29]. The distance walked in the six-minute walk period was recorded.

### 5.4.3 EXPERIMENTAL PROTOCOL

Compensatory head and pelvis movement patterns were measured during the 6MWT using two tri-axial accelerometers (Opal™ by APDM, sampling frequency 128Hz). The sensors were fixed to the participant’s head and pelvis as detailed in previous studies [17]. Briefly, the first tri-axial accelerometer was incorporated into a light plastic helmet liner (total mass 67g) and secured to the participant’s head. The second tri-axial accelerometer was rigidly attached to the participant’s pelvis between the posterior superior iliac spines using double-sided tape and a thick Velcro belt to reduce soft tissue artefact. During the 6MWT, data were reported according to a global vertical, body-centred heading, coordinate system [9]. As such, movements of the head and pelvis in the vertical (VT) direction were independent of body position or sensor orientation and were expressed relative to the global vertical. The anterior / posterior (AP) axis of the tri-axial accelerometers pointed forwards and parallel to the floor, while the medial / lateral (ML) axes were directed right (-ve) to left (+ve) perpendicular to the direction of travel.

Data were recorded continuously for the 6WMT duration. Participants completed laps of a 20-meter walkway. The walkway was marked with 1-meter incremented scale fixed to the floor. Data collection was run through custom built graphic user interface in MATLAB. Gait parameters were calculated using the middle 18-meters of each lap. The start and end of each 18-meter segment were annotated using

push buttons each time the participants passed the 1-meter and 19-meter markers. At the completion the test an alarm sounded, participants were instructed to stop and the distance the last part-lap input into the research software by the clinician using the 1-meter walkway scale. Distance walked was calculated by multiplying the number of laps by 20-meters plus the last part-lap distance.

The middle 18-meters of each lap were used in order to limit the effect of end turns and changes in walking speed on our planned analysis of straight line and 'steady state' walking. For the primary aims of unfatigued walking gait parameters were calculated using the first 18-meter lap segment to minimise the effect fatigue has on gait in PwMS [30]. The secondary analysis of inter-lap reliability used data from the first and second laps and the analysis of fatigue used the first and last laps.

### 5.4.4 DATA ANALYSIS

Custom software was developed in MATLAB to record and analyse the data. Our software used APDM's development protocols to communicate directly with the devices and maintain synchronization with external events. Walks by participants were synchronized with video footage in case confirmation of any aspect of their performance was required.

Measures of mobility included speed ($m.s^{-1}$), cadence ($steps.min^{-1}$), and step length (cm). Measures of gait variability and asymmetry included, stride time variability (ms), step time asymmetry (%), pelvic and head sway variability (cm). Measures of gait compensations included pelvis sway area ($cm^2$), head sway area ($cm^2$), pelvis asymmetry (%) and head asymmetry (%). Gait stability measures included harmonic ratios of both the head and pelvis in the vertical, anterior-posterior and medial-lateral axes.

For each lap, walking speed was calculated as the distance travelled (i.e. 18-meters) divided by the time taken to complete the distance. Heel strikes were measured by detecting the peak AP acceleration of the pelvis sensor each step cycle [31]. Cadence, stride time variability, and step time asymmetry (between left and right steps) were then calculated from the measured heel strikes [32]. Step length was calculated from the distance travelled divided by the number of steps. Stride time variability was reported as the standard deviation of stride times (two consecutive steps equals one stride). Stride time variability was reported in milliseconds as this is a well-established risk factor for falls [33]. Step time asymmetry was calculated as the percentage difference between the mean left and right step times

(Equation 1). Step time asymmetry was reported as an absolute value to prevent group means being erroneously close zero in the subsequent statistical analyses [32].

**Equation 1:** Step time asymmetry was calculated as the absolute percentage difference each lap

$$StepTimeAsymmetry = abs\left(\frac{mean(StepTime_{left}) - mean(StepTime_{right})}{\min\left(mean(StepTime_{left}),\ mean(StepTime_{left})\right)}\right) * 100\%$$

Left and right steps were determined from the ML movements of the head sensor over consecutive strides. During each swing phase the participants head was observed to reside primarily over the stance foot. Therefore, (over multiple strides) if the mean ML position of the head sensor during odd steps was greater than the mean ML position of the head during even steps, then the first step of the walk segment was a left step. For steady state straight line walking the step assignment algorithm was confirmed by video to be 100% accurate for people with and without MS.

The head and pelvic excursions during each gait cycle (Figures 5.1 & 5.2) were measured by twice integrating (using MATLAB's cumulative sum function) the corrected linear accelerations from the first lap of the 6MWT and high-pass filtered (using filter thresholds scaled to 0.25 and 0.5 of the step frequency) to obtain an accurate measurement of the stride to stride movements [9]. Measurements were based on previously validated methods with low Normalized Root Mean Squared Errors (NRMSE ≤4%) reported between the gold standard VICON motion capture data and the wearable device data [9]. Movement patterns from multiple gait cycles (Figure 1, thin lines) were overlaid in 3D space, which allowed a mean trajectory for the both the head and pelvis to be calculated separately (Figure 5.1, thick lines) and three new gait parameters were calculated (Equations 2-4).

**Equation 2:** Sway area was the product of the AP and ML 95% sway ranges in the transverse plane.

$$SwayArea = 95\%rangeML * 95\%rangeAP$$

**Equation 3:** Vertical asymmetry was the absolute difference between left and right mean vertical trajectory ranges divided by the minimum vertical trajectory range and expressed as a percentage.

$$AsymmetryVT = abs\left(\frac{rangeVT_{left} - rangeVT_{right}}{\min(rangeVT_{left}, rangeVT_{right})}\right) * 100\%$$

**Equation 4:** Sway variability (variance) was the standard deviation of trajectory spread in 3D space. Each gait cycle (stride) was partitioned into 100 points. At each point, the variance of trajectories for all gait cycles about the mean for that point was calculated and the standard deviations of all axes combined.

$$SwayVariance = \sqrt{\sum_{100}^{n=1} \frac{var(SwayAP_n) + var(SwayML_n) + var(SwayVT_n)}{100}}$$

Gait stability was measured using Harmonic ratios. Harmonic ratios along each axis were calculated as a validated measure of dynamic stability. Lower values indicate more out of phase disturbances during the gait cycle, reduced stability and increased risk of falling [22, 26]. Briefly, data from each stride (two steps as defined by heel strikes) were transformed into the frequency domain using a Fast Fourier Transformation. Harmonic ratios for each lap were then calculated using the first 20 harmonics. For the AP and VT axes the in phase 'stabilizing' accelerations repeat in multiples of two each stride and therefore the sum of the even harmonic amplitudes were divided by the sum of the odd harmonic amplitudes. For the ML axis this ratio was inverted to account for the different movement period [22].

### 5.4.5 STATISTICAL ANALYSIS

***Primary analyses***

For the primary analysis of unfatigued walking; analysis of variance (ANOVA) was used to assess the differences in gait, demographics and clinical scores for people with and without MS. A Chi-Square test was used to assess for differences in gender distribution. Because the PwMS walked significantly slower than the healthy age-matched controls, the effects of walking speed on the other gait parameters were assessed using analysis of covariance (ANCOVA). Because of the small sample size, in PwMS conservative Spearman's rank correlations were used to assess how the participant demographics and clinical scores related to the gait compensations. Values (≥+0.7 or ≤-0.7) indicated a strong correlation; (≥+0.5 or ≤-0.5) a moderate correlation; and (≥+0.3 or ≤-0.3) a weak correlation. Spearman's correlations were also used to investigate how gait compensations in PwMS related to their mobility,

gait variability, gait asymmetry and gait stability. Significance was set at $p \leq 0.05$ for all statistical tests.

Sample size calculations were based on reported walking speeds for PwMS of 86cm.s$^{-1}$ (standard deviation 27cm.s$^{-1}$) and healthy controls of 139cm.s$^{-1}$ (standard deviation 21cm.s$^{-1}$) [34]. A power of 0.99 to detect the expected between group differences with a two-tailed significance of $\alpha=0.05$ was used to inform the size of the study comprising PwMS (n=12) and healthy controls (n=12).

***Secondary analyses***

Intraclass correlation coefficients (ICC) were used to assess the inter-lap agreement between the first and second laps of the 6MWT. These ICCs were used for the secondary evaluation of reliability. Criterion referenced reliability ICC (2,1) was used and 95% confidence intervals reported. ICC values greater than 0.70 indicate good agreement and gait parameters that are suitable for group comparisons. ICC values greater than 0.90 indicate excellent agreement and gait parameters that are suitable to inform individual patient care [35]. A two-way ANOVA with repeated measures in one factor (lap number) was used for the secondary evaluation of fatigue during the 6MWT. The gait parameters for the first and last laps from each participant were used. For each gait parameter, the main effects for group (PwMS vs healthy controls) and time (first lap vs last lap) and the group by time interaction were calculated. Significance was set at $p \leq 0.05$ for all statistical tests.

## 5.5 RESULTS

***Primary analyses***

PwMS were a similar height and mass compared to the healthy controls (Table 5.1) but had significantly reduced passive ankle range of motion (87.9º vs 96.6º), active ankle range of motion (65.5º vs 102.4º), and shorter six-minute walk distances (330m vs 506m). The median EDSS of PwMS was 4.25 (interquartile range 1.1), representing a moderate level of disability.

MS significantly affected all aspects of gait mobility, variability and asymmetry compensations and stability ($p \leq 0.05$, Table 5.2). PwMS walked slower with more variable and asymmetric gait patterns. For healthy controls, regular and symmetrical head and pelvic movement patterns were observed (Figure 5. 2). For PwMS, head and pelvis compensatory movements during the swing phase of the affected leg were greater than during the swing phase of the unaffected leg (Figure 5.2). PwMS also had reduced

gait stability in all directions, as evidenced by lower harmonic ratios. The largest effect size was for gait stability (Cohen's *d* range = -1.61 to -3.06), followed by gait compensations (Cohen's *d* range = 1.14 to 1.85) and measures of mobility (Cohen's *d* range = -1.41 to -1.68).

After adjusting for differences in walking speed using ANCOVA (Table 5.2), PwMS still had significantly lower gait stability and greater VT asymmetry in their compensatory head and pelvic movements ($p \leq 0.05$). Furthermore, significant Group*Speed interactions were evident for cadence ($p=0.001$), stride time variability ($p=0.013$), head sway variability ($p=0.004$) and pelvis sway variability ($p=0.008$), head sway area ($p=0.011$) and pelvis sway area (p=0.006), which indicates that for PwMS quality of their gait is likely to respond differently to changes in walking speed compared to the quality of gait healthy controls (Figure 5.3).

Gait compensations in PwMS were significantly ($p \leq 0.05$) correlated with age and BMI (Table 5.3). Older PwMS and PwMS with higher BMI exhibited greater pelvic asymmetry ($r=0.57$) and less controlled head movements ($r=0.57$). Moderate to strong correlations were also observed between gait compensations and EDSS score and ankle active ROM, but not passive ROM. PwMS with higher EDSS scores had increased head sway area ($r=0.58$). PwMS with lower ankle active ROM had greater VT asymmetry of both the pelvis ($r=-0.71$) and head ($r=-0.58$). Gait compensations were also strongly correlated with reduced gait performances. Greater pelvic sway area was strongly correlated with reduced mobility (speed and cadence, $r=-0.76$). Greater sway area at both the head and pelvis was moderate to strongly correlated with increased stride time variability ($r=0.58$ to $0.83$) and increased sway variability ($r=0.75$ to $0.82$). Conversely, greater VT asymmetry was moderate to strongly correlated with increased step time asymmetry ($r=0.57$ to $0.72$). Increased gait compensations were also moderate to strongly correlated with decreased gait stability as measured by decreased harmonic ratios along various axes ($r=-0.56$ to $-0.76$).

***Secondary analyses***

The inter-lap reliability of the gait parameters was good to excellent (Appendix 5.1). The reliability of the new parameters describing gait compensations (ICC 0.87 to 0.95) was similar to the reliability of the established measures of mobility (ICC 0.82 to 0.98) and harmonic ratios (ICC 0.85 to 0.94). The

lowest reliability was observed for stride time variability and sway variability (ICC 0.70 to 0.79).

The unadjusted group differences reported for the primary gait assessments of unfatigued walking (ANOVA, p-value, Table 5.2) remained significant after considering the secondary effects of fatigue (first lap vs last lap, two-way ANOVA, Group-p, Appendix 5.2). Two main effects of fatigue were observed. Both PwMS and healthy controls experienced a significant decline in walking speed and cadence with time (Lap-$p \leq 0.02$). A significant interaction was observed for head sway variability (Group-by-Lap-$p=0.03$). Comparing the first lap to the last lap – healthy controls reduced their variability with time while PwMS increased their variability with time.

## 5.6 DISCUSSION

**Wearable technology reveals large gait compensations and reduced stability in PwMS**

The primary aim of this study was to quantify the head and pelvic movement patterns that occur in PwMS using wearable devices during unfatigued walking and determine how these secondary gait compensations may impact on gait mobility and stability. Our results demonstrate that PwMS with disability had greater compensatory movements at both the head and the pelvis (Table 5.2) that were strongly correlated to reduced mobility and increased gait variability (Table 5.3). Compared to healthy controls, PwMS had greater VT asymmetry in their head and pelvic movements (Cohen's $d$=1.85 & 1.60) and reduced gait stability as measured by harmonic ratios (Cohen's $d$=-1.61 to -3.06). Importantly, these differences in gait asymmetry and gait stability were found to be independent of the slower walking speeds observed in the MS population.

Consistent with previous research, our results confirmed that PwMS had greater gait impairments characterized by lower cadences, greater stride time variability and greater step time asymmetry [3, 34]. While most previous research has used electronic walkways to quantify spatiotemporal gait impairments in PwMS, our data, supports recent advances [13, 23, 24], which suggest wearable technology provides an accurate and accessible tool that is capable of completing comparable clinical assessments. Furthermore, for PwMS with disability, our results demonstrate wearable devices can provide additional reliable information about the compensatory movements and stability at both the

head and the pelvis (Figure 5.2), which may provide a more sensitive way to measure gait quality that is independent of group differences in walking speed.

**Gait compensations, active ankle ROM, disability level and the mobility/dynamic stability trade-off**

The unstable head and pelvis movements observed in PwMS were assumed to largely reflect secondary gait compensations resulting from lower limb muscle weaknesses and joint contractures (the primary gait restriction) [8]. A systematic review of common compensatory mechanisms, however, suggests a more complex scenario [8]. Although common impairments such as ankle contracture and foot drop often result in adaptive compensation strategies that increase pelvic tilt, rotation, elevation and abduction during walking, in PwMS the relative importance of passive physical effects versus active gait compensations may be debated [8]; particularly for head movements, which may be mechanically linked with pelvic movements. In this discussion, "gait compensations" therefore refers to secondary gait restrictions that could be both passive and active in origin. In agreement with previous research [36, 37], limited ankle range of motion in PwMS and ankle contractures likely contributed to these gait compensations. While large head and pelvis movements may have been necessary to accommodate muscle weaknesses and joint restrictions our analysis of harmonic ratios shows that these secondary gait compensations also reduced gait stability in PwMS.

The gait compensations observed in PwMS most strongly correlated with poorer active ankle ROM and higher EDSS scores (Table 5.3). Our results are consistent with previous research that found mean ankle ROM to be less during walking and was correlated to greater motor impairment [25]. Our results suggest that for people with more severe MS, larger secondary gait compensations at the head and pelvis were necessary to maintain function and continue to ambulate. The significant group*speed interactions observed for the sway area (head sway area $p$=0.011 and pelvis sway area p=0.006, Table 5.2) indicates an important trade-off between mobility (gait speed) and dynamic stability (control of sway area). For healthy people, the positive slope (Figure 5.3) indicates faster walking speed was achieved by more energetic stepping, which caused greater pelvic movement. However, for PwMS we hypothesize the negative slope (Figure 5.3) indicates that walking speed may have been limited by their ability to maintain control of their sway area. Additional experiments measuring sway area at different

walking speeds are required to confirm this. Screening for excessive head and pelvis compensatory movements in PwMS may therefore provide clinicians with new tools to quantify disease progression within the clinical setting. In addition to existing assessments of mobility, clinicians may also use the wearable device assessments gait symmetry and stability to help assess the effectiveness of various treatment modalities.

Gait compensations were quantified by abnormal movements occurring in the transverse (AP*ML sway area) and frontal planes (VT asymmetric displacements) during the 6MWT. Sway area during gait may provide a novel way to assess dynamic postural control and balance deficits in clinical populations during activities. Our results demonstrated that the sway area for PwMS was approximately double at the pelvis (22.4cm$^2$ vs 10.7cm$^2$) and head (19.2cm$^2$ vs 10cm$^2$) when compared to healthy controls. Results are consistent with previous research that found PwMS had increased trunk movements during gait [13, 24]. Quantifying abnormal movements in the frontal plane revealed significant differences in VT asymmetric displacements between the groups. Our results highlighted that PwMS have an inter-limb imbalance of more than 65% in head and pelvic symmetry. This significant inter-limb compensation is attributed to the variety of gait patterns observed in our sample (often observed in patients with neurological involvement), which included circumduction (swinging leg around), vaulting (hip hiking on one side while pushing off on the other side) and steppage gait (lifting the leg higher to avoid tripping).

**Gait stability, falls risk and rehabilitation**

Gait stability was measured using harmonic ratios (HR) along the ML, AP and VT axes. Our findings are consistent with previous work that showed PwMS had reduced gait smoothness and margin of stability [23, 38]. Unstable and variable gait has been associated with an increased risk of falls in people with Parkinson's Disease and older people [22, 26] and may provide clinicians with insightful metrics that are useful for screening at-risk individuals in MS populations [39].

With respect to variability, we found significant differences in head and pelvic sway trajectories when compared to healthy controls. The greater variability of trajectories may be explained by the additional compensatory movements of the lower limbs. Previous research has shown that PwMS have greater variability of the lumbar spine when compared to the sternum during gait because of the dampening effect of the spine [24]; however, our analysis did not support this finding.

Our study builds on previous research into gait impairments in PwMS [13, 23, 24, 38]. Specifically, our analysis combines assessments of mobility, stride time variability and step time asymmetry with assessments of gait compensations, gait stability and sway variability at both the head and pelvis. For PwMS and increasing disability, the additional patient-specific information about head movements may be important because head is a platform for sensory organs and therefore plays a vital role in maintaining dynamic balance and preventing falls.

With respect to rehabilitation, previous research has demonstrated the need for an intervention to treat the primary cause and not the secondary gait compensation [40]. While greater gait compensations were correlated with participant demographics, it is our view that active ankle range of motion (combining flexibility, lower limb strength and motor control) is both a modifiable and an important primary cause of secondary gait compensations in PwMS. Inability to dorsi-flex the foot during the swing phase may result in large compensatory movements at the pelvis (required to help clear the toe of the affected limb during the swing phase of gait) and large compensatory movements at the head (to help maintain balance over the stance leg). Our data suggest these large and unstable head and pelvic movements are both inefficient and may increase falls risk.

**Secondary analyses of reliability and fatigue**

The analysis of inter-lap reliability during the 6MWT showed that for an 18-meter segment of straight-line walking, wearable devices can reliably assess gait compensations (Appendix 5.1). Similar to the established measures of gait mobility and gait stability, good to excellent reliability (ICC 0.87 to 0.95) was observed. Reliability for stride time variability and sway variability was slightly lower, but sufficient for group comparisons in research [35]. With respect to providing patient specific advice reliability (particularly for measures of gait variability) may be further improved by averaging values from several 18-meter segments.

Both PwMS and healthy controls experienced a significant decline in walking speed and cadence over the 6MWT (Appendix 5.2). In line with previous work on walking-related motor fatigue [30], in our study PwMS reduced their walking speed on average by 10.3% between the first and last laps. Furthermore, fatigue was also observed to affect PwMS differently to healthy controls. For the measures of gait variability, asymmetry, compensations and stability, PwMS deteriorated between the first and last laps

while healthy people improved. These group-by-lap interactions were small compared to the main and primary group effects and were therefore non-significant (with the exception of head sway variability, p=0.03) as our study was not powered to detect these changes. This indicates a larger sample size should be used to further investigate the effects of fatigue gait compensations, gait variability and stability and fall risk in PwMS.

**Limitations and future research**

We acknowledge certain study limitations. Our small sample included participants with a median EDSS score of 4.25 representing a moderate level of disability within the MS population. Care must be taken before generalizing our findings to PwMS with all levels of disability. The severity of the disease can influence gait patterns, PwMS have a range of disabilities and this may affect their compensatory movements differently. Larger studies are required for additional subgroup analyses in people with different levels of disability and to further investigate the effects of fatigue on gait compensations, gait stability and fall risk. Although muscle strength was indirectly assessed through active ankle range of motion, the direct contribution of lower limb muscle strength should be further examined in the future through additional strength testing. In this study, stride time variability and step time asymmetry were based on the step times derived from the pelvic sensor; accuracy may be improved by using additional sensors on each foot or shank.

Future research should also focus on understanding the mechanisms behind gait compensations, the relative importance of passive physical effects versus active gait compensations and the changes that occur with differences in walking speed, ankle range of motion and fatigue in PwMS. Additionally, future research should focus on understanding the complex interactions between ankle range of motion, lower limb muscle strength and fatigue, and how these influences may affect all other elements of the kinetic chain.

## 5.7 CONCLUSION

Wearable technologies provide a clinically feasible, reliable and accurate method to assess gait quality, screen PwMS for excessive and unstable compensatory movements at the head and pelvis and

increased falls risk. Early detection of gait abnormalities may help clinicians to identify PwMS who are at risk of falling and facilitate the earlier implementation of targeted rehabilitation interventions to address the underlying primary gait restrictions that cause gait impairments. Future research is warranted to determine whether novel interventions that aim to treat ankle contractures and improve active ankle range of motion can reduce secondary gait compensations, improve gait mobility and stability and prevent falls in people with MS. Future research should also examine how alterations in active ROM of other elements in the kinematic chain influence gait mobility, stability and the effects of fatigue on gait compensations and gait stability in PwMS.

## Funding

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**Table 5.1** Participant characteristics, passive/active ankle range of motion and six-minute walking distance for people with MS and healthy controls. Data represent the mean and standard deviations except for gender which represents the number and percentage of males in each group. Test 1 = one-way ANOVA; Test 2 = Chi-Square test.

| | **People with MS** | | **Healthy Controls** | | Test | p-value |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | |
| **Gender [male]** | N=3 | 25% | N=4 | 33% | 2 | 0.65 |
| **Age [years]** | 52.0 | 9.1 | 55.8 | 12.23 | 1 | 0.40 |
| **Height [m]** | 1.69 | 0.06 | 1.65 | 0.09 | 1 | 0.21 |
| **Mass [kg]** | 71.5 | 17.9 | 72.3 | 9.91 | 1 | 0.89 |
| **BMI [kg/m$^2$]** | 25.1 | 5.7 | 26.8 | 3.34 | 1 | 0.39 |
| **Passive Ankle ROM [º]** | 87.9 | 7.8 | 96.6 | 5.92 | 1 | **0.006** |
| **Active Ankle ROM [º]** | 65.5 | 15.8 | 102.4 | 5.95 | 1 | **< 0.001** |
| **6MWT [m]** | 330 | 112 | 506 | 82.64 | 1 | **< 0.001** |

**Table 5.2** Unfatigued mobility, stability and symmetry measures assessed during the six-minute walk test for people with MS and healthy controls.

| | People with MS | | Healthy Controls | | ANOVA | Effect Size | ANCOVA | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | p-value | d | Group p | Group*Speed p |
| **Gait Mobility** | | | | | | | | |
| Speed [$m.s^{-1}$] | 0.97 | 0.35 | 1.50 | 0.28 | **<0.001** | -1.68 | - | - |
| Cadence [$steps.min^{-1}$] | 101.67 | 20.05 | 123.22 | 8.03 | **0.002** | -1.41 | 0.862 | **0.001** |
| Step length [cm] | 55.72 | 10.50 | 72.62 | 10.09 | **0.001** | -1.64 | 0.730 | 0.221 |
| **Gait Variability and Asymmetry** | | | | | | | | |
| Stride Time Variability [ms] | 52.27 | 47.59 | 22.27 | 8.47 | **0.043** | 0.88 | 0.839 | **0.013** |
| Step Time Asymmetry [%] | 9.01 | 9.21 | 2.65 | 1.63 | **0.028** | 0.96 | 0.516 | 0.105 |
| Pelvic Sway Variability [cm] | 2.24 | 1.06 | 1.25 | 0.34 | **0.006** | 1.26 | 0.337 | **0.008** |
| Head Sway Variability [cm] | 2.70 | 1.26 | 1.90 | 0.33 | **0.047** | 0.86 | 0.927 | **0.004** |
| **Gait Compensations*** | | | | | | | | |
| Pelvis Sway Area AP x ML [$cm^2$] | 22.45 | 11.01 | 10.7 | 3.7 | **0.002** | 1.43 | 0.140 | **0.006** |
| Pelvis Asymmetry VT [%] | 81.84 | 62.19 | 11.1 | 6.4 | **0.001** | 1.60 | **0.049** | 0.319 |
| Head Sway Area AP x ML [$cm^2$] | 19.24 | 11.14 | 10.0 | 3.0 | **0.011** | 1.14 | 0.677 | **0.011** |
| Head Asymmetry VT [%] | 75.86 | 51.00 | 8.6 | 5.5 | **<0.001** | 1.85 | **0.008** | 0.529 |
| **Gait Stability** (harmonic ratio)** | | | | | | | | |
| Pelvis - VT | 1.50 | 0.33 | 2.14 | 0.21 | **<0.001** | -2.31 | **0.006** | 0.0854 |
| Pelvis - AP | 1.43 | 0.19 | 1.91 | 0.19 | **<0.001** | -2.47 | **<0.001** | 0.0830 |
| Pelvis - ML | 1.00 | 0.13 | 1.44 | 0.22 | **<0.001** | -2.41 | **0.002** | 0.8822 |
| Head - VT | 1.53 | 0.26 | 2.36 | 0.28 | **<0.001** | -3.06 | **<0.001** | 0.2129 |
| Head - AP | 1.22 | 0.15 | 1.62 | 0.15 | **<0.001** | -2.65 | **<0.001** | 0.7949 |
| Head - ML | 1.05 | 0.20 | 1.33 | 0.15 | **0.001** | -1.61 | **0.042** | 0.1127 |

**ANCOVA –** Analysis of covariance adjusting for walking speed (group) and interactions with group vs speed

***Gait Compensations** = AP x ML = total sway area, VT = Ratio of asymmetry between left and right displacement in the vertical axis*

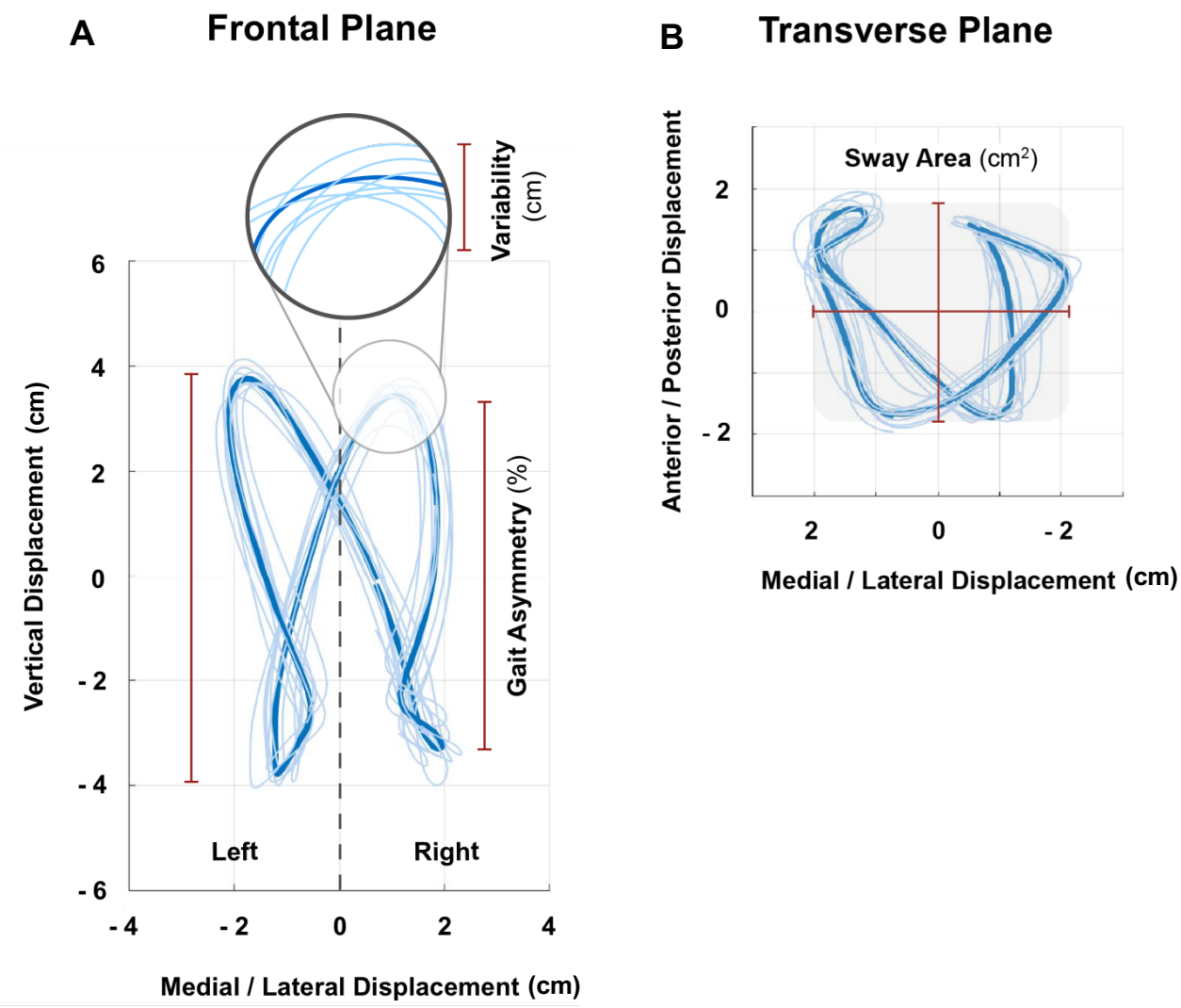
****Gait Stability** = Harmonic ratio VT - vertical axis, AP –anterior-posterior axis, ML – medial-lateral ax*

**Table 5.3** Correlations with gait compensations in PwMS

| | **GAIT COMPENSATIONS** | | | |
|---|---|---|---|---|
| | Pelvic Compensations | | Head Compensations | |
| | Sway Area [$cm^2$] | Asymmetry VT [%] | Sway Area [$cm^2$] | Asymmetry VT [%] |
| **Demographics** | | | | |
| Sex | 0.08 (0.80) | 0.03 (0.93) | -0.14 (0.67) | 0.25 (0.43) |
| Age | -0.08 (0.81) | 0.41 (0.19) | **0.57** (0.05)** | 0.12 (0.71) |
| Height | -0.10 (0.77) | -0.24 (0.44) | 0.11 (0.73) | 0.18 (0.57) |
| Mass | -0.18 (0.57) | 0.53 (0.08) | 0.20 (0.54) | 0.36 (0.25) |
| BMI | -0.03 (0.92) | **0.57** (0.05)** | 0.16 (0.62) | 0.31 (0.33) |
| **MS severity** | | | | |
| EDSS | 0.29 (0.36) | 0.52 (0.09) | **0.58** (0.05)** | 0.48 (0.12) |
| Years since diagnosis | 0.09 (0.77) | -0.14 (0.67) | 0.00 (0.99) | -0.02 (0.95) |
| **Ankle ROM** | | | | |
| Passive ROM | 0.25 (0.44) | -0.07 (0.83) | 0.36 (0.25) | -0.37 (0.23) |
| Active ROM | -0.39 (0.21) | **-0.71*** (0.01)** | -0.21 (0.50) | **-0.58** (0.05)** |
| **Gait Mobility** | | | | |
| Speed | **-0.76*** (0.01)** | -0.41 (0.19) | **-0.66** (0.02)** | -0.24 (0.44) |
| Cadence | **-0.76*** (0.01)** | -0.46 (0.13) | **-0.75*** (0.01)** | -0.24 (0.46) |
| Step length [cm] | **-0.69** (0.02)** | -0.39 (0.21) | -0.52 (0.09) | -0.34 (0.29) |
| **Gait variability and Asymmetry** | | | | |
| Stride Time Variability | **0.83*** (0.001)** | -0.07 (0.83) | **0.58** (0.05)** | -0.21 (0.51) |
| Step Time Asymmetry | 0.37 (0.24) | **0.72*** (0.01)** | 0.38 (0.22) | **0.57** (0.05)** |
| Pelvic Sway Variability | **0.78*** (0.005)** | 0.28 (0.38) | **0.76*** (0.01)** | 0.27 (0.40) |
| Head Sway Variability | **0.82*** (0.002)** | 0.30 (0.34) | **0.75*** (0.01)** | 0.22 (0.48) |
| **Gait Stability** | | | | |
| Pelvis HR VT | -0.44 (0.15) | -0.48 (0.12) | -0.51 (0.09) | -0.53 (0.08) |
| Pelvis HR AP | -0.35 (0.27) | **-0.76*** (0.01)** | **-0.62** (0.04)** | -0.47 (0.13) |
| Pelvis HR ML | 0.03 (0.92) | **-0.76*** (0.01)** | -0.51 (0.09) | **-0.69** (0.02)** |
| Head HR VT | -0.41 (0.18) | -0.29 (0.35) | **-0.61** (0.04)** | -0.29 (0.25) |
| Head HR AP | 0.15 (0.65) | -0.35 (0.27) | 0.08 (0.82) | -0.47 (0.13) |
| Head HR ML | -0.37 (0.24) | **-0.56** (0.05)** | -0.24 (0.44) | -0.41 (0.19) |

**Spearman's rank correlations – *r*-values** with **(*p*-values)** presented in brackets; significant correlations ($p \leq 0.05$) marked strong **(***)** moderate **(**)** or weak **(*)**. ***Gait Compensations –*** *Sway Area = AP x ML sway, Asymmetry VT = Ratio of asymmetry between left and right displacement in the vertical axis.* ***Gait Stability –*** *Harmonic ratio VT - vertical axis, AP –anterior-posterior axis, ML – medial-lateral axis.*

**Figure 5.1** Calculation of gait Parameters from a health age-matched participant




**(A) Front Plane -** Gait asymmetry was calculated using the difference in vertical displacement between left and right sides and expressed a percentage. Gait variability was calculated as the distance or spread of data away from the mean in centimetres.

**(B) Transverse Plane -** Sway area was the product of the AP and ML (95%) sway ranges in the transverse plane.

**Figure 5.2** Frontal Plane - Gait Asymmetry and Variance

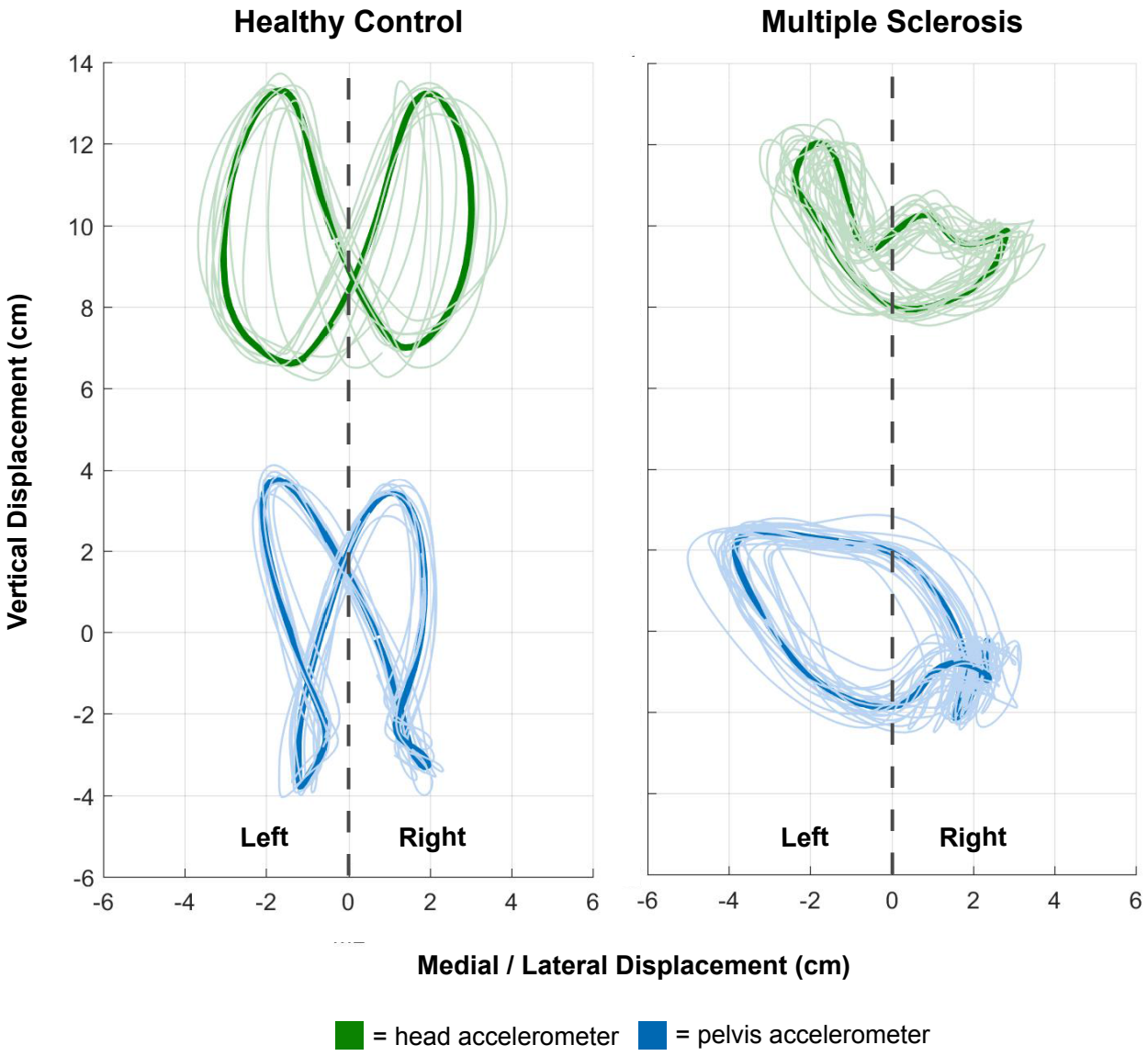



**Figure 5.2 -** Data from one lap of the 6-minute walk test by a person with MS (right panel) and their healthy age matched control are presented (left panel). The affected limb is the left leg for the PwMS. For this participant with MS, during the swing phase the left leg (affected limb) large compensatory movements at the pelvis (blue line) were observed that enabled greater toe clearance. During the swing phase of the left leg (affected limb) both the head (green line) and pelvis (blue line) moved to the right to counter balance the participant's center of mass over the stance leg.

**Figure 5.3** Group by Speed Interactions – The walking speed vs control of sway area trade off.

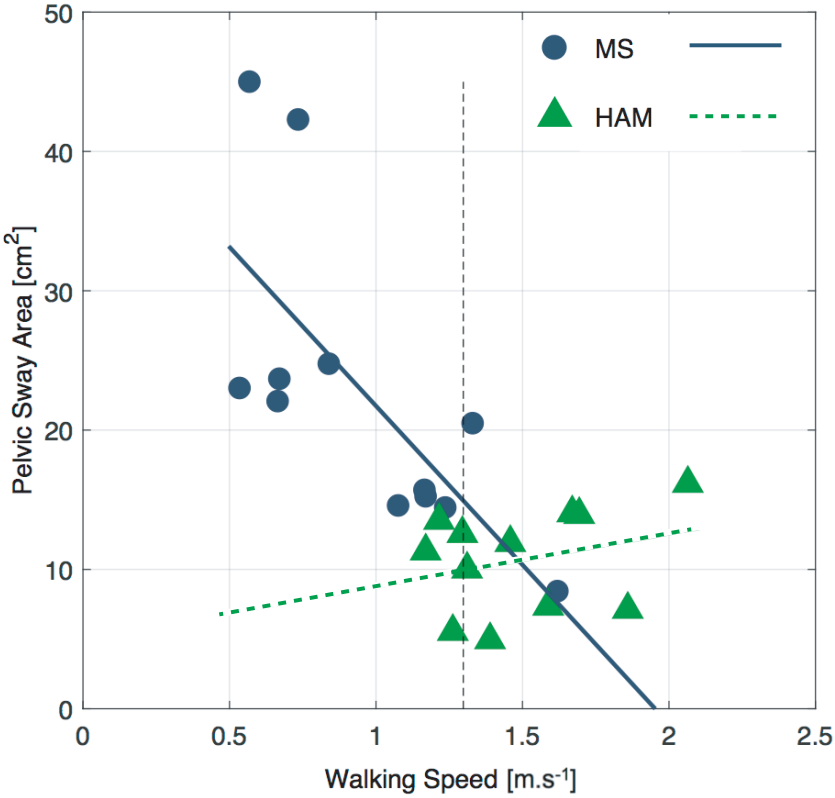



**Figure 5.3:** MS (circles) – people with multiple sclerosis. HAM (triangles) – health age matched controls. For pelvic sway area, a significant interaction was observed with walking speed (ANCOVA p-value 0.006). For people with MS, a strong negative correlation between walking speed at pelvic sway area (Spearman's *r*=-0.76, Table 3) was observed. Conversely, for the healthy controls a weak positive correlation (*r*=0.30) was observed. The existence of significant interactions indicates that the relationship between gait quality and walking speed may be different for people with and without MS.

**Appendix 5.1** Inter-lap reliability of gait assessed between the first and second laps of the six-minute walk test for people with MS and healthy controls.

| | ICC(2,1) | ICC 95% CI Lower bound | ICC 95% CI Upper bound |
|---|---|---|---|
| **Gait Mobility** | | | |
| Speed [$m.s^{-1}$] | **0.91*** | 0.81 | 0.96 |
| Cadence [$steps.min^{-1}$] | **0.98*** | 0.94 | 0.99 |
| Step length [cm] | 0.82 | 0.63 | 0.92 |
| **Gait Variability and Asymmetry** | | | |
| Stride Time Variability [ms] | 0.70 | 0.41 | 0.86 |
| Step Time Asymmetry [%] | 0.84 | 0.67 | 0.93 |
| Pelvic Sway Variability [cm] | 0.76 | 0.51 | 0.89 |
| Head Sway Variability [cm] | 0.79 | 0.56 | 0.90 |
| Pelvis Sway Area AP x ML [$cm^2$] | 0.87 | 0.72 | 0.94 |
| Pelvis Asymmetry VT [%] | **0.91*** | 0.80 | 0.96 |
| Head Sway Area AP x ML [$cm^2$] | 0.88 | 0.75 | 0.95 |
| Head Asymmetry VT [%] | **0.95*** | 0.89 | 0.98 |
| **Gait Stability** (harmonic ratio)** | | | |
| Pelvis - VT | **0.94*** | 0.87 | 0.97 |
| Pelvis - AP | 0.86 | 0.71 | 0.94 |
| Pelvis - ML | **0.92*** | 0.83 | 0.96 |
| Head - VT | **0.94*** | 0.86 | 0.97 |
| Head - AP | 0.85 | 0.69 | 0.93 |
| Head - ML | **0.91*** | 0.80 | 0.96 |

**ICC(2,1) –** Intraclass correlation coefficient for criterion referenced reliability. **ICC 95% CI** – associated lower and upper bounds for the ICC(2,1) 95% confidence interval. Values greater than 0.70 indicate acceptable reliability for group research, values greater than 0.90 marked **(*)** indicate excellent agreement between laps.

**Appendix 5.2** Analysis of fatigue during the six-minute walk test for people with MS and healthy controls

| | People with MS First Lap | | People with MS Last Lap | | Healthy Controls First Lap | | Healthy Controls Last Lap | | Two-way ANOVA p-values | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Group | Lap | Group-by-Lap |
| **Gait Mobility** | | | | | | | | | | | |
| Speed [$m.s^{-1}$] | 0.97 | 0.35 | 0.87 | 0.32 | 1.50 | 0.28 | 1.42 | 0.29 | **<0.01*** | **0.01*** | 0.80 |
| Cadence [$steps.min^{-1}$] | 101.82 | 19.91 | 96.37 | 23.39 | 123.30 | 8.02 | 121.94 | 8.04 | **<0.01*** | **0.02*** | 0.12 |
| Step length [cm] | 55.63 | 10.56 | 52.89 | 9.56 | 72.57 | 10.12 | 69.27 | 10.94 | **<0.01*** | 0.06 | 0.86 |
| **Gait Variability and Asymmetry** | | | | | | | | | | | |
| Stride Time Variability [ms] | 51.00 | 47.06 | 56.09 | 44.79 | 21.56 | 8.69 | 16.44 | 8.62 | **<0.01*** | 1.00 | 0.41 |
| Step Time Asymmetry [%] | 8.50 | 9.13 | 10.97 | 9.56 | 2.71 | 1.75 | 1.65 | 1.32 | **<0.01*** | 0.57 | 0.15 |
| Pelvic Sway Variability [cm] | 0.72 | 0.28 | 0.89 | 0.70 | 0.45 | 0.11 | 0.44 | 0.14 | **<0.01*** | 0.31 | 0.30 |
| Head Sway Variability [cm] | 0.90 | 0.37 | 1.11 | 0.65 | 0.75 | 0.16 | 0.65 | 0.18 | **0.01*** | 0.43 | **0.03*** |
| **Gait Compensations*** | | | | | | | | | | | |
| Pelvis Sway Area AP x ML [$cm^2$] | 27.17 | 14.59 | 35.01 | 32.32 | 11.68 | 4.09 | 11.70 | 3.19 | **<0.01*** | 0.28 | 0.28 |
| Pelvis Asymmetry VT [%] | 81.85 | 61.67 | 83.92 | 47.70 | 11.42 | 7.18 | 9.99 | 6.89 | **<0.01*** | 0.96 | 0.79 |
| Head Sway Area AP x ML [$cm^2$] | 29.67 | 18.89 | 46.62 | 52.17 | 12.68 | 3.95 | 12.21 | 4.73 | **<0.01*** | 0.18 | 0.14 |
| Head Asymmetry VT [%] | 75.30 | 50.48 | 79.69 | 47.14 | 8.95 | 5.52 | 4.92 | 4.61 | **<0.01*** | 0.98 | 0.48 |
| **Gait Stability** (harmonic ratio)** | | | | | | | | | | | |
| Pelvis - VT | 1.51 | 0.33 | 1.42 | 0.41 | 2.13 | 0.20 | 2.20 | 0.17 | **<0.01*** | 0.93 | 0.11 |
| Pelvis - AP | 1.43 | 0.19 | 1.40 | 0.34 | 1.90 | 0.18 | 1.95 | 0.26 | **<0.01*** | 0.84 | 0.53 |
| Pelvis - ML | 1.00 | 0.13 | 0.98 | 0.16 | 1.43 | 0.21 | 1.49 | 0.25 | **<0.01*** | 0.42 | 0.13 |
| Head - VT | 1.54 | 0.27 | 1.46 | 0.32 | 2.36 | 0.27 | 2.39 | 0.28 | **<0.01*** | 0.77 | 0.41 |
| Head - AP | 1.22 | 0.15 | 1.27 | 0.17 | 1.61 | 0.17 | 1.59 | 0.19 | **<0.01*** | 0.74 | 0.21 |
| Head - ML | 1.05 | 0.20 | 0.99 | 0.14 | 1.34 | 0.15 | 1.44 | 0.26 | **<0.01*** | 0.66 | 0.06 |

**Two-way ANOVA –** Analysis of variance with repeated measures in one factor; significance ($p \leq 0.05$) marked **(*)**; Group – PwMS vs Health Controls; Lap – First vs Last Lap (effect of fatigue); Group-by-Lap – tests if fatigue effect was different for PwMS vs Health Controls (interaction). ***Gait Compensations*** *= AP x ML = total sway area, VT = Ratio of asymmetry between left and right displacement in the vertical axis.* ***Gait Stability =*** *Harmonic ratio VT - vertical axis, AP –anterior-posterior axis, ML – medial-lateral axis*

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# **CHAPTER 6 -** THE VALIDITY AND RELIABLITY OF PASSIVE ANKLE DORSIFLEXION RANGE OF MOTION TECHNIQUES IN PEOPLE WITH MULTIPLE SCLEROSIS

## 6.1 PREFACE

The aim of this study was to evaluate the validity and reliability of techniques used to assess passive ankle dorsiflexion ROM in people with Multiple Sclerosis. Despite a large body of research surrounding the measurement of ankle ROM, measurement errors in testing can compromise accuracy and reduce the sensitivity of testing. This is problematic when exploring the effectiveness of an intervention to improve ankle ROM when small changes potentially remain undetected. We have developed a device for assessing standardised (torque-controlled) and reproducible measurements of ankle dorsiflexion. Accurate measurements of ankle ROM are important to identify the presence of an impairment to better guide treatment modalities in the clinical setting.

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The work presented in this chapter has been prepared for submission;

***Psarakis, M.,*** *Greene, D., Hoang, P., Lord, S., Herbert, R., & Gandevia, S. (2019). The validity and reliability of passive ankle dorsiflexion range of motion techniques in people with Multiple Sclerosis.*

## 6.2 ABSTRACT

**Background:** Over twenty techniques for measuring ankle range of motion (ROM) have been cited in the literature with many performed routinely in clinical practice. Unfortunately, measurement error and poor test-retest reliability compromise the accuracy of outcomes, potentially leading to inadequate diagnosis and subsequent treatment in the clinical setting. The aim of this study was to test the validity and reliability of a novel device (Flexometer) to measure ankle ROM compared to a common clinical test (Weight bearing lunge test - WBLT) in people with and without Multiple Sclerosis (MS).

**Methods:** Fifty-six participants were recruited to test the concurrent validity between the methods. A sub-group of thirty-three participants participated in a reliability measure 7 days after their first test. Each test was performed on both ankles (left and right) in 2 positions (knee-flexed and knee-extended) and were performed in random order. Concurrent validity was assessed using a Pearson correlation and Bland Altman test. Intra-rater reliability was assessed using Intraclass correlation coefficient (ICC), standard error of measurement (SEM) and minimal detectable change (MDC).

**Results:** Peason's correlations (r values) comparing the Flexometer to the WBLT indicated a (positive) high relationship with the knee flexed methods (Right: $r = 0.76$, Left: $r = 0.80$, $p = <0.001$), and a (positive) moderate relationship with the knee extended methods (Right: $r = 0.58$, Left: $r = 0.52$, $p = <0.001$). The ICC's for intra-rater reliability for both techniques ranged from good (0.86) to excellent (>0.90) for both techniques.

**Conclusion:** This study confirms the Flexometer as a reliable method for assessing ankle ROM in people with MS. Additionally, the WBLT is a good alternative in the clinical setting however, care must be taken with the suitability of this test and interpretation of results when using the knee extended version. While both tests are associated, results are not interchangeable.

***Keywords:*** Weight bearing lunge test, Ankle dorsiflexion, Lidcombe template, Passive range of motion

## 6.3 INTRODUCTION

Contracture is defined as a loss of passive joint range of motion (ROM). Contractures are a common complication in neurological conditions such as stroke [1], cerebral palsy [2], traumatic brain injury [3] and multiple sclerosis [4]. Ankle joint contractures are common in people with Multiple Sclerosis (MS) causing a significant reduction in dorsiflexion ROM [5]. Inadequate dorsiflexion ROM can prevent movement of the shank over the foot during the stance phase of gait [6], reduce foot clearance during the swing phase of gait [7] and increase the risk of trips and associated falls [8]. Therefore, adequate dorsiflexion ROM is essential for normal ambulation.

Ankle ROM measurements are often used in the diagnosis of ankle-related impairments such as contractures [9]. Over twenty techniques for measuring ankle ROM [10] have been cited in the literature with many performed routinely in clinical practice. Goniometry-based techniques are routinely performed in clinical practice however, measurement error and poor test-retest reliability [11] occurs. The weight bearing lunge test (WBLT) has higher test-retest reliability [12] however, the weight-bearing nature of the test is often too difficult or unsafe to perform with neurological patients. Poor measurements of ankle ROM make it difficult to identify if an impairment is present and could lead to inadequate treatment in a clinical setting.

As muscles and tendons respond differently depending on the amount of torque applied, it is argued that measurements of joint ROM should be conducted using standardised torques [10]. The Lidcombe Template (a torque-controlled method) has reported high reliability (ICC – 0.97) in both healthy unimpaired [9] and neurologically impaired patients [13]. Despite excellent reliability this method is time consuming as it requires post processing of photographs to obtain ankle angles and requires a 2-person operation. In an effort to further develop a torque-controlled method, an updated version of the Lidcombe Template was designed (Flexometer) to measure passive ankle flexibility. The ‘Flexometer’ is equipped with two digital inclinometers and a push-type load cell that can be operated by a single clinician. The device provides instantaneous resultant ankle angles allowing for faster data acquisition however, given the novel nature of the device, reliability and validity remains unknown.

Currently, there is no standardised method to assess ankle ROM making it difficult to compare and contrast results from the literature. The primary aim of this study was to test the validity and reliability of the Flexometer in comparison to the WBLT in people with and without MS.

## 6.4 METHODS

### 6.4.1 PARTICIPANTS

In total, 60 participants took part in the validation component of the study (n = 60). Twenty participants with MS (4 males and 16 females), twenty healthy age- and gender-matched controls (4 males and 16 females) and twenty healthy young adults, defined as being between the ages of 18 – 34 (10 males and 10 females). MS participants were recruited from an out-patient MS rehabilitation setting (Sydney, Australia). Inclusion criteria for eligible participants in the MS group included a confirmed diagnosis of MS by a neurologist. Participants were excluded if there was a presence of co-existent conditions, including pain secondary to the diagnosis of MS that would limit ankle range of motion (i.e. ankle surgery or fractures). Control participants were excluded if they had any history of surgical interventions effecting the ankle or pain secondary to an ankle injury. The study was approved by the Human Studies Ethics Committee at the Australian Catholic University (2018-139H). Informed consent was obtained from all participants prior to participation.

### 6.4.2 OVERVIEW

Day 1 testing data (n = 60) were used to assess the concurrent validity between the WBLT and the Flexometer. The relationship (Pearson's Correlation) and agreement (Bland Atman) between the 2 methods was used to determine concurrent validity. However, the WBLT was not suitable for all patients with MS (4/20), therefore their data was excluded from validity analysis (n = 56, 16 MS, 20 healthy age- and gender-matched controls, 20 healthy young adults).

A sub-group (n = 33, 11 MS, 11 healthy age- and gender-matched controls, 11 healthy young adults) participated in a reliability measure 7 days after their first test (i.e. Day 1 vs Day 2). Day 1 vs Day 2 testing data were used to assess the intra-rater reliability of the 2 methods. Reliability measures were taken 7 days apart to mimic clinical practice (i.e. weekly booking with a physiotherapist or exercise physiologist) and minimise assessor re-call of previous scores. Testing was performed on both ankles

(left and right) in 2 positions (knee-flexed and knee-extended). Ankle dorsiflexion, when measured in a position of knee extension, is an accepted measure of gastrocnemius length [14]. In comparison, ankle dorsiflexion measured in a position of knee flexion minimises the influence of the gastrocnemius and can reflect factors influenced by soleus muscle length and compliance of the talocrural (ankle) joint complex. All tests were performed 3 times and an average was used in subsequent analysis as previously suggested [13]. All participants were tested following a warm up that included continuous walking along a walking track (5 x 20m laps). Prior to data acquisition, all participants (ankles) were pre-conditioned (6 stretch cycles / repetitions). All tests were performed in a randomised order. In conjunction with ROM testing, muscle tone (spasticity) was assessed using a Modified Ashworth Scale [15].

### 6.4.3 INSTRUMENTATION & PROCEDURES

Flexometer

The 'Flexometer' is a revised version of the original Lidcombe Template [9] and provides instantaneous resultant ankle angles. The battery-operated device contains a microcontroller (Arduino-Uno) that powers two digital inclinometers (Inertial Measurement Unit - LSM6DS33) and a push-type load cell (micro parallel beam type load cell – TAL220). One inclinometer is contained within the base plate whilst the second is contained within a small case that is positioned on the shin at a distance of 15cm distal to the tibial tuberosity (providing shank angle relative to the foot). Small LED lights within the shank case allow for the visualisation of pre-determined torque cut offs. The base plate contains 2 velcro straps that cross over the dorsal surface of the foot and secure it in place without impeding ankle joint dorsiflexion. A laser is light located on the top/centre of the base plate to allow for consistent measures. Participants were placed in a long sitting position using a chair and foot stool and a foam roll (10cm diameter) was placed under the knee to flex at 90 degrees (Figure 1B). For the knee extended version, the roller was removed, and the stool moved further out to allow for full knee extension. To minimise effects of thixotrophy on muscle, the ankle was moved through 6 cycles before data was collected. The tester pushed on the load cell until a pre-determined torque cut off was reached and ROM was recorded. Torque cut off was set at 12Nm as previously outlined [1, 3].

Weight Bearing Lunge Test

The WBLT has previously been shown the have excellent reliability (ICC = 0.97 – 0.98) for measuring ankle dorsiflexion range [12]. An inclinometer (Rippstein - Plurimeter) was used during the lunge test and shank angle was measured for both testing variations (knee-flexed and knee-extended). A vertically taped line was placed perpendicular to the wall to help control subtalar joint movement as previously suggested within the literature [12, 16]. In addition, a taped line on the floor was used for participants to position their 2nd toe and centre of their heel to minimize subtalar pronation. Participants were instructed to place both hands on the wall in front of them and lunge forward to touch the wall with their knee (on the tape) while keeping the heel of their foot in contact with the ground. For the knee extended position, participants were instructed to first extend their knee fully and then lean forward while keeping their heel in contact with the ground (Figure 6.1A). The inclinometer was placed on the anterior border of the tibia (15cm from the tibial tuberosity) for data collection. Participants performed 6 pre conditioning 'lunge attempts' to find the maximum amount of ankle range whilst maintain full heel contact. To compare data, scores from the WBLT were added by 90 degrees to use the same reference system as the Flexometer. A larger number was indicative of a greater amount of dorsiflexion ROM. MS patients who required a 4-point walker were excluded from all WBLTs.

### 6.4.4 STATISTICAL ANALYSIS

A statistician blinded to assessor and measurement method undertook the analyses and confirmed normal distribution of data. To assess validity, a Pearson's correlation was calculated to assess the relationship between the WBLT and the Flexometer using day 1 data. Interpretation of Pearson correlation (r values) were as follow; < 0.5 low; 0.5 - 0.7 moderate; 0.7 - 0.9 high; > 0.9 very high [17]. The level of significance was set at $p < 0.05$ for correlation tests. An additional analysis using a Bland Altman test [18] was used to assess the degree of agreement between the methods. To assess reliability, data was tested for normal distribution and intraclass correlation coefficient (ICC) was performed on 33 samples at two different time points by a single rater. A two-way mixed-effects model based on average rating ($k = 3$) and absolute agreement was used to assess intra-rater reliability. Mean estimations and 95% confidence intervals were reported using SPSS statistical package version 24 (SPSS Inc, Chicago, IL). Interpretation of ICCs were as follows; <0.5 poor; between 0.5 and 0.75

moderate; between 0.75 and 0.9 good; and >0.9 excellent [19]. Standard error of measurement (SEM) and minimal detectable change (MDC) were calculated using methods described by Weir et al. [20]. SEM was calculated using the following equation; √mean square error taken from a 2-way repeated measures ANOVA. MDC was calculated using the following equation; SEM x 1.96 x √2. Smaller SEM and MDC indicate better reliability and sensitivity of the measures respectively.

## 6.5 RESULTS

There were no significant differences in descriptive characteristics between the MS and age-gender-matched controls however, there were significant differences when compared to young adults (table 6.1). MS patients had on average 15.2 years (SD±10.9) since their diagnosis. The average EDSS was 5.5 out of 10 (SD±1.6) representing a severe level of disability. On average muscle tone in MS patients was 1.5 out of 4 (SD±1.1) representing a slight to marked increase in tone according to the Modified Ashworth Scale [15].

Validity

Four out of twenty MS subjects did not partake in the WBLT as it was deemed unsafe and not feasible (i.e. participants required a 4-point walker to ambulate). Therefore, validity testing (day 1 data) comprised 56 participants. Peason's correlations (r values) comparing the Flexometer to the WBLT indicated a (positive) high relationship with the knee flexed methods (Right: r = 0.76, Left: r = 0.80, p = <0.001), and a (positive) moderate relationship with the knee extended methods (Right: r = 0.58, Left: r = 0.52, p = <0.001) (Figure 6.2). The degree of agreement between the methods was expressed in degrees. For the left knee flexion (Figure 6.3A), bias was 16.7 and limits of agreement were 5.1 (lower) and 28.3 (upper). For the right knee flexion (Figure 6.3B), bias was 16.2 and limits of agreement were 5.3 (lower) and 26.9 (upper). For the left knee extended (Figure 6.3C) bias was 18.5 and limits of agreement were 2.9 (lower) and 34.2 (upper). For the right knee extended (Figure 6.3D) bias was 21.3 and limits of agreement were 9.6 (lower) and 33.0 (upper).

Reliability

The ICC's for intra-rater reliability (Table 6.2) for both techniques ranged from good (0.86) to excellent (>0.90). Mean ROM data is reported for MS subjects, healthy controls and young adults for day 1 and day 2 (Supplementary Table 6.3).

## 6.6 DISCUSSION

The primary aim of this study was to test the validity and reliability of two methods (Flexometer and Weight Bearing Lunge) to assess ankle joint ROM in people with and without MS. Concurrent validity outcomes demonstrated that both methods were associated (moderate – high relationship) however, are not in perfect agreement and therefore cannot be used interchangeably. Our results demonstrate that the Flexometer has excellent test-re-test reliability for measuring ankle ROM with both the knee flexed and extended. Additionally, the WBLT (knee flexed) demonstrated excellent reliability however, results were less consistent with the knee extended.

The Flexometer (a torque-controlled method) has several advantages over previously described methods within the literature [12, 21, 22]. Firstly, the Flexometer provides instantaneous resultant ankle angles by the microcontroller via a connection to a computer. This allows for the tester to record consecutive measurements without interruption or post processing analysis. Additionally, designs requiring a 'pull type' load cell (or strain gauge) requires a 2-person operation making the method less efficient in the clinical setting [9, 22, 23]. Secondly, the Flexometer allows the talocrural joint (ankle joint) to move freely about its oblique axis of rotation. As the lateral malleolus sits both inferior and posterior to the medial malleolus, talocrural joint movement is combined with slight abduction and eversion [24], making the axis of rotation oblique to the shin (Figure 6.4). Methods using a hinge mechanism [12, 21, 22] that pivot the ankle perpendicular to the shank do not allow the joint to move freely about its natural (oblique) axis of rotation. The Flexometer does not restrict this movement and may be a better representation of true talocrural joint motion rather than forcing it to move perpendicular to the shank. Finally, while it was not explored in this study, there are additional advantages of using the Flexometer to collect ROM data. For example, in the current study, ROM output was terminated at a threshold of 12Nm. Data acquisition using the load cell and microcontroller enables the user to customize the output and collect multiple ROM measures at different torques throughout a single test. Collecting continuous torque-angle data may provide additional information about ankle compliance (extensibility) that is not available using a single ROM measure.

While this is the first study to assess the reliability of a WBLT in people with Multiple Sclerosis, building on previous research, our results demonstrate that the WBLT has good clinical utility. Results from our study are consistent with previous research and demonstrate higher ICC's for the knee flexed (WBLT) compared to the knee extended (WBLT) [12, 16]. Testing ankle ROM with the knees flexed versus knees extended can potentially help to differentiate what structures are involved in the impairment. For example, if there is tension in the gastrocnemius, ROM with the knee extended may be limited. In contrast, if there is tension in the soleus, ROM with the knee flexed may be limited. Therefore, it is important for both tests to be reliable as they can help guide treatment modality. Unfortunately, the knee extended version demonstrated larger measurement error and higher MDC's (~ 2 - 3 degrees) possibly due to difficulty in standardising the knee in extension while participants performed the test. While this does raise some concern regarding pre-post testing comparisons, the main limitation associated with the WBLT was that is not applicable for those who are more disabled. Within our sample, 20% of people with MS were excluded from this test as they were dependant on a walker due to unstable gait and poor balance. While overall the WBLT is a good alternative in the clinical setting, care must be taken when deciding both the suitability of this test for patients who are unstable and interpretation of results when using the knee extended version.

There is a moderate to high relationship between the Flexometer and WBLT (figure 6.2). However, the two methods are not in perfect agreement and due to the spread of data (figure 6.3) the tests are not interchangeable. The WBLT consistently produced higher ROM scores when compared to the Flexometer. Due to the nature of the WBLT, patients use their body weight to lunge forward and force the ankle into dorsiflexion. The Flexometer is a non-weight bearing test with only 12Nm of force applied across the joint. This considerable difference in torques (weight bearing vs non weight bearing) applied to the joint may explain why WBLT scores were higher than Flexometer scores.

We acknowledge certain study limitations. Firstly, our re-test reliability sample size may be considered small (n = 11 per group) compared to those recommended (n = 50) in previous research [25]. Fortunately, as sample size is based on the precision of an outcome [25], our results (post-hoc analysis) indicate narrow confidence intervals and measurement errors that are less than the smallest worthwhile effect. Based on this, results indicate a sufficient sample size was used as only 8 participants (per

group) would have sufficed [25]. Secondly, this study highlighted the reliability of a novel device (Flexometer) via intra-rater reliability measures. Therefore, care must be taken when generalising the results of our study given ROM (reliability) can be assessor dependent. A single assessor (practitioner with over 10 years' experience) conducted all ROM testing therefore, the reliability of the Flexometer by a novice/student practitioner remains unknown. Thirdly, it is common in clinical practice that the same practitioner would test then retest a patient following an intervention. As it was not feasible to blind the assessor on day 2 (retest measures), we minimised the possibility of assessor recall (day 1 results influencing day 2 results) by separating the testing by 7 days. This time period has previously been considered sufficient in reducing bias associated with assessor re-call [23]. Additionally, given the number of trials collected over a short period of time (~ 3 months – 1,440 trials) it would be difficult for the assessor to re-call results from previous testing and therefore we do not believe the lack of blinding influenced findings. Finally, recent research has suggested passive ROM can be significantly influenced by small amounts of involuntary muscle activity [26]. While our methods did not measure muscle activity (via electromyography) during passive testing, we do not believe this influenced the reliability of the device but may raise concerns regarding the validity of current passive ROM methods.

Despite the clinical significance of assessing ankle ROM, there is a lack of evidence to support the use of various methods in assessing ankle ROM in neurological populations. Future research should focus on standardising testing procedures (i.e. using torque-controlled methods) to make comparing results feasible. Additionally, methods capable of collecting continuous torque-angle data may be of benefit when examining ankle compliance (passive torque-angle curves) as contracture is often associated with a stiffening of the joint that single ROM measures may overlook.

## 6.7 CONCULSION

This study highlights the Flexometer is a reliable and valid method for assessing ankle ROM in people with MS. Additionally, the WBLT is a good alternative in the clinical setting however, care must be taken with the suitability of this test and interpretation of results when using the knee extended version. While both tests are associated, results are not interchangeable.

**Acknowledgements**

We would like to thank Dave Menardo from Neuroscience Research Australia (NEURA) for his assistance in the manufacturing and development of the Flexometer. His ingenuity and attention to detail resulted in a high-quality testing device.

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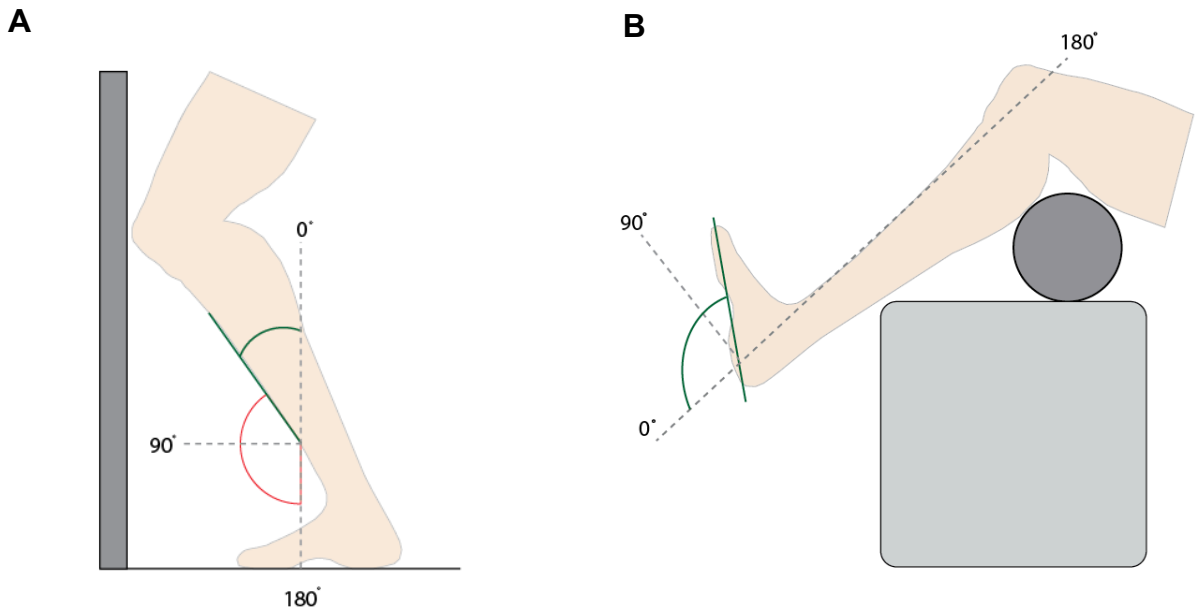
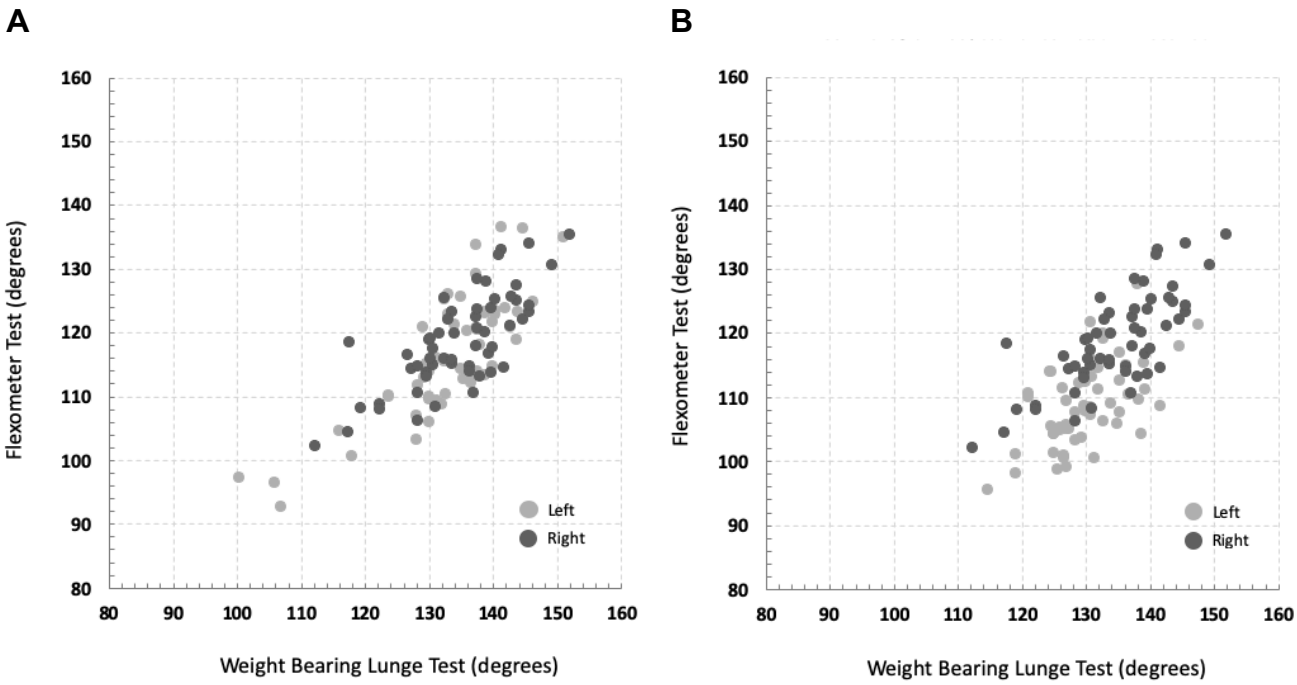
**Figure 6.1** Ankle Angle Measurement Setup



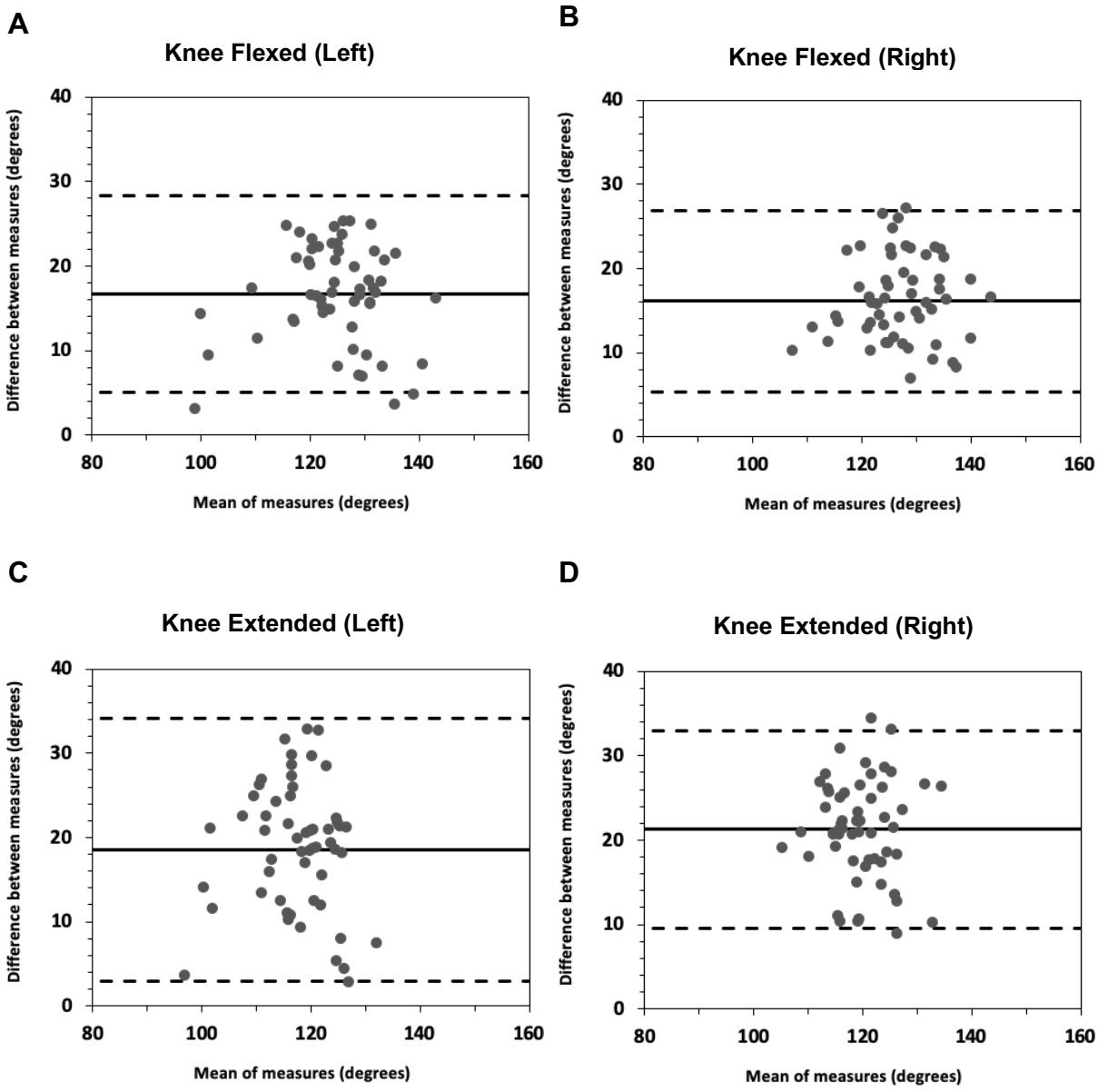

**A** - Weight Bearing lunge test shank angle (θ) measured (green) however resultant angle (red) was calculate; 90 + θ to compare data against Flexometer device. Greater the number = greater ROM
**B** - Long sitting position to test Flexometer with foam roller support under the knee.

**Figure 6.2** Pearson's correlation between weight bearing lunge and Flexometer (n = 56)



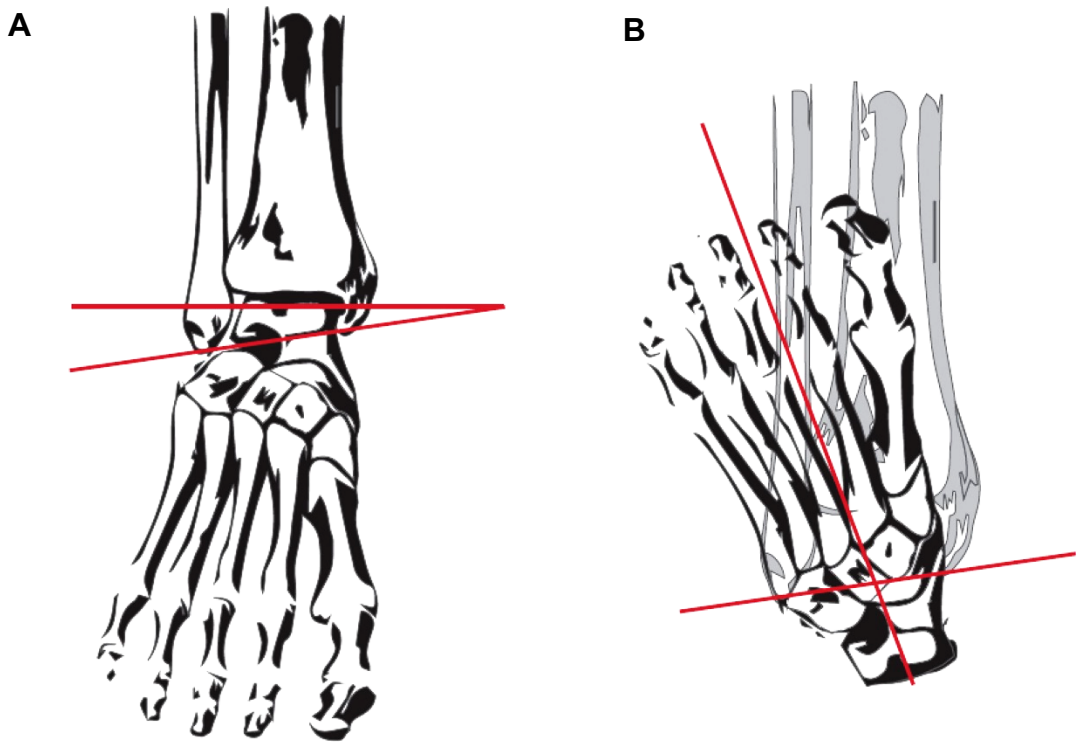

**A -** Knee Flexed Correlation; Right = 0.76, Left = 0.80 (high relationship – p = < 0.001)
**B -** Knee Extended Correlation; Right = 0.58, Left = 0.52 (moderate relationship – p = < 0.001)

**Figure 6.3** Bland-Altman plots for agreement between the weight bearing lunge and Flexometer (n = 56)




**A -** Knee flexed left = bias - 16.7, limits of agreement (lower - 5.1; upper - 28.3)
**B -** Knee flexed right = bias -16.1, limits of agreement (lower - 5.3; upper - 26.9)
**C -** Knee extended left = bias - 18.5, limits of agreement (lower - 2.9; upper - 34.2)
**D -** Knee extended right = bias - 21.3, limits of agreement (lower - 9.6; upper - 33.0)

**Figure 6.4** Ankle Joint Complex – Axis of Rotation




**A -** Oblique axis of rotation – lateral malleolus is inferior and posterior to the medial malleolus
**B -** Dorsiflexion with accompanied abduction and eversion

**Table 6.1** Participant characteristics

| | **1. Multiple Sclerosis** (n = 20) | | **2. Healthy Controls** (n = 20) | | **3. Young Adults** (n = 20) | | **ANOVA** | **Post-hoc t-tests** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | p-value | 1vs2 | 1vs3 | 2vs3 |
| **Age** (years) | 51.8 | 11.3 | 52.6 | 10.8 | 26.6 | 3.1 | **< 0.001** | 0.832 | **< 0.001** | **< 0.001** |
| **Height** (m) | 1.67 | 0.09 | 1.64 | 0.09 | 1.71 | 0.08 | **0.035** | 0.273 | 0.133 | **0.011** |
| **Mass** (kg) | 70.1 | 21.4 | 71.1 | 13.0 | 70.2 | 14.8 | 0.979 | 0.856 | 0.978 | 0.846 |
| **BMI** (kg/m2) | 25.2 | 7.2 | 26.6 | 4.8 | 24 | 3.3 | 0.267 | 0.472 | 0.442 | **0.039** |

**Table 6.2** Intra-tester reliability of dorsiflexion measurements

| Test | | | LEFT | | | RIGHT | | |
|---|---|---|---|---|---|---|---|---|
| | | | ICC (95%CI) | SEM (°) | MDC (°) | ICC (95%CI) | SEM (°) | MDC (°) |
| FLEXO* | Knee Flexed | Multiple Sclerosis | **0.99** (0.94 - 1.00) | 2.06 | 5.72 | **0.98** (0.92 - 0.99) | 2.05 | 5.68 |
| | | Healthy Control | **0.98** (0.93 - 1.00) | 1.49 | 4.13 | **0.97** (0.88 - 0.99) | 1.76 | 4.87 |
| | | Young Adult | **0.99** (0.94 - 1.00) | 1.06 | 2.95 | **0.99** (0.97 - 1.00) | 0.94 | 2.61 |
| WBLT | | Multiple Sclerosis | **0.98** (0.94 - 1.00) | 2.33 | 6.46 | **0.98** (0.93 - 1.00) | 1.62 | 4.50 |
| | | Healthy Control | **0.90** (0.65 - 0.98) | 1.63 | 4.52 | **0.98** (0.86 - 0.99) | 1.18 | 3.27 |
| | | Young Adult | **0.98** (0.94 - 1.00) | 1.28 | 3.56 | **1.00** (0.99 - 1.00) | 0.71 | 1.97 |
| | | | | | | | | |
| FLEXO* | Knee Extended | Multiple Sclerosis | **0.99** (0.96 - 1.00) | 1.48 | 4.12 | **0.94** (0.78 - 0.98) | 2.37 | 6.57 |
| | | Healthy Control | **0.98** (0.92 - 0.99) | 1.60 | 4.42 | **0.98** (0.93 - 1.00) | 1.35 | 3.74 |
| | | Young Adult | **0.96** (0.86 - 0.99) | 1.36 | 3.78 | **0.96** (0.83 - 0.99) | 1.30 | 3.60 |
| WBLT | | Multiple Sclerosis | **0.94** (0.78 - 0.98) | 3.72 | 10.32 | **0.96** (0.87 - 0.99) | 2.06 | 5.72 |
| | | Healthy Control | **0.95** (0.80 - 0.99) | 1.93 | 5.34 | **0.88** (0.58 - 0.97) | 2.95 | 8.17 |
| | | Young Adult | **0.86** (0.49 - 0.96) | 2.67 | 7.39 | **0.95** (0.82 - 0.99) | 1.60 | 4.42 |

**ICC** = Intraclass correlation coefficient, **SEM** = standard error of measurement, **MDC** = minimal detectable change, **FLEXO*** = Flexometer, **WBLT** = Weight bearing lunge test

**Supplementary Table 6.3** Group means and standard deviations for day 1 and day 2 testing

| | | | FLEXOMETER | | | | WEIGHT BEARING LUNGE | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Left | | Right | | Left | | Right | |
| | | | Day 1 | Day 2 | Day 1 | Day 2 | Day 1 | Day 2 | Day 1 | Day 2 |
| Knee Flexed | Multiple Sclerosis | Mean | 110.7 | 110.7 | 116.2 | 116.1 | 124.1 | 125.3 | 128.6 | 129.8 |
| | | SD | 11.5 | 11.3 | 9.3 | 9.9 | 11.8 | 13.6 | 9.4 | 8.7 |
| | Healthy Control | Mean | 121.7 | 121.8 | 122.6 | 122.0 | 136.7 | 136.4 | 138.6 | 137.4 |
| | | SD | 7.3 | 7.2 | 6.3 | 7.1 | 3.7 | 3.8 | 6.8 | 6.4 |
| | Young Adult | Mean | 120.5 | 119.6 | 121.5 | 121.2 | 138.2 | 138.1 | 137.3 | 137.1 |
| | | SD | 7.3 | 6.5 | 7.0 | 6.6 | 7.1 | 6.8 | 8.1 | 7.9 |
| Knee Extended | Multiple Sclerosis | Mean | 103.4 | 104.2 | 106.2 | 106.4 | 119.8 | 119.5 | 127.6 | 127.4 |
| | | SD | 9.8 | 10.0 | 7.5 | 6.3 | 10.4 | 10.8 | 7.5 | 7.4 |
| | Healthy Control | Mean | 113.8 | 114.1 | 112.2 | 111.8 | 129.1 | 129.4 | 133.5 | 132.1 |
| | | SD | 7.5 | 7.0 | 6.4 | 7.3 | 5.3 | 6.4 | 6.1 | 6.8 |
| | Young Adult | Mean | 111.4 | 110.5 | 110.5 | 110.6 | 129.7 | 129.2 | 130.5 | 130.0 |
| | | SD | 5.6 | 4.8 | 4.2 | 4.3 | 4.4 | 6.2 | 4.8 | 5.3 |

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# **CHAPTER 7 -** DO ECCENTRIC EXERCISE INTERVENTIONS IMPROVE ANKLE FLEXIBILITY? – A SYSTEMATIC REVIEW

## 7.1 PREFACE

Immobilising a muscle in a shortened position has shown to negatively impact its passive extensibility. Additionally, immobilisation has shown to reduce the number of sarcomeres in series and contribute to shorter muscle fascicle lengths. A contracture reduces the available ROM that may simulate an immobilised (stretch deprived) muscle that causes shorter, stiffer muscles in people with MS. Our recent study demonstrated people with MS who have developed an ankle contracture have shorter muscle fascicles that are less extensible (Appendix A). Eccentric exercise has shown to alter muscle morphology by improving muscle fascicle length. Therefore, adaptations from eccentric exercise could potentially target deficits present within muscles affected by contracture. As there is a lack of consensus regarding the benefits of eccentric exercise to improve ankle flexibility, the aim of this study was to systematically review and evaluate existing knowledge of changes in ankle flexibility following eccentric exercise interventions.

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The work presented in this chapter has been prepared for submission;

***Psarakis, M.,*** *Greene, D., Hoang, P. (2019). Do eccentric exercise interventions improve ankle flexibility? – A Systematic Review*

Associated work related to this chapter has been prepared for submission (Appendix A);

*Hoang, P.,* ***Psarakis, M.,*** *Diong, J., Kwah, L.K., Gandevia, S., Herbert, R. (2019). Passive mechanical properties of the gastrocnemius in people with multiple sclerosis who have developed ankle contractures. Clinical Biomechanics.*

## 7.2 ABSTRACT

**Background:** Eccentric exercise may stimulate muscle remodelling and increase both the length and extensibility of a muscle. However, there is a lack of consensus regarding the benefits of eccentric exercise as an intervention to improve ankle flexibility.

**Objective:** To systematically review and evaluate existing knowledge of changes in ankle flexibility following eccentric exercise interventions.

**Methods:** Databases searched include; Cochrane Central Register of Controlled Trials (Cochrane Library): SportDiscus with Full Text (EbscoHost), The Allied and Complementary Medicine Database (AMED), Web of Science & Medline. Full journal articles were included if; (i) the 'intervention' was greater than 4 weeks in duration; (ii) only contained eccentric intervention; (iii) there was a direct measurement of passive ankle ROM and/or muscle length (e.g. fascicle length).

**Results:** A total of seven studies met the inclusion criteria. Five out of the seven studies showed eccentric training had a significant (positive) effect on ankle flexibility while two showed eccentric training had no significant effect. However, the overall methodological quality for these studies was considered poor – fair.

**Conclusions:** Based on the seven studies included in this systematic review, there appears to be evidence to support the use of eccentric exercise to improve ankle flexibility. However, care must be taken when interpreting these findings given the high risk of bias and poor methodological quality of the included studies.

***Keywords:*** Dorsiflexion, Range of motion, Fascicle length, Muscle Tendon Unit, Sarcomerogenesis

## 7.3 INTRODUCTION

The talocrural joint (ankle joint) is a synovial, uniaxial hinge joint that moves within the sagittal plane. Movements occurring in this plane include plantarflexion (PF) and dorsiflexion (DF) that play an important role in everyday activities. Reduced DF during the mid-stance of gait can limit the amount of tibial progression (over the foot) causing inefficient gait patterns [1]. Additionally, limited ankle DF range of motion (ROM) has been linked to increased patellofemoral joint loading [2], reduced knee flexion displacement on landing and increased ground reaction forces during landing [3], making it a risk factor for lower limb injuries. Therefore, interventions designed to increase DF ROM are essential to improve gait patterns and reduce injuries across a range of populations.

Stretching is commonly prescribed as the primary treatment to improve ROM in the clinical setting [4]. Chronic adaptions from static stretching have been evaluated, with transient effects often associated with improvements in the viscoelastic behaviour and stretch tolerance of muscles rather than adaptations in muscle morphology [5]. Emerging research in the field of eccentric exercise provides promising results that overcome these limitations and improve ROM via adaptations in muscle morphology that may be more valuable in the clinical setting [6-12].

Eccentric exercise involves the active lengthening of a muscle that is resisting an opposing force. Eccentric exercise has shown to increase joint ROM and lengthen muscle fascicle lengths [6-12]. While the mechanism is still unclear, it is hypothesised that eccentric training induces muscle fibre lengthening (sarcomerogenesis) that stimulates muscle remodelling and increases the length and extensibility of a muscle [13]. Despite these findings, there is a lack of consensus regarding the benefits of eccentric exercise as an intervention to improve ankle flexibility.

Therefore, the purpose of this study was to systematically review and evaluate existing knowledge of changes in ankle flexibility following eccentric exercise interventions. This systematic review is intended to further inform clinical decision making in the rehabilitation setting.

## 7.4 METHODS

### 7.4.1 STUDY DESIGN

This study was a systematic review on the effect of eccentric interventions on ankle ROM. This study was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [14].

### 7.4.2 SEARCH STRATEGY

The following electronic databases were searched: Cochrane Central Register of Controlled Trials (Cochrane Library): SportDiscus with Full Text (EbscoHost), The Allied and Complementary Medicine Database (AMED), Web of Science & Medline. Database searches were conducted between 20 and 24 March 2019. Terms used in search strategy include: Eccentric, “negative work”, “Active stretching”, “Range of motion”, ROM, fascicle*, “joint flexib*”, PROM, “muscle length”, Stiffness, “muscle?tendon”, dorsiflexion, Ankle, gastrocnemius, Soleus, “triceps surae”, achilles, “calf muscle”, “plantar flexor”. Truncation, phrase searching and controlled language (MESH and Subject Headings) were used with concepts being searched across subject fields and ‘entire records’ for each database (Table 7.1). After the initial search, all titles and abstracts were screened for eligibility by two authors and disagreements were solved by consensus using a third independent reviewer.

### 7.4.3 STUDY SELECTION CRITERIA

Study eligibility criteria were developed prior to searching to minimise bias. All peer-reviewed articles were examined for suitability with no restrictions placed on publication date. Studies were not limited to randomized controlled trials (RCT’s). No limitations were placed on populations however, studies were limited to human experiments only. Conference proceedings, qualitative studies, sources pertaining to nursing, medicine, social work and other allied health professionals were excluded. Studies were excluded if; (i) the ‘intervention’ (eccentric exercise protocol) was less than 4 weeks in duration; (ii) a combination of eccentric and concentric exercise was used a primary intervention (i.e. Interventions must have been pure eccentric protocols); (iii) there was no direct measurement of muscle length (e.g. fascicle length) or passive ROM measurements were not reported. As longer fascicle lengths correlate with increased ROM [13], both ROM and fascicle length measures were included in this systematic review which collectively represent ankle flexibility.

### 7.4.4 QUALITY ASSESSMENT

A modified checklist by Downs and Black [15] was used to assess the risk-of-bias and methodological quality in the included studies. This checklist accounts for both randomized controlled trial and non-randomized studies included in this systematic review and was performed independently by two authors. The modified version has a maximum score of 28 with study quality classified as “excellent” (24-28 points), “good” (19-23 points), “fair” (14-18 points) or “poor” (<14 points).

### 7.4.5 DATA SYNTHESIS

As the outcome measures in this review were diverse, pooled data (meta-analysis) could not be completed. Data were presented as mean changes (improvements / decrements) in ROM or muscle fascicle lengths. Additionally, authors of included studies were contacted to confirm data reported if not presented in their respective studies.

## 7.5 RESULTS

**Search results**

The initial search yielded 1109 items that was reduced to 624 after duplicates were removed (Figure 7.1). Titles and abstracts were screened for relevance and resulted in the removal of 594 articles leaving 30 full text articles to be considered. Full text articles were retrieved, and a more detailed analysis performed that resulted in seven studies that met the eligibility criteria and therefore included in the systematic review. Of these seven studies, five were randomised in design [6, 8, 16-18] and two [5, 19] were cohort studies.

**Risk of Bias & Quality**

Results from the modified Downs and Black checklist ranged from 10 – 19 out of a possible of 28 (Figure 7.2). Of the seven studies, five were rated as “poor” quality [5, 6, 8, 16, 19], one was rated as “fair” [18] and only one study was rated “good” [17] for methodological quality.

**Description of studies**

*Participants*

In total, 177 participants were included in the seven studies (Table 7.2). Mean ages ranged from 12 – 53 years. Five of the seven studies examined healthy participants [5, 6, 8, 16, 18], while two studies examined participants with pathologies, achilles tendinosis [19] and cerebral palsy [17].

*Protocols*

Eccentric protocols and training techniques varied across the studies (Table 7.2). Four studies utilised the "Alfredson Protocol" - eccentric heel drops [8, 16, 18, 19] that consists of 3 sets of 15 repetitions performed daily. One of these four studies included an additional eccentric program in-conjunction with this protocol [16] however, the program was poorly outlined and therefore the composition of the program was unknown [16]. One study utilised a seated calf raise machine and a leg press machine [6] while another study utilised backwards downhill treadmill walking to complete their eccentric training protocol [17]. The final study utilised an isokinetic dynamometer to perform their eccentric training. Dosage of eccentric exercise varied across the studies however, on average, eccentric interventions were 8 weeks in duration (range = 4 to 14 weeks) with the total number of sessions ranging from 12 to 42 sessions.

*Outcomes*

Outcome measures varied across the studies (Table 7.2). Two studies used a weight bearing lunge test (WBLT) and reported passive ankle dorsiflexion ROM in degrees [8, 18]. One study used an isokinetic dynamometer and also reported passive ankle dorsiflexion ROM in degrees [5]. Three studies used ultrasonography to directly measure resting muscle fascicle length (millimetres) as an outcome measure post eccentric intervention [6, 17, 19]. The final study combined both ultrasonography (muscle fascicle length) and ankle dorsiflexion ROM measurements using an isokinetic dynamometer [16].

**Description of results**

*Range of motion:*

Mahieu et al. [8] demonstrated a significantly greater improvement in dorsiflexion ROM post eccentric exercise compared to a control group completing usual activities (mean change = 5.97° vs 0.48° respectively). Similarly, Aune et al. [18] demonstrated eccentric exercise provided significantly greater improvements in ROM when compared to a myofascial release (foam rolling) group (mean change =

5.1° vs 2.6° respectively). Kay et al. [5] reported the largest improvements after eccentric exercise (mean improvement = 14.7°) however, there was no control group for comparison. In contrast, Foure et al. [16] found no significant difference with eccentric training when compared to a control group completing usual activities .

*Ultrasonography:*

Duclay et al. [6] reported significant improvements in fascicle length (mean increase = 2.96mm) compared to control group (mean decrease = 0.13mm). Similarly, Crill et al. [19] reported significant improvements for the medial gastrocnemius (mean change = 6.3mm) but not the lateral gastrocnemius (mean change = 0.2mm) however, there was no control group for comparison. In contrast, Foure et al. [16] and Hosl et al. [17] reported no significant changes in fascicle length following eccentric training.

## 7.6 DISCUSSION

**Summary of results**

The purpose of this study was to systematically review and evaluate existing knowledge of changes in ankle flexibility following eccentric exercise interventions. Five out of the seven studies showed eccentric training had a significant (positive) effect on ankle flexibility [5, 6, 8, 18, 19] while two showed eccentric training had no significant effect [16, 17]. However, care must be taken when interpreting study outcomes given the high risk of bias and poor methodological quality of the included studies. Conflicting findings presented in this review may be attributed in part to; various outcome variables used to assess ankle flexibility; variability in eccentric protocols; and the type of participants included in the studies.

**Outcomes & Measurement Techniques**

There is no standardised protocol, position or technique for assessing ankle ROM making comparison of outcomes problematic. Mahieu et al. [8] and Anue et al. [18] demonstrated significantly greater improvements in ankle ROM (5.97° and 5.1° respectively) following a 4 - 6 week eccentric intervention. These findings are larger than that previously presented in a systematic review evaluating the effects of static stretching on dorsiflexion range of motion [20]. Static stretching had small but significant effects on dorsiflexion range of motion (~2°-3° improvement compared to controls). Therefore, the data

presented by Mahieu et al. [8] and Anue et al. [18] provide some evidence that eccentric exercise may be more effective than static stretching for improving dorsiflexion ROM.

Despite these findings, care must be taken when generalising ROM results as they may be subject to measurement error. Typically, for a change to be clinically significant, measured differences must be greater than the minimal detectable change (MDC). On average, according to a systematic review by Powden et al. [21], the WBLT has a MDC of approximately 5 degrees. The measurement error increases to approximately 7 degrees when using a goniometer [22], as has been done by Mahieu et al. [8]. Therefore, these findings could fall within measurement error for the WBLT rather than actual improvements produced by the eccentric intervention.

An alternative way to measure ROM in the laboratory setting was explored by two studies presented within this review [5, 16]. Isokinetic dynamometry testing allows for the calculation of range at known torques. Foure et al. [16] showed improvements (~ 2 - 3 degrees) in an eccentric group compared to a control group however, results were not significant. In contrast, Kay et al. [5] demonstrated large, significant improvements in ROM following an eccentric intervention (~ 15° ). Unfortunately, as there was no control group, we cannot determine if the large effects were due to the intervention or other confounding issues contributing to these results. For example, peak passive ROM data were collected at the 'point of discomfort' determined by the subject, rather than standardising torque and measuring ROM at a known torque pre-post intervention.

Ultrasonography is often used to measure muscle fascicle lengths (in vivo) as they are correlated with increases in ROM [13]. Duclay et al. [6] and Crill et al. [19] demonstrated significantly longer fascicles (2.96mm and 6.3mm respectively) following 7 - 8 weeks of eccentric training. These findings are in contrast to Foure et al. [16] and Hosl et al. [17] who found no significant difference in fascicle lengths post eccentric intervention. These contrasting results may be attributed to measurement error associated with ultrasound techniques. Measurement error in ultrasound studies of the gastrocnemius muscle have shown fascicle length errors from 2mm to 7mm [23, 24]. A range of findings have been found in other muscle groups, (such as in the bicep femoris – long head) where MDCs have been reported to be approximately 10 mm [25]. Ultrasonography has multiple sources of measurement error

and can be highly tester dependent. Therefore, increases in fascicle lengths presented may be due to measurement error and may not be clinically significant.

**Eccentric Protocols**

The protocols presented in this review varied in both dosage (frequency, intensity, duration) and modes. The 'Alfresdon Protocol' was the most commonly prescribed eccentric intervention but may have contributed to inconsistent findings [8, 16, 18, 19]. The 'Alfresdon Protocol' is commonly used in symptomatic populations (e.g. Achilles tendinopathy) and may lack the intensity and progressive overload required for adequate muscle remodelling. Intensity and duration are important factors in delayed on-set muscle soreness (DOMS) that can contribute to muscle damage and subsequent remodelling [26]. Anue et al. [18] applied a unique form of eccentric exercise (backwards walking downhill) in children with Cerebral Palsy. Despite no improvements in muscle fascicle length, this mode has shown to elicit high level DOMS and resulted in one subject incurring a grade II muscle tear [27]. However, eccentric exercise intensities by Anue et al. [18] were lower than that found in this study. Kay et al. [5] reported the largest improvements in ROM in the least number of training sessions (12 sessions). Whilst care must be taken when interpreting these findings, it is worth noting that the high training intensities (maximal voluntary contractions) used within this study may provide a plausible explanation to intensity being a prerequisite for muscle remodelling.

**Patients**

This review combined both healthy and pathological populations. This could be problematic as patients (with achilles tendinopathy) may be limited by pain and therefore potentially influence intervention outcomes. Additionally, neurological populations (such as CP) have shown to have less satellite cells when compared to typically developing children [28]. Satellite cells are involved in the regulation of muscle synthesis and may have influenced the findings reported by Aune et al. [18] by limiting longitudinal muscle growth.

**Limitations & Future research**

There are two major limitations of this review. Firstly, our search strategy was not limited to RCTs. While RCTs are considered the strongest type of evidence, they are still at risk of bias if poorly conducted. Given the lack of evidence in this area, we believe our decision was well justified to include all studies to allow us to better answer our research question. Secondly, all studies (irrespective of their quality),

were included in this review. However, to minimise the risk of drawing conclusions based on poor quality research, the Downs and Black checklist [15] was used to assess the quality of individual studies within this review. Care was taken when considering these findings to ensure study outcomes were not misinterpreted.

Further research is required to better understand the mechanism by which eccentric exercise can increase muscle fascicle length. For example, Mahieu et al. [8] and Duclay et al. [6] did not compare eccentric training to another exercise intervention. These studies demonstrated that muscle contractions (eccentric training) are better than completing usual activities (control). In other muscle groups (i.e. Vastus Lateralis), changes in muscle fascicle lengths don't appear to be contraction-specific, meaning both concentric and eccentric training groups improved muscle fascicle lengths [29]. Therefore, RCTs in the future should investigate if there is a contraction-specific effect or if both eccentric and concentric muscle contractions alter muscle fascicles lengths. Additionally, this review highlights the diverse measurement techniques used in research to measure ankle ROM. Future studies should focus on using torque-controlled ROM testing as ROM varies depending on the amount of force applied.

## 7.7 CONCLUSION

Based on seven studies included in this systematic review, there appears to be evidence to support the use of eccentric exercise to improve ankle flexibility. However, the current evidence highlighted in this review is limited by poor methodological quality and compromised measurement techniques. More rigorous research is required to determine if these findings are clinically significant before they can be used to inform clinical practice.

### Acknowledgements

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**Figure 7.1** PRISMA Flow Diagram

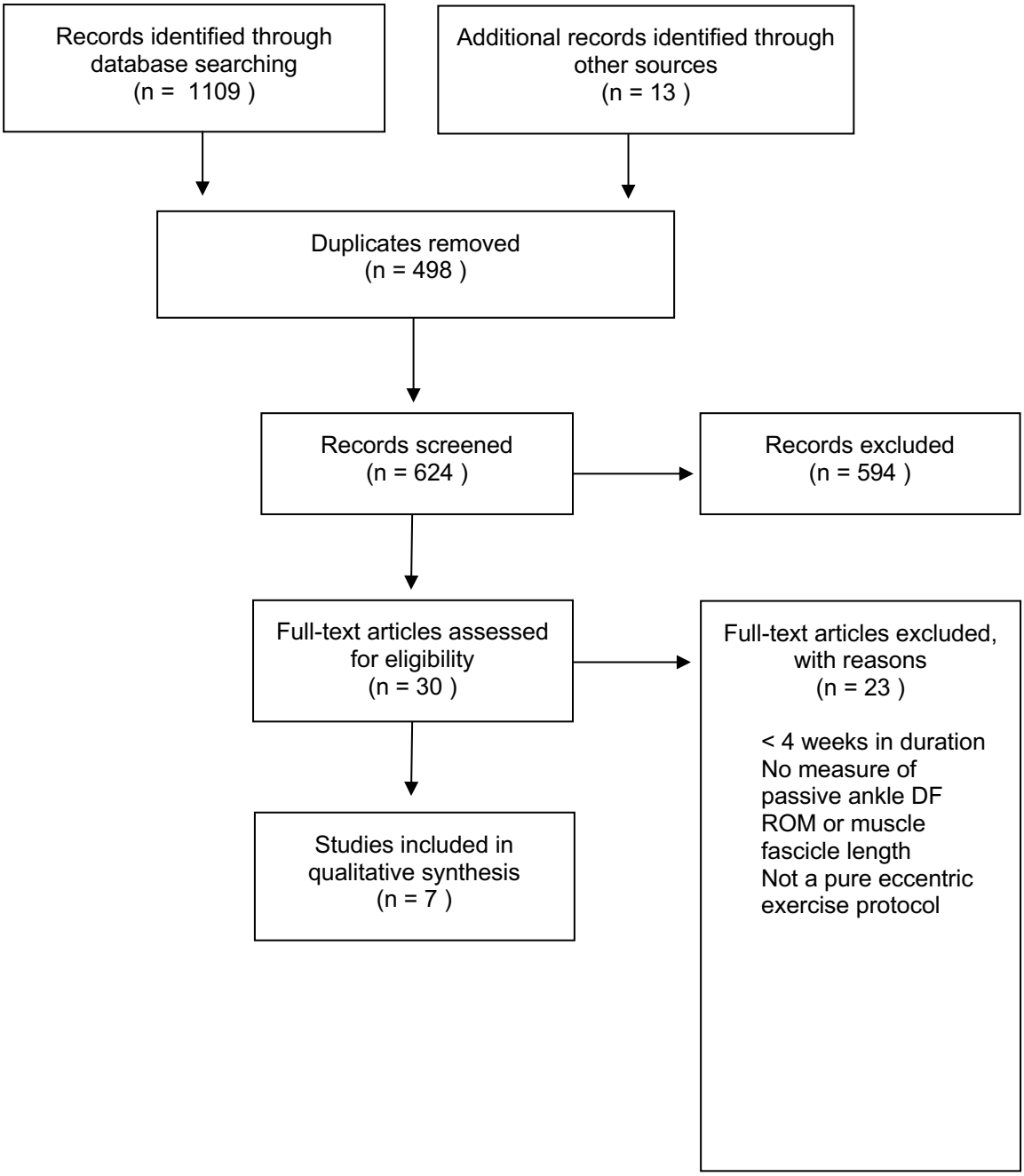

**Figure 7.2** Modified Downs and Black – Risk of Bias. Study quality classified as “excellent” (blue), “good” (green), “fair” (yellow) or “poor” (red).

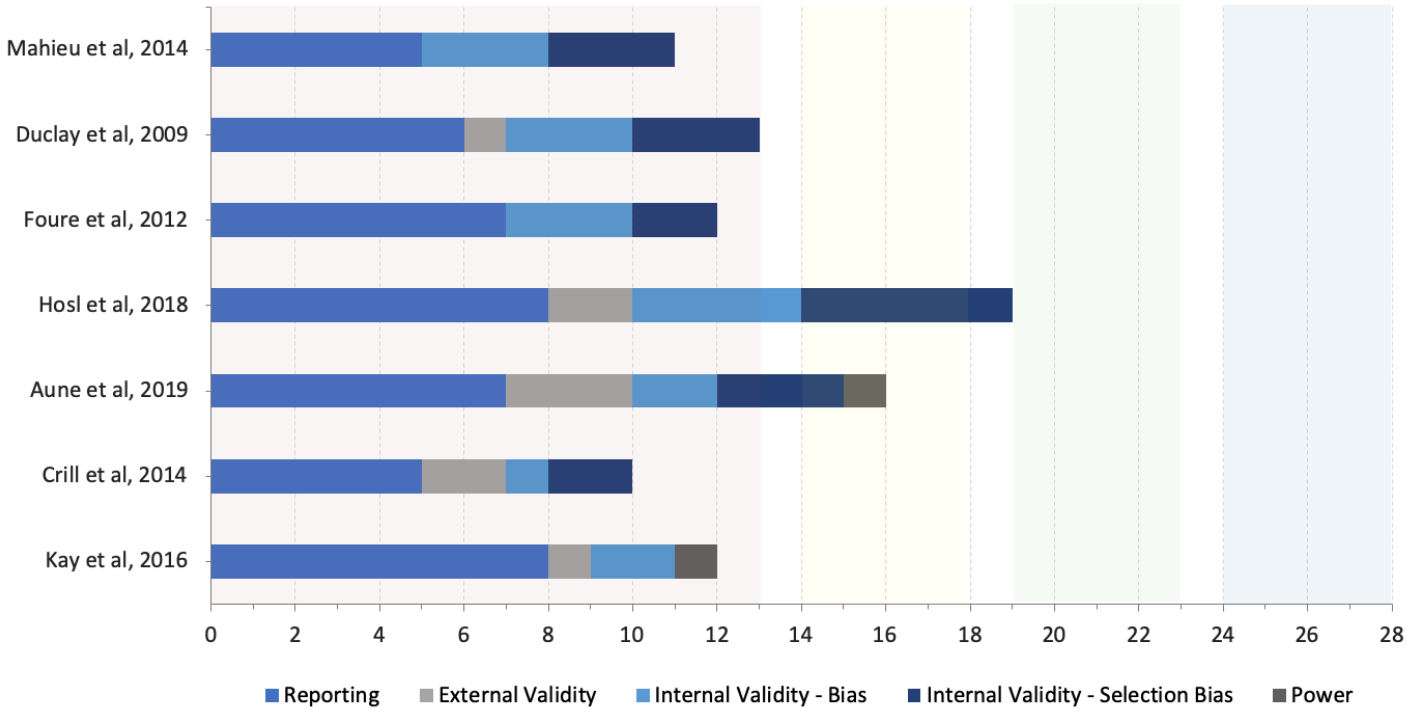

**Table 7.1**

Search Strategy Applied - Medline

| | |
|---|---|
| #1 | Eccentric OR "negative work" OR "Active Stretching" |
| #2 | "Range of motion" OR ROM OR fascicle* OR "joint flexib*" OR PROM OR "Muscle length*" OR extensib* OR stiffness OR "muscle?tendon" OR dorsiflexion |
| #3 | Ankle OR gastrocnemius OR Soleus OR "triceps surae" OR achilles OR "Calf muscle" OR "plantar flexor" |
| #4 | #1 AND #2 AND #3 |

**Table 7.2** Comparison of Eccentric Exercise Interventions

| STUDY | PARTICIPANTS | | STUDY DETAILS | | | | |
|---|---|---|---|---|---|---|---|
| **Author \| Year** | **n** | **Details** | **Intervention** | **Weeks** | **Design** | **Outcome** | **Results** |
| Mahieu et al, 2014 | **A.** Control = 29<br>**B.** Eccentric = 35 | Active Healthy<br>*(22 – 23yrs mean age)* | **A.** Usual activities<br>**B.** 3 sets x 15 reps single leg heel drops – knee extended (7 sessions/week - Total = 42 sessions) | 6 | Randomized control trial | Passive ankle DF ROM WBLT – Goniometer (degrees) | **A.** ↑ 0.48°<br>**B. ↑ 5.97° ( * )** |
| Duclay et al, 2009 | **A.** Control = 8<br>**B.** Eccentric = 10 | Active Healthy<br>*(23 – 24yrs mean age)* | **A.** Usual activities<br>**B.** 2 types of eccentric exercises at 120% 1RM:<br>- 6 sets x 6 reps seated calf raise – knee flexed position (1 session / week)<br>- 6 x 6 calf raise – knee extended (2 sessions / week)<br>- Total sessions = 21 sessions | 7 | Randomized control trial | Ultrasound - resting fascicle length gastrocnemius medialis (millimetres) | **A.** ↓ 0.13mm<br>**B. ↑ 2.96mm ( * )** |
| Foure et al, 2012 | **A.** Control = 13<br>**B.** Eccentric = 11 | Active Healthy<br>*(21yrs mean age)* | **A.** Usual activities<br>**B.** 2 types of eccentric exercises:<br>- 3 sets x 15 reps single leg heel drops – knee extended<br>- Eccentric contractions – drop jump *(protocol unclear, lacking information / detail)*<br>- Total = 34 sessions | 14 | Randomized control trial | Ultrasound - resting fascicle length gastrocnemius medialis and lateralis (millimetres) | *Gastrocnemius lateralis*<br>**A.** ↓ 1.1mm<br>**B.** ↑ 0.9mm<br>*Gastrocnemius medialis*<br>**A.** ↑ 0.1mm<br>**B.** ↑ 0.3mm |
| | | | | | | Passive ankle DF ROM Isokinetic dynamometer (degrees) | *Knee Flexed*<br>**A.** ↓ 1°<br>**B.** ↑ 3°<br>*Knee Extended*<br>**A.** 0°<br>**B.** ↑ 2° |
| Hosl et al, 2018 | **A.** Stretch = 5<br>**B.** Eccentric = 5 | Patients with Cerebral Palsy<br>*(12yrs mean age)* | **A.** Static Stretching<br>- 7 exercises x 5 reps per leg x 20 sec (3 sessions/week - Total = 27 sessions)<br>**B.** Backward downhill treadmill training<br>- > 23 minutes at 50% of forward walking speed at 10-15% incline (3 sessions/week - Total = 27 sessions | 9 | Randomized crossover trial | Ultrasound - resting fascicle length gastrocnemius medialis (millimetres) | *Gastrocnemius medialis*<br>**A. ↓ 0.1mm ( * )**<br>**B.** ↓ 0.1mm |
| Aune et al, 2019 | **A.** Massage = 12<br>**B.** Eccentric = 11 | Soccer Players<br>*(18yrs mean age)* | **A.** 3 sets x 60 sec calf foam rolling (7 sessions/week – total = 42 sessions)<br>**B.** 3 sets x 15 reps single leg heel drops – knee extended (7 sessions/week – total = 42 sessions) | 4 | Randomized trial | Passive ankle DF ROM WBLT - Inclinometer (degrees) | **A.** ↑ 2.6°<br>**B. ↑ 5.1° ( * )** |
| Crill et al, 2014 | Eccentric = 25 | Achilles Tendinosis<br>*(53yrs mean age)* | 3 sets x 15 reps single leg heel drops – knee extended (7 sessions/week = 42 sessions) | 8 | Cohort Study | Ultrasound - resting fascicle length gastrocnemius medialis and lateralis (millimetres) | *Gastrocnemius lateralis*<br>↑ 0.2mm<br>*Gastrocnemius medialis*<br>**↑ 6.3mm ( * )** |
| Kay et al, 2016 | Eccentric = 13 | Soccer Players<br>*(20yrs mean age)* | 5 sets x 12 reps maximal voluntary isokinetic eccentric contraction (2 sessions / week = 12 sessions) | 6 | Cohort Study | Passive ankle DF ROM Isokinetic dynamometer (degrees) | **↑ 14.7° ( * )** |

**( * )** = significant <0.05, ↑ = improvement, ↓ = deterioration**, yrs** = years, **WBLT** = weight bearing lunge test, **DF** = dorsiflexion, **ROM** = range of motion

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# **CHAPTER 8 -** SAFETY, FEASIBILITY AND EFFICACY OF AN ECCENTRIC EXERCISE INTERVENTION IN PEOPLE WITH MULTIPLE SCLEROSIS WITH ANKLE CONTRACTURES – A CASE SERIES

## 8.1 PREFACE

The aims of this study were to investigate the safety and feasibility of an eccentric exercise program in people with Multiple Sclerosis who have ankle contracture and explore the efficacy of eccentric exercise on ankle joint ROM and functional mobility. This is the first case study to explore the effects of eccentric exercise as a therapeutic modality for the management of ankle joint contractures within a neurological population. Positive outcomes have the potential to replace current conservative interventions prescribed in the clinical setting and could be used as an alternative to more invasive treatments such as surgery to improve, treat and manage ankle joint contractures in MS patients.

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The work presented in this chapter has been published and cited as;

***Psarakis, M.,*** Greene, D., Lord, S. R., Hoang, P. (2019). Safety, Feasibility and Efficacy or an Eccentric Intervention in People with Multiple Sclerosis with Ankle Contractures. *International Journal of MS Care*

## 8.2 ABSTRACT

**Background -** The primary aim of this study was to investigate the safety and feasibility of an eccentric exercise program for people with Multiple Sclerosis (MS) who have ankle contractures, i.e. reduced ankle range of motion (ROM). Secondary aims were to explore the efficacy of eccentric exercise on ankle joint ROM and functional mobility.

**Methods -** Five people with MS (3 females & 2 males, mean age 50.8 ± 9.4, duration of MS 7.6 ± years) completed two eccentric exercise training sessions (between 10 - 45 min) per week for twelve weeks (total = 24 sessions). The training involved walking backwards downhill on an inclined treadmill (gradient = 10 - 14°) at a self-selected pace. The intervention was assessed for its safety (adverse events) and feasibility (recruitment rates, adherence rates, enjoyment levels, difficulty and discomfort) along with clinical outcomes including passive/active ankle ROM and distance walked in six minutes.

**Results -** There were no adverse events during or following the eccentric training. There was a 100% adherence rate. All participants enjoyed the training and experienced low levels of muscle soreness/discomfort. The training program improved passive and active ankle ROM in all participants, however, improvements did not translate to improvements in walking for all participants.

**Conclusions -** Eccentric exercise (walking backwards and downhill) is a safe and feasible training modality for people with MS with ankle contractures. Clinical outcomes (greater passive and active ankle ROM) following training were evident. However, translation to clinically meaningful changes in walking function require further examination.

***Keywords:*** Ankle contracture, Multiple Sclerosis, Eccentric, Range of motion, Backwards-Downhill-Walking.

## 8.3 INTRODUCTION

People with multiple sclerosis (MS) often present with sensory and motor deficits that limit their functional mobility and physical independence [1]. MS symptoms often result in muscle weakness and other soft tissue consequences such as joint contractures. A recent population-based study of prevalence of joint contractures in MS reported that ~80% of people with MS who are still ambulant (with or without assistive devices) have developed joint contractures with the ankle joint as the most common site [2]. A significant consequence of ankle contractures is the debilitating impact on gait and functional mobility such as impaired heel to toe progression during gait [3]. Similarly, ankle contractures may also contribute to the high frequency of falls in people with MS [4] due to reduced foot clearance during the swing phase of gait with consequent trips and slips, which account for 48% of falls in people with MS[5]. Therefore, interventions that can reduce ankle contracture should improve gait and functional mobility as well as reduce trips, slips and falls.

Currently, the most common interventions for the prevention and treatment of joint contracture are various types of muscle stretching. However, a Cochrane systematic review of 35 randomised trials which examined the effects of stretching interventions concluded that there is moderate-to-high quality evidence that stretching does not have clinically useful immediate, short-term or long-term effects on joint range of motion (ROM) [6]. Therefore, there is a need to develop alternative interventions to prevent and treat joint contractures in neurological populations.

Recent developments in the field of eccentric exercise may be promising in this regard [7-13]. Eccentric exercise requires a muscle to generate force by actively contracting while it is forcefully lengthened. Experimental data from both animal [14] and human studies [15] suggest that levels of soreness diminish with repeated bouts of eccentric exercise because muscle remodeling increases muscle length. Furthermore, a number of studies have shown that eccentric exercise can increase joint ROM and lengthen muscle fascicles via stimulating muscle remodeling and increasing both the length and extensibility of a muscle [7-13]. Although these studies were conducted on people without contracture, they provided some evidence that eccentric exercise can increase the extensibility of muscles in healthy adults. However, to date, no study has examined the use of eccentric exercise intervention to treat ankle contractures in populations with neurological conditions such as people with MS, spinal cord injury

or stroke.

Therefore, the primary aim of this pilot study was to investigate the safety and feasibility of an eccentric exercise program in people with MS who have ankle contractures. Secondary aims were to explore the efficacy of eccentric exercise on ankle joint ROM and on mobility in people with MS who have developed ankle contractures.

## 8.4 METHODS

### 8.4.1 DESIGN

This study was an exploratory research design aimed to determine if walking backwards (downhill) on an inclined treadmill was safe and feasible in five people with MS with ankle joint contractures.

### 8.4.2 PARTICIPANTS

Five participants with MS (2 male, 3 female) were recruited from an outpatient MS rehabilitation setting (Sydney, Australia). Inclusion criteria were: a confirmed diagnosis of MS by a neurologist, an Expanded Disability Status Scale (EDSS) of $\leq$ 6 (EDSS was calculated using Toronto EDSS Calculator®, developed by NeuroApps Toronto, scored by the therapists who screened potential participants), an ankle contracture - defined as less than 90 degrees of passive ankle dorsiflexion ROM when a dorsiflexion torque of 10Nm was applied to the forefoot of the relaxed ankle [16], no relapses in the preceding 12 weeks and free from any other disease, injury or illness preventing participant from exercising. People who were not mobile or had fixed contractures in the ankle were excluded. The study was approved by the Human Studies Ethics Committee at the University of New South Wales (2013312N). Informed consent was obtained from all participants prior to participation.

### 8.4.3 ASSESSMENTS

Baseline assessment was conducted seven days before the first training session. Re-assessments were conducted within three days after their last training session (Figure 8.1).

*ii. Safety and Feasibility*

Safety was calculated by the number of adverse events (accidents or injuries related to the intervention) reported by patients both during and after each treatment session. Aspects of feasibility were assessed by recruitment rates, acceptability (based on adherence rates and enjoyment levels) and practicality (intervention difficulty and discomfort) [17]. Recruitment rates were calculated by dividing the number of participants included in the study by the number of participants who were assessed for eligibility. Enjoyment levels were calculated using the physical activity enjoyment scale (PACES) questionnaire at the conclusion of the study [18]. The original 18-item PACES [17] scale was used to assess enjoyment. Respondents were asked to rate "how you feel at the moment about the physical activity you have been doing" using a 7-point bipolar rating scale. Eleven items are reverse scored. Higher PACES scores reflect greater levels of enjoyment (highest score = 126). The perceived difficulty of each session was monitored using Rated Perceived Exertion (RPE) scale where participants rated how difficult they perceived the training was. Participants were asked to give an overall (session) RPE after resting for 10 minutes (post-session) from 0 (nothing all) to 10 (very heavy) [18]. Participants reported their muscle soreness and discomfort (DOMS - delayed onset of muscle soreness) using a visual analogue scale (VAS) from 0 (no pain) to 10 (unbearable pain) after each session and over a 72hr period. Peak DOMS was recorded for the 24 sessions.

*iv) Ankle Range of Motion*

Passive and active ROM were measured on the more affected ankle of potential participants with MS. Participants were placed in a long sitting position using a chair and foot stool with the knee extended. To minimise effects of thixotrophy on muscle, the ankle was moved through 6 cycles before data was collected [16]. Passive ROM was measured by applying 100N of pulling force (~ 10 kg on an analogue spring loaded force gauge) to the heads of the metatarsals (of the affected ankle) and pulled toward the knee (parallel to the shank) and the ankle angle was measured using an inclinometer [16]. To measure active ROM, participants were required to actively dorsiflex the ankle as far as they could and again ankle angle was measured using an inclinometer.

*v) Functional Mobility Assessment*

The 6-minute walk test was chosen to evaluate if the improvement in the ankle ROM following eccentric exercise helped improve functional mobility. Participants completed a 6-minute walk test at self-selected walking speeds on a 20m marked walking pathway. Participants were given standard instructions to "walk as far as possible for 6 minutes". Participants were reminded that they would be walking for 6 minutes and could stop and rest if needed. Participants were given standardised encouragement after each minute [19]. The distance walked in the six-minute walk period was recorded.

### 8.4.4 INTERVENTION

Eccentric exercise training (twice a week for 12 weeks = 24 sessions) was conducted under the supervision of an accredited Exercise Physiologist. Participants performed eccentric exercise by walking backwards downhill on an inclined (10 – 14 degrees) treadmill (h/p/cosmos – model: pulsar 3p) using a previously published protocol [21]. Each training session included a 5-minute warm-up consisting of slow (self-selected) forward walking on a treadmill followed by 10 concentric/eccentric contractions of the plantar flexor muscles (calf raises/lower) of the leg with ankle joint contracture. After the warm up, the belt of the treadmill was turned in the reverse direction. Participants were then instructed to step as far backward as possible with the affected leg in a toe-to-heel pattern while keeping the knee straight (to maximise the stretch on the gastrocnemius). After each step with the affected leg, the unaffected leg stepped backwards in a normal pattern. Participants were instructed to use hand rails for support only if needed. The first two sessions were considered as an introductory training period where participants were trained for between 10 and 20 minutes at a self-selected speed. After these sessions, participants were encouraged to walk continuously, at the speed they were comfortable with (i.e. self-selected), for as long as they could tolerate with the maximal time being 60 minutes [22]. An overhead support harness was offered as an additional level of safety. The chest-belt (harness) was connected to an emergency stop button on the treadmill to cut power if more than 8kg of pulling force was applied to the harness (supplementary video shows a participant with MS performing the intervention).

### 8.4.5 DATA ANALYSIS

This study aimed to explore the efficacy of an eccentric exercise training program on reduced ankle ROM (secondary aim). Therefore, here we only reported the magnitude of the differences before and after intervention and 95% confidence intervals. No formal statistical analysis was performed.

## 8.5 RESULTS

***Safety and Feasibility***

There were no adverse events recorded during or following the intervention. Each participant spent an average of 24 (supervised) hours to complete the intervention. Sixteen participants indicated an initial interest in the study (Figure 8.1) but only twelve out of the sixteen (75%) followed up and were assessed for study eligibility. Five out of the twelve (42%) did not meet the inclusion criteria of having less than 90 degrees of passive ankle ROM. Two out of the twelve (17%) declined the offer to participate due to lack of time. Recruitment uptake was therefore calculated to be 42%.

There was a 100% adherence rate for all participants included in the study. All participants enjoyed the intervention with PACES score = 105/126 ± 15 (mean ± SD). In addition, participants reported a low level of discomfort/soreness with peak DOMS = 2.7 / 10 ± 2 (mean ± SD). Participants perceived the difficultly of the intervention to range from 2.2 (easy) to 5.4 (hard) out of 10.

***Ankle Range of motion***

All participants had greater mean passive ROM at post-intervention (93˚) compared to baseline (82˚) (mean difference: 11˚, 95% CI = 5˚ - 17˚). Similarly, all participants had a greater active ROM at post-intervention (77˚) compared to baseline (67˚) (difference: 10˚, 95% CI = 1.2˚ - 19.2˚ (see Table 8.3 and Figure 8.2). According to a recent Cochrane review [23], the difference in this study (on average) was greater than that of a clinically meaningful improvement (~ 5˚).

***Functional Mobility***

The 6MWT distance was slightly greater after training (mean: 354 m) than at baseline (339 m; difference: 15m, 95% CI = -21.5m to 51.4m; Table 8.3 and Figure 8.2). According to a European

multicenter study [24] the difference in this study was slightly short of a clinically meaningful improvement (~ 22m).

## 8.6 DISCUSSION

The results of this study showed that backwards walking on an inclined treadmill was safe and feasible for patients with MS who have ankle contractures. Additionally, preliminary observations supported our hypothesis that this intervention could improve ankle ROM and functional outcomes in patients with MS.

Backwards walking is an emerging rehabilitation strategy within neurological conditions such as stroke [25] and children with cerebral palsy [26]. Yang et al [25] reported that adding backward walking training to walking forward on a (flat) treadmill could improve asymmetric gait pattern in patients post stroke. Kim et al[26] reported that backward walking on inclined treadmill may strengthen the rectus femoris and tibialis anterior in walking training for children with cerebral palsy. In both studies researchers utilised backwards walking tasks to improve forward walking impairments. In MS, it has been suggested that backward walking tests (with or without a cognitive task) are an effective way to examine walking difficulties in individuals with MS with relatively minimal walking impairment [27]. Extending on previous literature, we hypothesised that backwards, downhill walking on an inclined treadmill (a form of eccentric exercise) could result in improvements in ankle contractures in people with MS who are mobile via changes in the soft tissues around the ankle. This, in turn, could improve mobility.

It was observed that ankle joint ROM (passive and active) improved by approximately 10˚ in participants following eccentric exercise training. A recent Cochrane review [23] comparing traditional stretching interventions in people with and without neurological conditions highlighted that any possible benefit (in ROM) achieved from stretching did not exceed 4˚. Therefore, eccentric exercise may provide greater improvements in ROM than traditional (stretching) interventions.

Previous research suggests that increases in ROM following eccentric exercise is due to muscle damage and subsequent remodeling at longer lengths [7-13]. However, levels of DOMS reported in our study was low, suggesting that observed changes in passive and active ROM in this study may not be

solely related to muscle remodeling and could be due to changes in non-muscle stiffness such as a reduction in capsular stiffness. Significant changes in active ROM may be attributed to a combination of factors including an increase in tibialis anterior (TA) activation in conjunction with less overall (passive) ankle dorsiflexion stiffness. Previous research in cerebral palsies patients who walked backwards downhill at a gradient of 10% showed a significant increase in TA muscle activation[26]. These results in conjunction with improved passive ankle ROM provides a plausible explanation of the overall improvements in active ROM in MS participants who have developed ankle contractures.

Our results demonstrated that on average, participants improved 6-MWT distance by only 15m. In a large multicenter study, it was suggested that clinically meaningful changes for 6-MWT in people with MS is ~22m [24]. In older adults a small meaningful change in 6-MWT distance is 19 - 22m and a substantial meaningful change is 47 - 49m [28]. In populations with lung diseases the clinically meaningful change for 6-MWT was from 14.0 - 30.5m [29]. Taken together all these criteria, only three participants in our study had a small clinically meaningful changes in function. It is possible that concomitant motor fatigue that is common in people with MS may have limited improvements in the 6-minute walk test. Future research may consider comparison of 10-meter walk test with fast as slow speed, which may reveal greater results.

Fatigue is an important issue in people with MS and needs to be considered with regard to safety during exercise, especially in relation to the type of eccentric exercise applied in this study. Accordingly, we gradually trained the participants and closely monitored them during the exercise by monitoring their sessional RPE and adjust the intensity in the following session if needed. In addition, we monitored any adverse events (i.e. tripping or reduced balanced or falls) during and after the exercise sessions: none were reported by the study participants. In this study we set a target of maximal 60 minutes of walking backward per session, none of participants could achieve this. Future studies may consider shorter periods or breaks during the session so that participants can exercise longer and, therefore, get more benefits from this type of exercise.

We acknowledge several limitations and future recommendations within this study. Firstly, the small sample size of our study limits the interpretation and generalisation of data. Secondly, as our

participants were only “moderately” affected by MS (average EDSS = 4.1), our intervention may be limited to those who are more ambulant but not for advanced cases of MS. Thirdly, the outcome measures were only collected twice over a 3-month period. Due to the high day-to-day variability in people with MS, a single assessment occurring over a 3-month period may be misrepresentative of the participants performance throughout the intervention [30]. More frequent testing of outcome measures throughout an intervention may serve to overcome this limitation in future studies. Finally, post intervention measurements were taken within 3 days after the intervention. It is not known if these results are transient and can be maintained following the intervention. Future studies should consider a longer-term follow-up period to investigate the effectiveness of this type of intervention with more regular intervals of testing, which may help track changes in people with MS.

While the backward walking training applied in this study was found to be safe and feasible, several recommendations need to be addressed in preparation for a larger study based on the criteria suggested by Thabane et al. [31]. Firstly, 42% of participants assessed were excluded from the study as they had greater than 90 degrees of passive ankle ROM. Given that normal ambulation requires ~10 degrees of dorsiflexion [32], our criteria may be too strict and require modification to reduce exclusion rates. Secondly, the low levels of DOMS reported in our study may be attributed to the low intensity (speed), poor muscle activation (coordination) and knee hyper-extension during the intervention. Previous research in healthy participants using a similar protocol reported high levels of DOMS and resulted in one participant incurring a grade II muscle tear [21]. Participants in this study achieved higher levels of intensity (speed) proposing a plausible link between the intensity of the intervention and the magnitude of muscle damage. A lack of muscle activation whilst stepping backwards on the treadmill may also reduce the amount of eccentric load and therefore, presumably, reduce the amount of muscle damage. For eccentric exercise to be effective, patients must actively contract the muscle (triceps surae complex) with sufficient force whilst it is forcibly lengthened (stepping backwards downhill) to facilitate muscle damage. Lower limb paresis and muscular weakness most likely limited the intensity (speed) and duration (time) of the intervention, thereby potentially lessening its effect. Additionally, we noted that all participants demonstrated various amounts of knee hyperextended during the intervention. Knee hypertension places additional load through the posterior knee capsule and may decrease the load on the triceps surae complex. Therefore, future studies should consider using a brace to control knee

hyperextension throughout the intervention to maximise the eccentric load placed on the triceps surae complex.

## 8.7 CONCULSION

The current study demonstrates that backwards downhill walking is a safe and feasible training modality in people with MS with ankle contractures. Clinical outcomes (passive and active ROM) following backwards downhill walking are promising. However, translation to clinically meaningful changes in walking function require further examination.

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**DECLARATIONS OF INTEREST**

The authors report no conflicts of interest.

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**Table 8.1** Baseline characteristics of the participants

| Participant # | Gender | Age | Height | Mass | Time since diagnosis | MS type | EDSS | Affected leg |
|---|---|---|---|---|---|---|---|---|
| | (M/F) | (yrs) | (m) | (kg) | (yrs) | | (0 – 10) | (R/L) |
| 1 | M | 56 | 1.81 | 90 | 3 | RRMS | 4.5 | R |
| 2 | M | 43 | 1.77 | 100 | 4 | PPMS | 6 | R |
| 3 | F | 40 | 1.58 | 59 | 11 | SPMS | 3 | R |
| 4 | F | 66 | 1.64 | 60 | 17 | RRMS | 3 | R |
| 5 | F | 49 | 1.68 | 96 | 3 | RRMS | 4 | R |
| Average | | 50.8 | 1.7 | 80.9 | 7.6 | - | 4.1 | |
| SD | | 9 | 0.1 | 17.8 | 5.6 | - | 11 | |

M = male, F = female, Dx = Diagnosis, MS = Multiple Sclerosis, RRMS = Relapsing-Remitting MS, PPMS = Primary Progressive MS, SPMS = Secondary Progressive MS, EDSS = Expanded Disability Status Scale, R = right

**Table 8.2** Minimum and maximum values of participants intervention data recorded over 24 sessions

| Participant # | Speed (km/hour) | | Gradient (°) | | Duration (min) | | RPE (/10) | |
|---|---|---|---|---|---|---|---|---|
| | Min | Max | Min | Max | Min | Max | Min | Max |
| 1 | 1.3 | 2 | 10 | 14 | 10 | 45 | 1 | 7 |
| 2 | 0.8 | 1 | 10 | 14 | 10 | 45 | 3 | 5 |
| 3 | 0.8 | 1.1 | 10 | 14 | 1 | 46 | 2 | 5 |
| 4 | 0.8 | 1.7 | 10 | 14 | 15 | 50 | 2 | 4 |
| 5 | 1 | 2.7 | 10 | 14 | 15 | 30 | 3 | 5 |
| Average | 0.9 | 1.7 | 10 | 14 | 13 | 43.2 | 2.2 | 5.4 |
| SD | 0.2 | 06 | 0 | 0 | 2.4 | 6.9 | 0.7 | 1.0 |

RPE = rating of perceived exertion scored out of 10.

**Table 8.3** Enjoyment, Soreness/Discomfort, Ankle range of motion and Functional Mobility

| Participant # | Enjoyment | Soreness | Ankle range of motion (°) | | | | Mobility | |
|---|---|---|---|---|---|---|---|---|
| | PACES* | DOMS** | Passive | | Active | | 6-MWT (m) | |
| | Post | Peak | Pre | Post | Pre | Post | Pre | Post |
| 1 | 125 | 4.2 | 84 | 92 | 79 | 80 | 371 | 402 |
| 2 | 116 | 1.3 | 80 | 92 | 56 | 77 | 264 | 303 |
| 3 | 95 | 5.2 | 87 | 92 | 71 | 83 | 281 | 249 |
| 4 | 98 | 0.2 | 82 | 93 | 59 | 68 | 368 | 400 |
| 5 | 91 | 0.5 | 79 | 97 | 71 | 79 | 410 | 415 |
| Average | 105 | 2.3 | 82 | 93 | 66 | 77 | 339 | 354 |
| SD | 13 | 2 | 3 | 2 | 8 | 5 | 56 | 66 |

PACES score = / 126, **DOMS score = 0 – 10, 6MWT = 6-minute walk test

**Figure 8.1** Study recruitment and approximate intervention time investment.

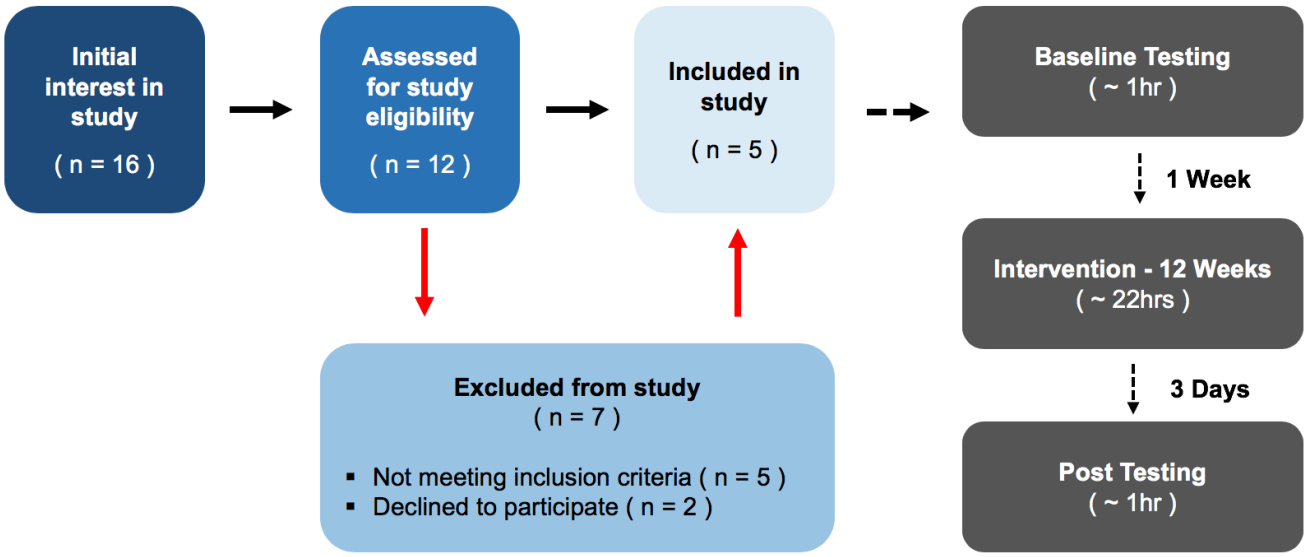
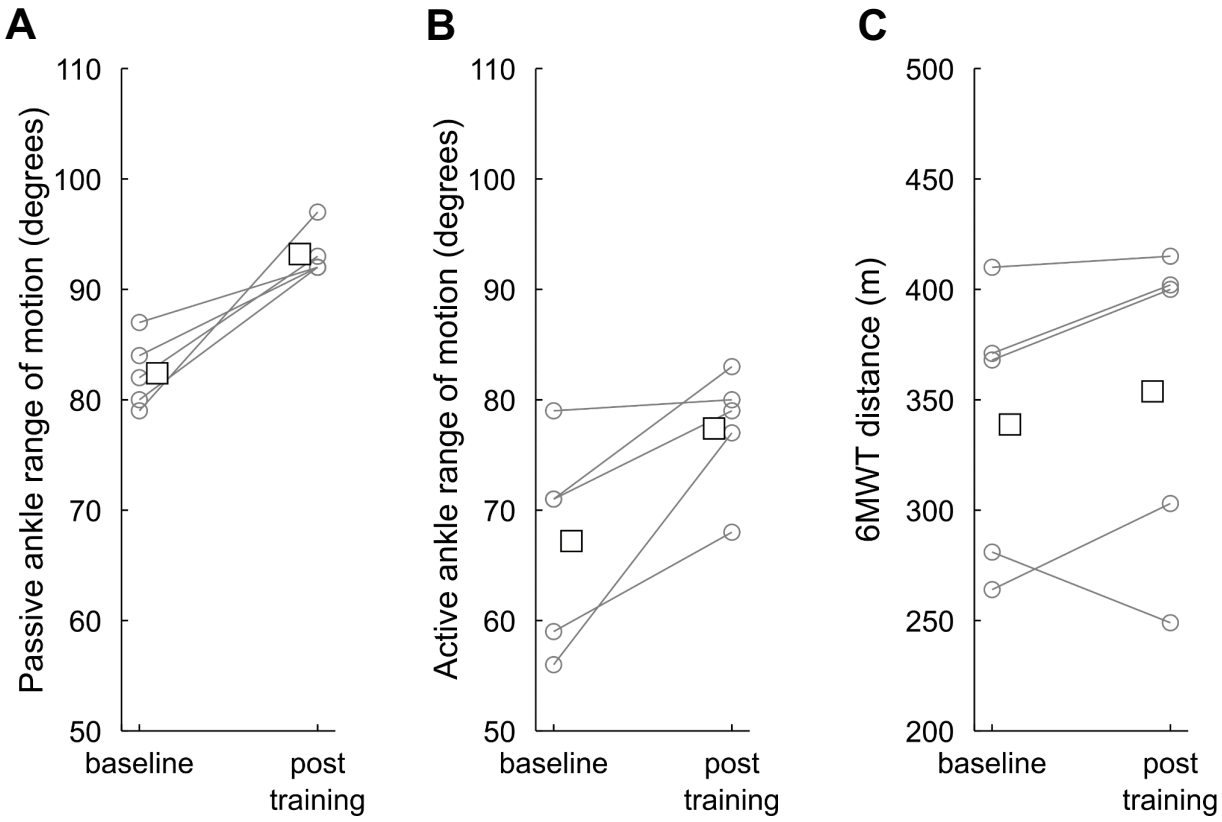


**Figure 8.2** Pre-Post Intervention Outcomes




Passive range of motion of the ankle **(A)**, active range of motion of the ankle **(B)** and 6MWT distance **(C)**. The individual grey unfilled circles represent the data points for each participant. Grey lines connect data from the same participant at baseline and post-training. The black unfilled squares represent the mean of all participants.

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# CHAPTER 9 - DISCUSSION

## 9.1 OVERVIEW

The aim of this thesis was to contribute new knowledge to the implications, measurement and treatment of ankle contractures in people with MS. This thesis highlighted novel methods to investigate these areas of focus. This section will summarise key findings and conclusions along with the potential implications and clinical utility of the research.

## 9.2 STUDY 1 - IMPAIRED HEEL TO TOE PROGRESSION DURING GAIT IS RELATED TO REDUCED ANKLE RANGE OF MOTION IN PEOPLE WITH MULTIPLE SCLEROSIS

### 9.2.1 KEY FINDINGS

Chapter 4 highlighted the novel use of a pressure sensitive walkway to calculate heel-to-toe progression in people with and without MS. To the best of our knowledge, our study was the first to apply this method and quantify heel-to-toe progression in the clinical setting. Results from this study demonstrated that heel-to-toe progression is impaired in people with MS. Compared to healthy controls, people with MS spent less time in the contact phase and more time in the mid-stance phase of gait. Heel-to-toe progression proved to be a sensitive measure and capable of differentiating between people with and without MS. Furthermore, our method (heel-to-toe progression) exposed gait abnormalities related to gait symmetry that traditional spatiotemporal measures were not able to not detect. Large effect sizes observed for both the contact phase and the mid-stance phase of gait indicates the potential clinical utility of assessing heel-to-toe progression objectively. Impaired heel-to-toe progression in people with MS was correlated with reductions in both ankle ROM and six-minute walk distance, highlighting a plausible functional pathway between clinically assessed contracture, inefficient gait patterns and reduced mobility in people with MS.

### 9.2.2 RESEARCH IMPLICATIONS & CLINICAL UTILITY

Pressure sensitive walkways require relatively little setup time, capture multiple footfalls and have been used successfully in a variety of populations including children [1], young adults, elderly [2] and people with MS [3]. Heel-to-toe progression is an objective measure that is easy to perform in the clinical setting (i.e. during a six-minute walk test). Ankle function is often inferred from static measurements (active

and passive ROM) and may not be a true representation of the impairment during walking. This method provides clinicians with a functional measure to assess ankle function in a dynamic setting that may help better inform rehabilitation interventions.

## **9.3 STUDY 2 -** WEARABLE TECHNOLOGY REVEALS GAIT COMPENSATIONS, UNSTABLE WALKING PATTERNS AND FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS

### 9.3.1 KEY FINDINGS

Chapter 5 highlighted the novel use of wearable devices to quantify compensatory head and pelvic movement patterns that occur in people with MS. Results from this study revealed compensation patterns strongly correlated with poorer ankle ROM and higher disability scores. Adaptive compensation strategies (such as hip hiking) could be necessary to clear the toe of the affected limb during the swing phase of gait. However, these compensation strategies resulted in asymmetries that negatively impacted gait stability. People with MS had reduced gait stability and therefore are at a higher risk of falls. Novel measures of gait symmetry and stability presented were found to be independent of the slower walking speeds observed in the people with MS. Furthermore, fatigue affected people with MS differently to healthy controls. Measures of gait variability, asymmetry, compensations and stability, deteriorated in people with MS between the first and last laps. The opposite occurred in healthy controls highlighting fatigue can exacerbate gait abnormalities in people with MS.

### 9.3.2 RESEARCH IMPLICATIONS & CLINICAL UTILITY

Wearable device technology provides a new inexpensive way to screen for excessive compensatory movements and provides clinically important information that impacts on both mobility and gait stability in people with MS. The method presented here may provide clinicians with insightful metrics that are useful for screening at-risk individuals in MS populations. Early detection of gait abnormalities can help clinicians identify people with MS who are at risk of falling and facilitate the earlier implementation of targeted rehabilitation interventions to address the underlying causes of gait impairments. While the underlying mechanisms behind the gait impairments have not yet been fully explored, asymmetries in gait patterns have functional implications related to walking symmetry and stability that can be detected using wearable device technology.

## **9.4 STUDY 3 -** THE VALIDITY AND RELIABILITY OF PASSIVE ANKLE DORSIFLEXION RANGE OF MOTION TECHNIQUES IN PEOPLE WITH MULTIPLE SCLEROSIS

### 9.4.1 KEY FINDINGS

Chapter 6 highlighted the use a novel device (Flexometer) that was developed to measure passive ankle range of motion in the clinical setting. The Flexometer design was influenced by previously established methods. However, our design improved on efficiency (i.e. instantaneous resultant ankle angles) and efficacy (i.e. single tester operation). Results demonstrated that the Flexometer had excellent test-re-test reliability in both positions (knee flexed and extended). While the WBLT can be used an alternative test in the clinical setting, the suitability of this test for patients with MS combined with inconsistent results (knee extended position) suggest care must be taken when interpreting these findings. Both methods were associated (moderate – high relationship) however, were not in perfect agreement and therefore not interchangeable.

### 9.4.2 RESEARCH IMPLICATIONS & CLINICAL UTILITY

Measurements of ankle ROM play an important role in the diagnosis of ankle contractures. Therefore, techniques must be both valid and reliable to increase the accuracy of the diagnosis. Unfortunately, current techniques are susceptible to measurement error and compromise the accuracy of testing. We developed a device for making standardised (torque-controlled) and reproducible measurements of ankle dorsiflexion. This device lays the foundation for standardised testing that can be used to classify contractures according to their severity, thus allowing for interventions to be implemented earlier in the disease progression to improve the likelihood for success.

## **9.5 STUDY 4 -** DO ECCENTRIC EXERCISE INTERVENTIONS IMPROVE ANKLE FLEXIBILITY? – A SYSTEMATIC REVIEW

### 9.5.1 KEY FINDINGS

Chapter 7 systematically reviewed and evaluated the existing knowledge of research in the field of eccentric exercise. Recent studies have found that commonly used interventions (such as stretching) for treating contractures do not elicit clinically significant results, warranting the need to investigate alternative treatment options (i.e. eccentric exercise). Eccentric exercise has the potential to alter muscle morphology and increase the length and extensibility of a muscle, thereby improving flexibility.

Based on the studies within our review, eccentric exercise appears to have a positive effect on ankle flexibility. However, due to the poor methodological quality of the studies within our review, the validity of previous findings must be interpreted with caution.

### 9.5.2 RESEARCH IMPLICATIONS & CLINICAL UTILITY

This review emphasised the lack of high-quality research focusing on eccentric exercise as an intervention to improve ankle flexibility. The lack of consensus regarding the outcomes, protocols, participants and study designs made it unsuitable to pool the results (i.e. conduct a meta-analysis) to summarise the effects of the intervention. This study was intended to assist clinical decision making in the rehabilitation setting however, further research is required to improve our understanding of the effectiveness of eccentric exercise to improve ankle flexibility.

## **9.6 STUDY 5 -** SAFETY, FEASIBILITY AND EFFICACY OF AN ECCENTRIC EXERCISE INTERVENTION IN PEOPLE WITH MULTIPLE SCLEROSIS WITH ANKLE CONTRACTURES – A CASE SERIES

### 9.6.1 KEY FINDINGS

Chapter 8 highlighted the use of a novel training modality (eccentric exercise - backwards walking downhill) in people with MS who have an ankle contracture. To date, no study had explored the potential benefit of backwards downhill walking to maximise eccentric loading in an attempt to improve ankle contractures in people with MS. Our study demonstrated backwards downhill walking was a novel, safe and feasible training modality in people with MS with an ankle contracture. These results were encouraging given preliminary observations reported large improvements in both passive and active ankle ROM, suggesting this training modality could be used to treat and manage ankle joint contractures in people with MS.

### 9.6.2 RESEARCH IMPLICATIONS & CLINICAL UTILITY

This study provides the foundation required to perform a more robust study (i.e. randomized controlled trial) that uses eccentric exercise to improve, treat and manage ankle joint contractures in people with MS. Given contractures are often associated with the severity of the disease (i.e. less ambulate patients) backwards walking downhill may be limited to those who are more ambulant given the complexity of the task. While we found improvements in ROM, such improvements did not clearly

translate to greater walking function and therefore requires further examination to be clinically meaningful for patients with MS. Eccentric exercise may play an important role in the prevention of contractures rather than being the antidote.

## 9.7 FUTURE RESEARCH & RECOMMENDATIONS

New techniques developed in this thesis provide applied methods that can be used to better define, diagnose and treat ankle joint contractures in people with MS. The applied nature of this thesis provides clinicians with new practical ways of improving the clinical care they offer their patients. However, there are several areas that require further investigation. This section will integrate the shortcomings and future research regarding current definitions, diagnosis and subsequent treatment of contractures in people with MS. Additionally, recommendations based on these findings are presented.

While there is no standardised definition for a contracture, they are associated with a reduction in ROM and an increase in joint stiffness. However, to date, much of the research has focused on using only measurements of ankle ROM as a diagnostic tool. We assessed passive ankle ROM using a torque-controlled method to identify ankle contractures in people with MS (< *90 degrees PROM @ 12Nm* = *Ankle Contracture*). While this method is commonly accepted, certain limitations associated with this definition could in fact play an important role in the subsequent treatment of ankle contractures in people with MS.

Contractures have been described previously as being either “elastic or rigid” in nature [4]. Elastic contractures are said to ‘give’ under loads such as passive resistance applied by a clinician or the patient’s body weight such as during gait. In contrast, a rigid contracture does not yield and is effectively fixed. In a way, contractures can be separated into different levels of “available movement” thereby categorising contractures by varying levels in ‘stiffness’. A proposed theoretical continuum is presented in figure 9.1 where a rigid contracture is associated with an increase in contracture severity that lessens as it progresses to elastic and ultimately non-existent (i.e. compliant). By categorising contractures based on severity, clinicians are able to make informed decisions regarding a patients rehabilitation and take a more appropriate course of action. Unfortunately, using the currently accepted definition, contractures are identified as being either present (i.e. 89 degrees) or absent (i.e. 91 degrees) and

lacks the capacity to account for the severity of the contracture based on the individual. Therefore, a more robust definition is required to classify people with MS into categories based on the severity of the contracture that can better inform clinical practice.

**Figure 9.1** Proposed continuum to explain ankle stiffness.


Given measures of ankle "stiffness" have been overlooked in the current diagnosis of a contracture, this thesis builds an excellent platform for the novel methods presented such as the implementation of the Flexometer and dynamic measures of ankle impairment to better classify contractures. Quantifying ankle "stiffness" in the clinical setting is challenging given large (lab-based) equipment and specialist training are often required. While not explored in this thesis, the Flexometer may overcome this limitation by allowing data output of continuous torque-angle curves (i.e. passive ankle stiffness). The Flexometer is portable and cheap (in comparison to an isokinetic dynamometer) that captures data outputs that are normally only available in a lab-setting. The accessibility of the device allows future research to assess ankle stiffness (in the clinical setting) that could prove useful in identifying and understanding ankle contractures from a "stiffness" standpoint that is often overlooked by single ROM methods. Using the theoretical contracture continuum (Figure 9.1), elastic contractures that yield under bodyweight (such as during gait) warrants the need for dynamic measures of ankle function to be included in the identification of an ankle contracture. Currently, ankle impairments are inferred from static measures with no research focusing on applying dynamic measures of ankle function to determine the severity of contracture. We reported various dynamic methods that have the potential to investigate the severity of a contracture based on how they impact gait and mobility. Future research is required to determine to what extent novel interventions aimed at treating contractures can influence gait mobility, stability and compensations in people with MS.

We presented eccentric exercise as a novel method to treat/manage ankle contractures in people with MS. While the mechanism of contractures still remains unclear, it is believed that contractures have both neural and non-neural components [5]. Non-neural components, such as adaptations in muscle morphology seem to be isolated to muscle fascicles in people with MS (i.e. shorter and stiffer fascicles). Therefore, interventions (eccentric exercise) aimed at improving the extensibility and length of a muscle would be of great benefit to target the non-neural component of contractures. Additionally, eccentric interventions may be useful to alter the neural component of contractures. Stretch reflexes are often used as indicators of spasticity [6]. Eccentric exercise has been shown to reduce the stretch reflex sensitivity of muscles [7]. This could be advantageous for people who are affected by spasticity as it is associated with increased excitability of stretch reflexes. Therefore, eccentric interventions could play a role in reducing the both the neural and non-neural components of contractures warranting the need for further investigation.

While improving ROM (i.e. improving contractures) is important, little research has focused on how this translates to function. Arguably, improving function is the most important aspect of rehabilitation. Therefore, interventions that improve ROM must translate to functional outcomes to enhance the efficacy of the intervention. For an intervention to be clinically worthwhile, it ultimately should improve the quality of life of the recipient. Thus, it poses the question, *"Are there any plausible connections between improvements in ankle ROM and improvements in quality of life?".* While there is no evidence to directly answer this question, the link is plausible given gait is perceived as the most valuable bodily function in people with MS [8]. Therefore, if improvements in ROM translate to meaningful improvements in gait, it seems reasonable to believe that it will improve quality of life by empowering people with MS to regain their functional independence. Ensuring future research that focuses on the translational capacity of outcomes to improvements in quality of life is vital if we are to continue to seek benefits for people with MS.

Recommendations for future research aimed at identifying ankle contractures should focus on broadening the scope of the current definition. For normal ambulation, a minimum of 10 degrees (i.e. 100 degrees) of dorsiflexion is necessary [9]. Therefore, the current inclusion criteria (< 90 degrees) may be too strict and limit the applicability for intervention-based studies. For example, Chapter 8

highlighted this issue as 42% of patients with MS were excluded from the study as (by definition) they did not have a contracture. We believe that by expanding the current inclusion criteria (< 100) we will be able to include more patients with "impaired" ankle ROM in interventions that could be used to restrict ankle contracture decline rather than waiting for the condition to sufficiently deteriorate in order to meet inclusion criteria.

Additionally, we recommend exploring the degree of stiffness present in the joint and not just the amount of range available. The saying, *"all roads lead to Rome",* can't be applied to this case as patients can achieve the same outcome (end range of motion) but have very different torque-angle curves (i.e. passive ankle stiffness), therefore, *"not all roads lead to Rome"*. Measures of stiffness provide meaningful data related to extensibility of the joint that can influence function. Ankle function is often inferred from static measurements but may not be a true representation of the impairment during walking. Therefore, there is a need to combine static measures (ROM + Stiffness) with dynamic measures of ankle impairment to better classify contractures based on their severity and impact.

Finally, measures of range, stiffness and function should account for individual-interlimb-variability. If a patient is naturally "hypermobile" despite having a contracture, they are less likely to fit the 'one size fits all' diagnosis. For example, a patient with MS could have 135 degrees of ankle ROM on their "less affected" side and 105 degrees on their "more affected" side. As the patient scored more than 100 degrees of ROM on their "affected" side (as per our new definition) they are still considered to not have a contracture. However, when compared to their "less affected side", a difference (20 degrees) indicates that the affected ankle has compromised range. Therefore, measurements must be performed on both the affected and un-affected sides in order for direct comparison to occur. Further research is needed to better implement an asymmetry ratio that will help account for individual variability.

By improving the current definition of ankle contractures, we can carefully and accurately monitor the progression of contractures in people with MS by tracking them longitudinally over the course of their disease. This will help us better understand the trajectory of ankle contractures to help inform when interventions are most likely to be implemented and the likelihood of their success (i.e. prevention is better than a cure).

## 9.8 FINAL REMARKS

Ankle contractures are common in people with MS and negatively impact gait. Current diagnostic criteria may lack the sensitivity to detect ankle contractures in people with MS. Methods explored in this thesis may overcome these limitations by combining measures of range, stiffness and function to classify people with MS into categories based on the severity of their contracture that can better inform clinical practice. Ankle contractures alter muscle morphology leading to shorter, stiffer muscle fascicles in people with MS. There is evidence to suggest that eccentric exercise may counteract these changes and was explored via novel methods (backwards walking downhill) within this thesis. While preliminary results were promising, additional research is required to better treat and manage ankle joint contractures in people with MS.

## 9.9 REFERENCES


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# APPENDICES

## APPENDIX A - MANUSCRIPT DRAFT

*SHORT COMMUNICATION*

### PASSIVE MECHANICAL PROPERTIES OF THE GASTROCNEMIUS IN PEOPLE WITH MULTIPLE SCLEROSIS WHO HAVE DEVELOPED ANKLE CONTRACTURES

Phu Hoang[1], **Michael Psarakis[2]**, Joanna Diong[1,3], Li Khim Kwah, Simon Gandevia[1], Rob Herbert[1].

[1] Neuroscience Research Australia, (NEURA)
[2] Faculty of Health Sciences, Australian Catholic University, Australia
[3] School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, Australia

**Background -** Ankle contractures are common in people with multiple sclerosis. This study aimed to investigate the mechanisms of contracture in multiple sclerosis by comparing passive mechanical properties of gastrocnemius muscle-tendon units, muscle fascicles and tendons in people with multiple sclerosis who had ankle contractures with able-bodied controls.

**Methods -** Passive gastrocnemius length-tension curves were derived from passive ankle torque-angle data obtained from 15 multiple sclerosis participants with ankle contractures and 30 able-bodied controls. Ultrasound images of muscle fascicles were used to partition length-tension curves into fascicular and tendinous components. Main comparisons were stiffness and lengths of gastrocnemius muscle-tendon units, lengths of muscle fascicles and tendons at specific tensions.

**Findings -** Slack lengths of muscle fascicles were significantly shorter in multiple sclerosis participants (mean, 3.0 cm) compared with able-bodied controls (mean, 3.8 cm; $p = <0.001$). Multiple sclerosis participants had significantly shorter muscle fascicles lengths at 100N (mean, 4.4 cm) than able-bodied controls (mean, 5.1 cm; $p = 0.024$). There were no significant differences in the muscle tendon unit or tendon between groups.

**Interpretation -** These results suggest altered passive mechanical properties of the gastrocnemius in multiple sclerosis participants who have developed an ankle contracture could be isolated to adaptations occurring in the muscle fascicles. Understanding the mechanism of contracture may help with the development of interventions to prevent and treat ankle contractures in people with multiple sclerosis.

**Key words:** Ankle Range of Motion, Muscle Tendon Unit, Slack length, Ultrasound, Muscle Fascicles

## 1. INTRODUCTION

Contractures (loss of passive joint range of motion) are common in neurological conditions such as multiple sclerosis [1]. Joint contractures affect approximately 57% of all those with multiple sclerosis and the ankle joint is the most common site for contractures [2]. Ankle contractures are disabling as they impede ankle range of motion. Full ankle range of motion is essential for normal ambulation [3] consequently, ankle contractures play a role in the loss of mobility and physical independence in people with multiple sclerosis [4, 5].

While the exact mechanism of contracture remains unknown, it is hypothesised that contractures alter the passive mechanical properties of muscles. Previous research investigating the mechanism of contracture has examined the passive mechanical properties of the gastrocnemius muscle in various neurological conditions such as spinal cord [6], stroke [7, 8], cerebral palsy [9] and multiple sclerosis [10]. However, findings seem to be somewhat conflicting. Spinal cord injured patients demonstrated stiffer but not shorter gastrocnemius muscle tendon units when compared to able bodied controls. Conversely, stroke patients demonstrated shorter muscle tendon units and muscle fascicles but only when measured at high tensions. These results were consistent with previous research that highlighted stiffer, shorter muscle fascicles in stroke patients [8]. Similarly, young adults with cerebral palsy appear to have stiffer muscle fascicles [9]. These studies provide evidence that the adaptations occurring in ankle joint contractures are not consistent and depend on the condition.

Investigations into the mechanism of contracture in people with multiple sclerosis found no significant differences in the compliance of the gastrocnemius muscle tendon units when compared to able bodied controls [10]. These results may be attributed at least in part to the patients assessed. Multiple sclerosis patients who participated in the study did not have an ankle contracture therefore, may not have had alterations in their muscle morphology. It was presumed that being highly ambulant may help preserve the passive properties of gastrocnemius and therefore requires further investigation.

Therefore, extending on previous literature, we aim to determine the mechanisms of contracture by comparing the passive mechanical properties of gastrocnemius muscle in people with multiple sclerosis who have an ankle contracture with able-bodied controls.

## 2. METHODS

### *2.1 Participants*

Fifteen people diagnosed with multiple sclerosis and 30 able bodied controls participated in the study. To be included in the study, multiple sclerosis participants had to have; i) a confirmed diagnosis of multiple sclerosis by a neurologist; ii) an ankle contracture – defined as less than or equal to 90 degrees of ankle dorsiflexion range of motion when a dorsiflexion torque of 12Nm was applied to their relaxed

ankle; iii) free from any other disease, injury or illness preventing them from participating in the testing procedure. Participants were excluded if they had any prior history of ankle fractures or surgery. All participants gave written informed consent and the study was approved by the Human Research Ethics Committee at the University of Sydney.

### *2.2 Measurement of Passive Length-Tension and Muscle Fascicle Lengths*

Techniques developed by Hoang et al. (2007) allow for the isolation of the gastrocnemius muscle tendon unit from other structures to better understand the involvement of muscle fascicles and tendons on the total muscle tendon unit. Ultrasound images of muscle fascicles are partitioned into length-tension curves that divide components into fascicular and tendinous contributions at known tensions.

This methodology has previously been published by Diong et al. (2012) and Kwah et al. (2012). Briefly, ankle torque-angle data was collected with participants laying supine with 1 foot secured onto a footplate. The footplate collected data using a force transducer and potentiometer that was sampled at 50Hz. To minimise effects of thixotrophy on muscle, the ankle was moved passively for 6 cycles through maximum available range of motion before recording data. Torque-angle data were recorded throughout 3 full cycles (plantar flexion to dorsiflexion) and repeated for 6 knee angles (~ 0°,20°,40°,60°,80°,100°) with their order randomised. To ensure participants were relaxed (muscle were passive), muscle activity was monitored using surface electromyography (EMG). Electrodes (10 mm diameter) were placed on the lateral gastrocnemius and tibialis anterior muscles (30 mm spacing). EMG signals were band-pass filtered (30-1000Hz) and sampled at 2000Hz. Any activity of EMG throughout trials were discarded prior to subsequent analysis.

Torque-angle data were used to estimate passive length tension curves of the gastrocnemius and combined with ultrasound data that measured muscle fascicle lengths of the gastrocnemius. Ultrasound data was collected using two portable systems (LA523E linear array, 7.5-12MHz operating at 12MHz, 46-mm field of view) that were connected to increase the field of view. Image quality was supervised by an experienced qualified sonographer to ensure fascicles could be clearly identified. Ultrasound images were sampled at 15Hz with a dual channel video capture card and digitally stitched together generating a single video with a field of view 110mm wide and 40mm deep.

Custom software was used to track three fascicles at each of the 6 knee angles (18 fascicles per participant). Tracked muscle fascicles were plotted alongside their corresponding gastrocnemius muscle tendon unit length and a “typical fascicle” was selected by an assessor who was blinded as to whether data were from a multiple sclerosis or control participant. The length of the tracked fascicles and the length of gastrocnemius were fitted with a piecewise third order polynomial and used to calculate (at what) gastrocnemius muscle tendon length did muscle fascicles fall slack and what was the corresponding fascicle slack length. Tendon length was estimated by subtracting the longitudinal displacement of muscle fascicles from the muscle-tendon unit. Muscle fascicles were measured at 100N (high tension) and measured fascicle slack length (low tension) in all subjects.

*2.3 Data analysis*

Linear models were used to make comparisons between groups for the following outcome variables: slack length of the muscle tendon unit, stiffness index of the muscle tendon unit and lengths of the muscle tendon unit, muscle fascicles and tendons. Comparison of lengths were made at the length in which fascicles fell slack and 100N. Likelihood ratio tests were used to assess the possibility that these comparisons were confounded by differences between groups in age and sex. Where results were significant (P<.05) adjustments for confounders were made by including them into the linear models.

## 3. RESULTS

Characteristics of multiple sclerosis and able-bodied controls are shown in table 1. The mean years living with multiple sclerosis from time of diagnosis to data collection was 15 years (SD = 11). People with multiple sclerosis had significantly reduced ankle dorsiflexion range of motion (mean, 78 ° vs 95 ° ; p = <0.001) and longer shank lengths (mean, 43.0 cm vs 40.5 cm ; p = 0.05). Due to the differences in shank lengths between groups outcomes were adjusted by shank lengths to reduce variability between subjects.

*Muscle Tendon Unit*

Muscle-tendon unit length-tension curves of multiple sclerosis and able-bodied participants are shown in Figure 1. There were no significant differences between groups in all comparisons (Table 2).

*Fascicle*

People with multiple sclerosis had shorter fascicle slack lengths compared to able bodied controls (table 2). Additionally, multiple sclerosis participants had shorter muscle fascicles lengths at 100N than able bodied controls (Table 2). There was no significant difference in the change of length from 1-100N between groups.

*Tendon*

There were no significant differences between groups in other outcomes (Table 2).

## 4. DISCUSSION

Our results demonstrate that people with multiple sclerosis who have an ankle contracture had altered passive mechanical properties of the gastrocnemius muscle. Contrary to previous findings [10], we observed that people with multiple sclerosis had shorter muscle fascicles and shorter fascicle slack lengths relative to able-bodied controls. There was no significant difference in the muscle tendon unit or tendon between groups. These findings suggest altered passive mechanical properties of the gastrocnemius muscle may be isolated to adaptations occurring within the muscle fascicles in people with multiple sclerosis.

Our findings of shorter fascicle lengths may be attributed at least in part to the reduction of sarcomeres in series. Skeletal muscle is highly adaptive and can remodel depending on its functional demands [11]. Stretch has shown to be an important signal for remodelling via longitudinal muscle growth known as sarcomerogenesis [11]. In contrast, when a muscle is deprived of stretch (i.e. immobilised) the opposite can occur [12]. In contracture, a reduction in the available range of motion may simulate an immobilised (stretch deprived) muscle causing a reduction in muscle fascicle length. Additionally, immobilising a muscle in a shortened position can negatively impact its passive extensibility [12]. Our study suggests ankle contractures cause a leftward shift in muscle fascicle slack lengths, meaning muscle fascicles develop passive tension at shorter lengths. Ultimately, the combination of shorter muscle fascicles and shorter fascicle slack lengths means less compliant (stiffer) muscle fascicles in people with multiple sclerosis who have developed ankle contractures. Our findings are somewhat consistent with previous research in young adults with cerebral palsy that found ankle stiffness to be associate with the inability of muscle fascicles to lengthen when passively stretched.

Despite having significantly less ankle range of motion when measured clinically, our data showed no significant differences in total muscle tendon unit stiffness or length. These results are in contrast to previous findings that have shown less joint range when clinically measured resulted in greater muscle tendon unit stiffness [6]. Our study ran parallel to others previously published in spinal cord injured patients [6] and stroke patients [7] (table 3). The comparison between the groups demonstrates that the impact of contractures seems to vary depending on the condition, with few studies reporting consistent measures. One measure consistent to MS patients and stroke patients was shorter muscle fascicles. This information is important for future research aimed at improving muscle fascicle lengths. Treatment modalities, (such as eccentric exercise) have shown to alter muscle morphology by improving muscle fascicle length. Therefore, eccentric exercise may target the deficit present within muscles affected by contracture in MS patients and stroke patients.

## 5. CONCLUSION

People with multiple sclerosis who have developed an ankle contracture have altered passive mechanical properties of the gastrocnemius muscle that are isolated to changes in muscle fascicles. Understanding the mechanism of contracture may help with the development of interventions to prevent and treat ankle contractures in people with multiple sclerosis.

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**Table 1.** Characteristics of participants.

| | **Control** (n = 25) | **Multiple Sclerosis** (n = 15) | **p** |
|---|---|---|---|
| Age (years) | 48.0 ± 21 | 52.8 ± 12 | 0.42 |
| Gender (M:F) | 10 : 15 | 10 : 5 | - |
| Height (m) | 1.69 ± 0.09 | 1.75 ± 0.12 | 0.08 |
| Weight (kg) | 72 ± 17 | 77 ± 14 | 0.34 |
| Shank length (cm) | 40.5 ± 3.2 | 43.0 ± 4.5 | **0.05 *** |
| Clinical ankle range at 12 Nm (°) | 95 ± 12 | 78 ± 8 | **< 0.001 *** |
| Year's with Multiple Sclerosis | - | 15 ± 11 | - |

Data expressed as mean ± SD, expect where indicated

*** Significant between-group differences (p < 0.05).**

**Table 2.** Passive mechanical properties of gastrocnemius muscle-tendon units, muscle fascicles and tendons in multiple sclerosis and control participants.

| Structure | Control | | | Multiple Sclerosis | | | Difference (95% CI) | p |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | **Adj*** | Mean | SD | **Adj*** | | |
| **Muscle-tendon unit** | | | | | | | | |
| Slack length (cm) | 35.1 | 4.9 | 36.0 | 38.6 | 5.3 | 37.2 | 1.2 ( - 1.4 to 3.9 ) | 0.355 |
| Stiffness ($m^{-1}$) | 54.4 | 17.7 | 53.4 | 62.8 | 25.5 | 64.5 | 11.1 ( - 3.4 to 25.7 ) | 0.128 |
| Length at 100 N (cm) | 44.4 | 3.6 | 45.3 | 47.1 | 4.4 | 45.5 | 0.2 ( - 0.7 to 1.2 ) | 0.631 |
| Length at fascicle slack (cm) | 41.7 | 3.5 | 42.6 | 44.6 | 5 | 42.9 | 0.3 ( - 0.7 to 1.3 ) | 0.583 |
| **Fascicle** | | | | | | | | |
| Slack length (cm) | 3.8 | 0.6 | 3.8 | 3.1 | 0.6 | 3.0 | -0.8 ( - 1.2 to - 0.4 ) | **< 0.001*** |
| Length at 100 N (cm) | 5.1 | 0.9 | 5.1 | 4.4 | 0.7 | 4.4 | -0.7 ( - 1.3 to - 0.1 ) | **0.024*** |
| Change in length from 1-100 N (cm) | 1.3 | 0.7 | 1.2 | 1.3 | 0.7 | 1.3 | 0.1 ( - 0.4 to 0.5 ) | 0.713 |
| **Tendon** | | | | | | | | |
| Slack length (cm) | 37.9 | 3.5 | 38.8 | 41.4 | 4.7 | 39.9 | 1.0 ( - 0.2 to 2.1 ) | 0.054 |
| Length at 100 N (cm) | 39.4 | 3.6 | 40.2 | 42.7 | 4.6 | 41.2 | 0.9 ( - 0.1 to 1.9 ) | 0.069 |
| Change in length from 1-100 N (cm) | 1.4 | 0.5 | 1.4 | 1.3 | 0.5 | 1.3 | -0.1 ( - 0.4 to 0.3 ) | 0.600 |

Adj* = means adjusted by shank lengths

*** Significant between-group differences (p < 0.05).**

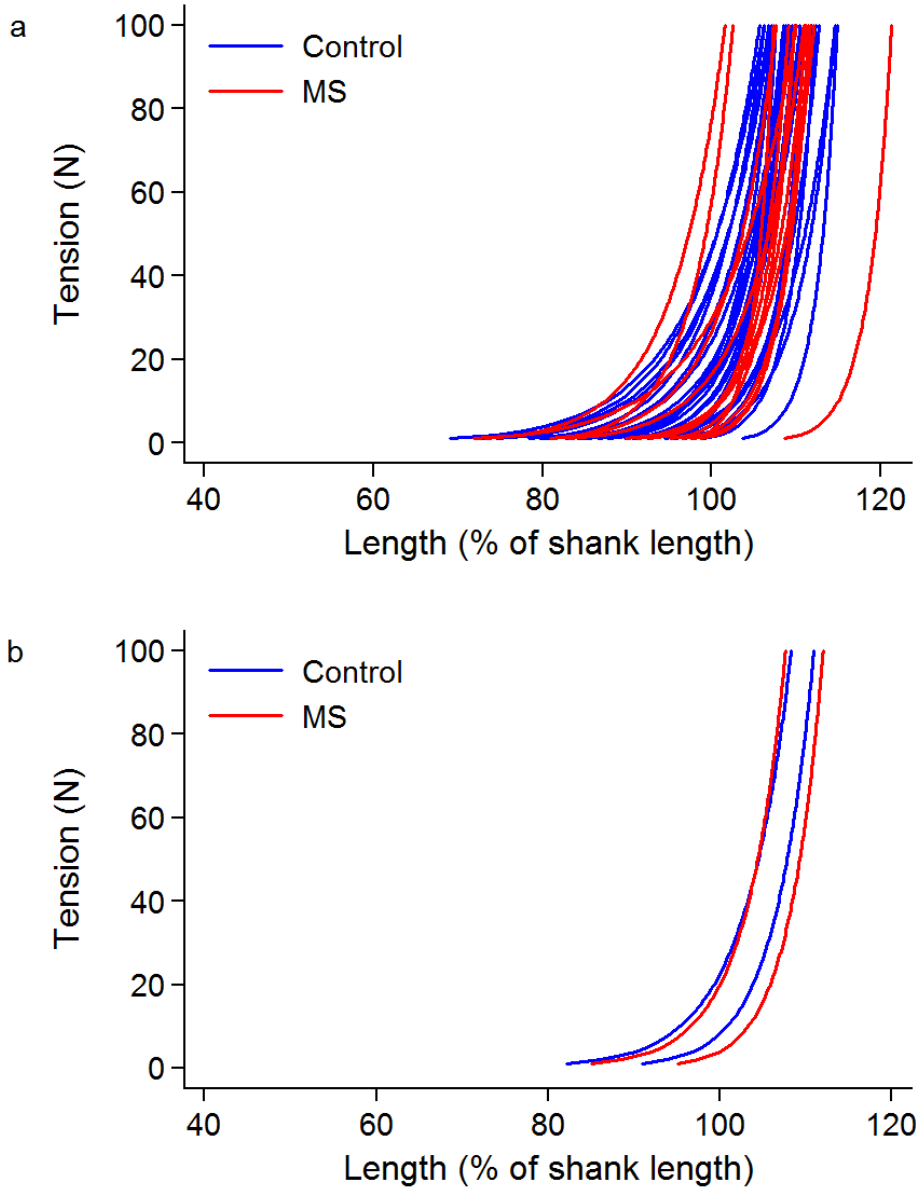
**Table 3.** Group means comparison of passive mechanical properties of gastrocnemius muscle-tendon units, muscle fascicles and tendons. All means were adjusted by shank lengths.

| Structure | Control | Multiple Sclerosis | Spinal Cord* | Stoke** |
|---|---|---|---|---|
| **Muscle-tendon unit** | | | | |
| Slack length (cm) | 36.0 | 37.2 | 36.9 | - |
| Stiffness ($m^{-1}$) | 53.4 | 64.5 | 75.2 | 63 |
| Length at 100 N (cm) | 45.3 | 45.5 | 43.9 | 43.6 |
| Length at fascicle slack (cm) | 42.6 | 42.9 | - | 41.6 |
| **Fascicle** | | | | |
| Slack length (cm) | 3.8 | 3.0 | 3.6 | 3.5 |
| Length at 100 N (cm) | 5.1 | 4.4 | 4.7 | 4.4 |
| Change in length from 1-100 N (cm) | 1.2 | 1.3 | 1.1 | 0.8 |
| **Tendon** | | | | |
| Slack length (cm) | 38.8 | 39.9 | 37.8 | 38.0 |
| Length at 100 N (cm) | 40.2 | 41.2 | 39 | 38.8 |
| Change in length from 1-100 N (cm) | 1.4 | 1.3 | 1.4 | 1.3 |

* Diong et al. 2012 [6]

** Kwah et al. 2012 [7]

**Figure 1:** Length tension curves of muscle tendon units.




**a)** Muscle-tendon unit length-tension curves of multiple sclerosis and control participants.

**b)** 95% CI of mean muscle-tendon unit length-tension curves of multiple sclerosis and control participants. Curves were generated by calculating 95% CIs about mean muscle-tendon length at each tension.

## APPENDIX B - ETHICS

Dear David,

Ethics Register Number : 2013 312N
Project Title : EFFECTS OF ECCENTRIC TRAINING ON ANKLE JOINT CONTRACTURE IN PEOPLE WITH MULTIPLE SCLEROSIS
Data Collection Date Extended : 30/05/2017

Thank you for sending the extension approval letter from UNSW for your project.

The Deputy Chair of the Human Research Ethics Committee has noted the modification. The new expiry date for the project is the 30/05/2017.

We wish you well in this ongoing project.

Regards,

Pratigya

**Pratigya Pozniak**
**Project Officer, Research Support | Research**
**Australian Catholic University**

ACU AUSTRALIAN CATHOLIC UNIVERSITY

Level 4, 21 Berry Street, North Sydney, NSW 2060
**T:** +61 2 9739 2182 **F:** +61 2 9739 2870

**E:** Pratigya.Pozniak@acu.edu.au **W:** www.acu.edu.au

**From:** Ms Pratigya Pozniak <pratigya.pozniak@acu.edu.au>
**Date:** 5 July 2018 at 11:35:46 am AEST
**To:** "Assoc. Prof. David Greene" <david.greene@acu.edu.au>
**Cc:** Ms Pratigya Pozniak <pratigya.pozniak@acu.edu.au>
**Subject: 2013 312N Extension approved**

Dear David

Ethics Register Number : 2013 312N
Project Title : EFFECTS OF ECCENTRIC TRAINING ON ANKLE JOINT CONTRACTURE IN PEOPLE WITH MULTIPLE SCLEROSIS
Data Collection Date Extended : 12/05/2019

Thank you for returning the Ethics Progress Report for your project.

The Deputy Chair of the Human Research Ethics Committee has approved your request to extend the project. The new expiry date for the project is the 12/05/2019 .

We wish you well in this ongoing project.

Kind regards,
Ms Pratigya Pozniak

Research Ethics Officer | Office of the Deputy Vice-Chancellor (Research)
Australian Catholic University
T: 02 9739 2646 E: res.ethics@acu.edu.au

[redacted]

THE UNIVERSITY OF NEW SOUTH WALES

28 November 2008

RECEIVED DATE 5-12-08 BY ATR

HUMAN RESEARCH ETHICS COMMITTEE (HREC)

Dr Phu Hoang
Prince of Wales Medical Research Institute
PO Box 82,
St Pauls NSW 2031

Dear Dr Hoang,

**Muscle contractures in multiple sclerosis- Prevalence and rehabilitation**
*(HREC 08288)*

Thank you for your email and attachments to Mrs Annamarie D'Souza dated 17 November 2008.

At the Executive Meeting held on 25 November 2008, the Committee provided approval for the above project to proceed. In accordance with the guidelines set out in the National Statement on Ethical Conduct in Research Involving Humans* (NS) and exercising the authority delegated by the Deputy Vice-Chancellor (Research), I give permission for this project to proceed.

Would you please note:-

- approval is valid for five years (from the date of the executive meeting i.e.25 November 2008);
- you will be required to provide annual reports on the study's progress and any adverse events to the HREC, as recommended by the National Statement on Ethical Conduct in Research Involving Humans;
- you are required to immediately report anything which might warrant review of ethical approval of the protocol (NS 2.37), including:

  (a) serious or unexpected adverse effects on participants;
  (b) proposed changes in the protocol; and
  (c) unforeseen events that might affect continued ethical acceptability of the project;

- any modifications to the project must have the prior written approval of the Committee;

.. 1 ..

UNSW SYDNEY NSW 2052
A U S T R A L I A
Telephone: +61 (2) 9385 4234
Facsimile: +61 (2) 9385 6648
Email: ethics.sec@unsw.edu.au
Location: Rupert Myers Building
C/o Research Office Ethics
Gate 14 Barker Street Kensington
ABN 57 195 873 179

(08288. cont'd)



- the Ethics Secretariat should be notified if serious or unexpected outcomes are experienced by research participants of if there are unforseen events;
- consent forms are to be retained within the archives of the Institute and made available to the Committee upon request;
- if this approval relates to a clinical trial any serious adverse event arising in the course of the study should be reported promptly using the proforma on the Human Research Ethics website at http://www.ro.unsw.edu.au/ethics/human/

Yours sincerely,

[redacted]

A/Professor Andrew Metcalfe
Presiding Member
HREC

* http:/www.nhmrc.gov.au

HUMAN RESEARCH ETHICS
COMMITTEE (HREC)

19-May-2014
Dr Phu Hoang
Sydney NSW 2052

Dear Dr Hoang,

HREC Ref: # HC14073
**EFFECTS OF ECCENTRIC TRAINING ON ANKLE JOINT CONTRACTURE IN PEOPLE WITH MULTIPLE SCLEROSIS**

The Human Research Ethics Committee considered the above protocol at its meeting held on 13-May-2014 and is pleased to advise it is satisfied that this protocol meets the requirements as set out in the National Statement on Ethical Conduct in Human Research*. Having taken into account the advice of the Committee, the Deputy Vice-Chancellor (Research) has approved the project to proceed.
Would you please note:-

- approval is valid from 13-May-2014 to 12-May-2019;
- you will be required to provide annual reports on the studys progress to the HREC, as recommended by the National Statement;
- you are required to immediately report to the Ethics Secretariat anything which might warrant review of ethical approval of the protocol (National Statement 3.3.22, 5.5.7: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf) including:
  - serious or unexpected outcomes experienced by research participants (using the Serious Adverse Event proforma on the University website at http://research.unsw.edu.au/human-ethics-forms-and-proformas ;
  - proposed changes in the protocol; and
  - unforeseen events or new information (eg. from other studies) that might affect continued ethical acceptability of the project or may indicate the need for amendments to the protocol;
- any modifications to the project must have prior written approval and be ratified by any other relevant Human Research Ethics Committee, as appropriate;
- if there are implantable devices, the researcher must establish a system for tracking the participants with implantable devices for the lifetime of the device (with consent) and report any device incidents to the TGA;
- if the research project is discontinued before the expected date of completion, the researcher is required to inform the HREC and other relevant institutions (and where possible, research participants), giving reasons. For multi-site research, or where there has been multiple ethical review, the researcher must advise how this will be communicated before the research begins (National Statement 3.3.22, 5.5.7: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf);
- consent forms are to be retained within the archives of the APPP - Sch of Medical Sciences and made available to the Committee upon request.

Sincerely,

[redacted]

Professor Heather Worth
Presiding Member
Human Research Ethics Committee

* http://www.nhmrc.gov.au

Human Research Ethics Committee (HREC)
The University of New South Wales
UNSW Sydney, NSW, Australia, 2052
E: humanethics@unsw.edu.au
W:https://research.unsw.edu.au/human-research-ethics-home

15-Apr-2015

Dear Dr Phu Hoang,

| | |
|---|---|
| **Project Title** | EFFECTS OF ECCENTRIC TRAINING ON ANKLE JOINT CONTRACTURE IN PEOPLE WITH MULTIPLE SCLEROSIS |
| **HC No** | HC14073 |
| **Re** | Modification request received from Phu Hoang dated 10 April 2015 re: request for extension until May 2017. |

The modification to this project submitted on 10-Apr-2015 was **approved** by the **HREC Executive** on 14-Apr-2015.

If this project is a multicentre project you must forward a copy of this letter to all Investigators at other sites for their records.

If this project is a multicentre project you must forward a copy of this letter to all Investigators at other sites for their records.

Should you require any further information, please contact the Ethics Administrator at:

E: humanethics@unsw.edu.au
W:https://research.unsw.edu.au/human-research-ethics-home

The HREC Executive wishes you every continued success in your research.

Kind Regards

[redacted]

Professor Heather Worth
HREC Presiding Chairperson

# PARTICIPANT INFORMATION LETTER

**PROJECT TITLE:** Effects of eccentric exercise on calf muscle contracture in people with multiple sclerosis

**PRINCIPAL INVESTIGATOR:** Dr David Greene
**CO INVESTIGATORS:** Dr Michael Baker
Dr Phu Hoang

Dear Participant,

You are invited to participate in the research project described below.

***What is the project about?***
The research project investigates the effects of a novel approach to treatment of muscle contracture in people with multiple sclerosis (MS). You were selected as a potential participant in this study because you have been diagnosed with MS and have an ankle contracture (or stiff ankle) as a result of MS.

***Who is undertaking the project?***
This project is being conducted by Dr David Greene in the School of Exercise Science in collaboration with Neuroscience Research Australia (NeuRA).

***What will I be asked to do?***
If you decide to participate, we will ask you to visit NeuRA (on Barker St, Randwick) for testing of your ankle. The testing will take approximately two hours. Testing involves using a machine to measure the stiffness and strength of your ankle muscles. The test is painless and is not associated with any risks. You will be asked to perform a walking test and fill out a questionnaire about your perceived difficulty in mobility. In addition, you will be asked to place your foot on a wooden board, while sitting in a chair, and asked to perform 30 trials of dorsiflexion (pulling your toes towards you with your heel on the ground) to touch a metal rod. This is a painless test with no risk of injury.
After testing we will allocate you to one of two groups. You have an equal chance of being allocated to either group. You will not be able to choose which group you will be allocated to. Regardless which group you are allocated, we ask you not to change your current physical activities or exercise regime. One of researchers (Dr Phu Hoang) will be available for consultations regarding exercises.
Participants in one group will be asked to visit a gym (MS Studdy Centre in Lidcombe or Australian Catholic University in Strathfield, depending on your convenience) two times each week for twelve weeks (24 visits). Each visit will last about 45-60 minutes. During the visit we will exercise your ankle muscles by walking backwards and downhill on a treadmill.

***Are there any risks associated with participating in this project?***
There are three possible negative consequences of completing the exercises: this type of exercise is known to produce muscle soreness - the same sort of soreness that people normally experience after they participate in unaccustomed physical activity. We expect that, if you are allocated to the group that does this exercise, you will experience muscle soreness. However, the muscle soreness will gradually be less and less over the 12-week period. To minimize this muscle soreness, you will be trained at low intensity at the start of the project with gradually increasing intensity over the first 8 sessions.

***How much time will the project take?***
Initial and final testing will take about two hours. Each visit will last approximately 45-60min two times each week for twelve weeks (24 visits).

***What are the benefits of the research project?***
We cannot and do not guarantee or promise that you will receive any benefits from this study. Participants assigned to the exercise group will receive an individual exercise program to complete onsite. As a consequence, participants assigned to this group may experience improvements in mobility. All participants will receive an individual report outlining their performance in the study. Individual results will not be disclosed to any other people associated with the study.

***Can I withdraw from the study?***
Participation in this study is completely voluntary. You are not under any obligation to participate. If you agree to participate, you can withdraw from the study at any time without adverse consequences. Your withdrawal will not affect your relationships with MS Clinic at Brain and Mind Research Institute or MS Australia ACT/NSW/VIC or Neuroscience Research Australia or Australian Catholic University. Your withdrawal will not either affect your ongoing treatment.

***Will anyone else know the results of the project?***
Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission, except as required by law. If you give us your permission by signing this document, we plan to publish the results in relevant scientific journals. In any publication, information will be provided in such a way that you cannot be identified.

***Will I be able to find out the results of the project?***
Group means will be published in peer-reviewed scientific journals and may be disseminated at State, National, and International conferences. All participants will receive an individual report outlining their performance in the study.

***Who do I contact if I have questions about the project?***
If you have any additional questions, Dr David Greene (telephone 9701 4377) will be happy to answer them.

***What if I have a complaint or any concerns?***

The study has been approved by the Human Research Ethics Committee at Australian Catholic University (approval number 2013 312N). If you have any complaints or concerns about the conduct of the project, you may write to the Chair of the Human Research Ethics Committee care of the Office of the Deputy Vice Chancellor (Research).

Chair, HREC
c/o Office of the Deputy Vice Chancellor (Research)
Australian Catholic University
Melbourne Campus
Locked Bag 4115
FITZROY, VIC, 3065
Ph: 03 9953 3150
Fax: 03 9953 3315
Email: res.ethics@acu.edu.au

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

***I want to participate! How do I sign up?***
Potential participants are asked to contact Dr David Greene on (02) 9701 4377 or david.greene@acu.edu.au and if eligibility criteria are met then consent forms will be forwarded for completion.

Yours sincerely,

**Dr David Greene – Principal Supervisor**

**Dr Michael Baker – Co Supervisor**

**Dr Phu Hoang – Co Supervisor**

## CONSENT FORM

*Copy for Researcher / Copy for Participant to Keep*

TITLE OF PROJECT: Effects of eccentric exercise on calf muscle contracture in people with multiple sclerosis

PRINCIPAL INVESTIGATOR: Dr David Greene

I ..... *(the participant)* have read (*or, where appropriate, have had read to me)* and understood the information provided in the Letter to Participants. Any questions I have asked have been answered to my satisfaction. I agree to participate in this research project requiring me to be randomly allocated to either an exercise or control group. I understand that the exercise group will complete backwards downhill walking on a treadmill twice a week for 12 weeks (24 sessions). I understand that I will complete a dorsiflexion test at the start and end of the study. I understand that the control group will complete home-based gentle stretching and strengthening exercises two - three times a week for 12 weeks (24-36 sessions), realising that I can withdraw my consent at any time without adverse consequences. I agree that research data collected for the study may be published or may be provided to other researchers in a form that does not identify me in any way.

NAME OF PARTICIPANT: .....

SIGNATURE ..... DATE .....

SIGNATURE OF PRINCIPAL INVESTIGATOR (or SUPERVISOR):.....

DATE:……..

## APPENDIX C - POSTER PRESENTATIONS

# WEARABLE TECHNOLOGY REVEALS GAIT COMPENSATIONS, UNSTABLE WALKING PATTERNS AND FATIGUE IN PEOPLE WITH MULTIPLE SCLEROSIS

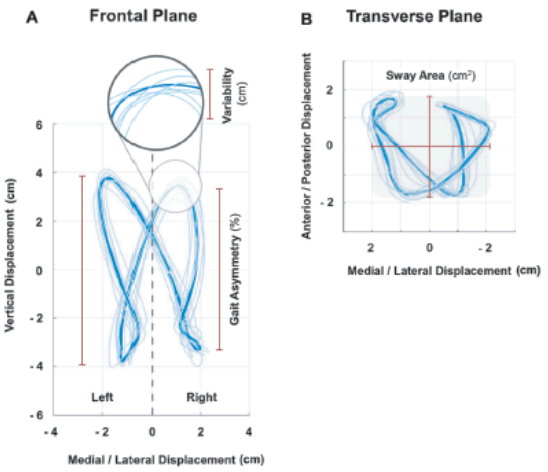
Michael Psarakis, David Greene, Michael Cole, Stephen Lord, Phu Hoang & Matthew Brodie

### BACKGROUND

People with Multiple Sclerosis (PwMS) often experience a decline in gait performance, which can compromise their independence and increase falls. Ankle joint contractures in PwMS are common and often result in compensatory gait patterns to accommodate reduced ankle range of motion (ROM). Using advances in wearable technology, the aim of this study was to quantify head and pelvis movement patterns that occur in PwMS and determine how these secondary gait compensations impact on gait stability.

### METHODS

Twelve healthy participants and twelve PwMS participated in the study. Head and pelvis movements were measured using two tri-axial accelerometers. Measures of gait compensation, mobility, variability, asymmetry, stability and fatigue were assessed during a six-minute walking test.

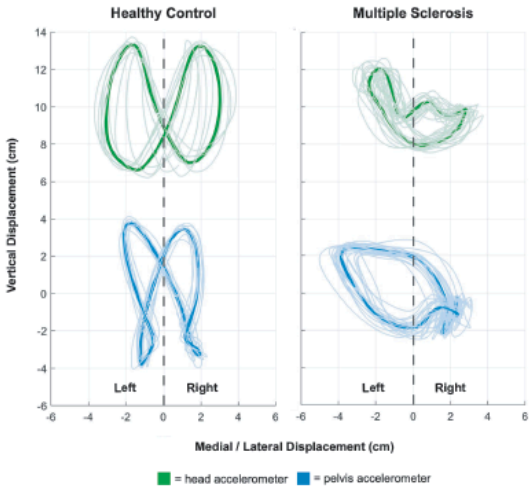



**(A)** Front Plane - Gait asymmetry was calculated using the difference in vertical displacement between left and right sides and expressed a percentage. Gait variability was calculated as the distance or spread of data away from the mean in centimeters.

**(B)** Transverse Plane - Sway area was the product of the AP and ML (95%) sway ranges in the transverse plane.

### RESULTS

Compared to healthy controls, PwMS had greater vertical asymmetry in their head and pelvic movements (Cohen's d=1.85 & 1.60). Lower harmonic ratios indicated that PwMS were more unstable than controls (Cohen's d=-1.61 to -3.06), even after adjusting for their slower walking speeds. In the PwMS, increased compensatory movements were correlated with reduced ankle active ROM (r=-0.71), higher disability (EDSS) scores (r=0.58), unstable gait (r=-0.76), reduced mobility (r=-0.76) and increased variability (r=0.83).




### CONCLUSION

Wearable device technology provides an efficient and reliable way to screen for excessive compensatory movements often present in PwMS and provides clinically-important information that impacts on mobility, stride time variability and gait stability. This information may help clinicians identify PwMS at high risk of falling and develop better rehabilitation interventions that, in addition to improving mobility, may help target the underlying causes of unstable gait.

### IMPLICATIONS FOR RESEARCH

- Wearable technology provided a low-cost way to screen for compensatory gait patterns
- Methods presented provide a sensitive measure of gait quality independent of walking speed

Faculty of Health Sciences, Australian Catholic University, Australia
Neuroscience Research Australia, University of New South Wales, Australia
Graduate School of Biomedical Engineering, UNSW, Australia

# SAFETY AND FEASIBILITY OF AN ECCENTRIC EXERCISE INTERVENTION IN PEOPLE WITH MULTIPLE SCLEROSIS WITH ANKLE CONTRACTURES – A CASE SERIES OF FIVE SUBJECTS

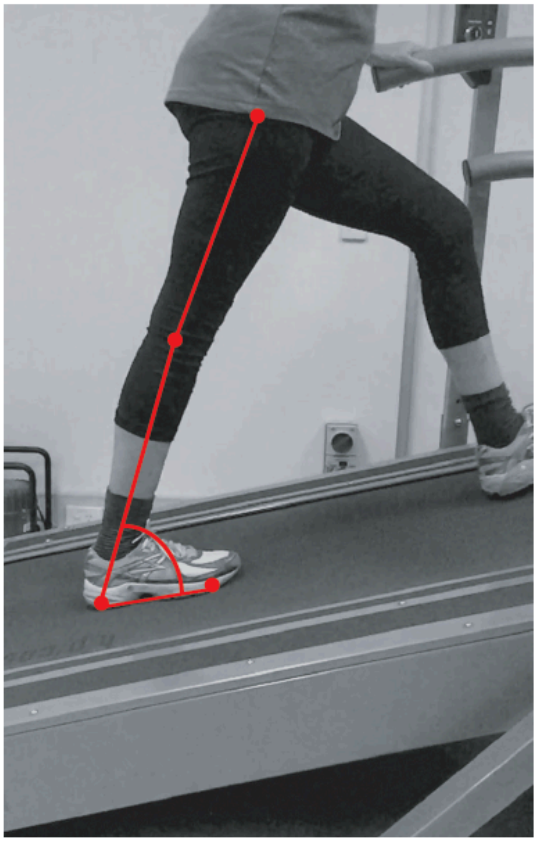
Phu Hoang, Michael Psarakis, David Greene, Stephen Lord

## PURPOSE

The primary aim of this study was to investigate the safety and feasibility of an eccentric exercise program in people with Multiple Sclerosis who have an ankle contracture. Secondary aims were to explore the efficacy of eccentric exercise on ankle joint range of motion and functional mobility.

## METHODS

Five people with Multiple Sclerosis completed two eccentric training sessions a week for twelve weeks (total = 24 sessions). Eccentric training involved walking backwards downhill on an inclined treadmill. The intervention was assessed for its safety and feasibility along with outcomes including; ankle range of motion (passive and active) and distance walked in the six-minute-walk test.



## RESULTS

There were no adverse events during or following the backwards downhill walk training. There was a 100% adherence rate and participants reported that they enjoyed the training intervention and experienced low levels of muscle soreness/discomfort. The training program significantly improved (mean) outcomes of passive and active range of motion for all participants.

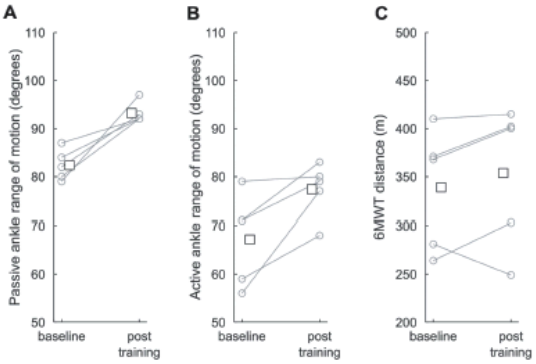



**Figure 1:** The individual grey unfilled circles represent the data points for each participant. Grey lines connect data from the same participant at baseline and post-training. The black unfilled squares represent the mean of all participants.

## CONCLUSION

The current study describes backwards downhill walking as a safe and feasible training modality in people with Multiple Sclerosis with ankle contractures. Clinical outcomes (passive and active range of motion) following backwards downhill walking are promising, however translation to clinically meaningful changes in walking function require further examination.

## IMPLICATIONS FOR RESEARCH

- Backwards downhill walking is a safe and feasible training modality for people with Multiple Sclerosis who have an ankle contracture.

- Clinical outcomes (passive and active range of motion) following backwards downhill walking are promising, however translation to clinically meaningful changes in walking function require further examination.

Faculty of Health Sciences, Australian Catholic University, Australia
Neuroscience Research Australia, University of New South Wales, Australia

## APPENDIX D - ONLINE PUBLICATIONS

- ***Psarakis, M.,*** Greene, D., Moresi, M., Baker, M., Stubbs, P., Brodie, M., Lord, S., & Hoang, P. (2017). Impaired heel to toe progression during gait is related to reduced ankle range of motion in people with Multiple Sclerosis. *Clinical Biomechanics*.

- ***Psarakis, M.,*** Greene, D., Cole, M. H., Lord, S. R., Hoang, P., & Brodie, M. A. (2018). Wearable technology reveals gait compensations, unstable walking patterns and fatigue in people with Multiple Sclerosis. *Physiological Measurement*.

- Brodie, M. A., ***Psarakis, M.,*** & Hoang, P. (2016). Gyroscopic corrections improve wearable sensor data prior to measuring dynamic sway in the gait of people with Multiple Sclerosis. *Computer Methods in biomechanics and biomedical engineering*.

- Ade, V., Schalkwijk, D., ***Psarakis, M.,*** Laporte, M. D., Faras, T. J., Sandoval, R., ... & Stubbs, P. W. (2018). Between session reliability of heel-to-toe progression measurements in the stance phase of gait. PloS one, 13 (7).