Measurement of Gait Kinematics in Multiple Sclerosis Using a Portable Sensor

Aeshah Alosaimi, B.ASc (Physical Therapist)

School of Physical and Occupational Therapy
Faculty of Medicine
McGill University, Montreal, Quebec, Canada
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ABBREVIATIONS

2D	Two-Dimensional
3D	Three Dimensional
6MWD	Six-Minute Walking Distance
6MWT	Six-Minute Walk Test
AAC	Area Above the Curve (0 axis)
AAV	Ankle Angular Velocity
AUC	Area Under Curve (0 axis)
CI	Confidence Intervals
CIS	Clinically Isolated Syndrome
ClinRO	Clinician -reported outcome
CNS	Central Nervous System
CoV	Coefficient of Variation
EDSS	Expanded Disability Status Scale
EMG	Electromyography
ICF	International Classification of Functioning, Disability and Health
IQR	Inter-quartile range
m-6MWT	Modified Six-Minute Walking Test
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PerfRO	Performance-based measures
PPMS	Primary Progressive Multiple Sclerosis

PRO	Patient-reported outcome
RPMS	Relapsing-Progressive Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SD	Standard deviation
SPMS	Secondary Progressive Multiple Sclerosis
SRO	Self-reported outcome
TechRO	Technology-reported outcome
WHO	The World Health Organization

ABSTRACT

Multiple sclerosis (MS) is a common cause of disability in young adults. Currently, around 93,000 Canadians are living with the disease and the prevalence is increasing in Canada and worldwide. MS course and clinical features vary from one individual to another and are based on type. Mobility limitations are reported in early MS and progress over the years with walking difficulties perceived as the most challenging sequela.

The importance of walking limitations in defining progression of MS has raised a suggestion of using gait changes for earlier detection of disease progression. Although the Expanded Disability Status Scale (EDSS) - a measure of disease progression - relies heavily on walking ability, multiple studies have reported changes in gait that are not translated into changes in the EDSS score. However, long-term changes in the EDSS were predicted by earlier gait limitations such as slow walking speed. Measures of gait kinematics, that better characterize gait quality could be early indicators of MS disability and MS progression. The development of wearable sensors made the assessment of gait kinematics more accessible and holds promise for self-monitoring and self-management.

The objective of this thesis is to contribute evidence as to the relevance of measures of gait kinematics to quantify disability in MS. The work on this thesis was made possible because of access to data from people with MS whose gait quality was assessed using a new wearable Heel2Toe^{TM} sensor (PhysioBiometrics Inc.). The thesis comprises one manuscript with two objectives. The primary objective is to estimate the extent to which personal factors and functional indicators are associated with gait quality parameters (gait kinematics) – measured using the Heel2Toe sensor - among ambulatory people with MS and the association of gait quality parameters with measures of physical capacity. The secondary objective is to estimate the extent

to which gait quality parameters - changed over 3 months period among people with MS participating in an exercise intervention that did not include gait-targeted treatment.

Correlational analysis was used to link MS impairments of leg weakness, leg heaviness, leg power, impaired coordination, fatigue, bladder dysfunction and mood with parameters related to gait kinematics. The strongest relationships ($r \geq 0.4$) were observed between measures of leg power (vertical jump) and mood with both the power and balance cycles of the gait cycle. Of physical capacity measures, gait quality parameters were most strongly associated ($r \geq 0.5$) with the Six-Minute Walk Test. Over 3 months period, without any specific gait training, parameters of gait kinematics deteriorated in multiple participants, improved in others, and remained the same in few participants, but these proportions did not differ from uniform distribution. However, some of the gait parameters changed concordantly.

ABRÉGÉ

La sclérose en plaques (SEP) est une cause fréquente d'incapacité chez les jeunes adultes. À l'heure actuelle, environ 93,000 Canadiens vivent avec la maladie et la prévalence augmente au Canada et dans le monde. L'évolution de la SEP et les caractéristiques cliniques varient d'un individu à l'autre et dépendent du type. Des limitations de mobilité sont signalées dans la SEP précoce et progressent au fil des années, les difficultés à marcher étant perçues comme la séquelle la plus difficile.

L'importance des limitations de la marche dans la définition de la progression de la SEP a soulevé la suggestion d'utiliser les changements de démarche pour détecter plus tôt la progression de la maladie. Bien que l'échelle élaborée des incapacité (EDSS) – une mesure de la progression de la maladie – repose fortement sur la capacité de marche, plusieurs études ont rapporté des changements dans la démarche qui ne se traduisent pas par des changements dans le score EDSS. Cependant, des changements à long terme de l'EDSS ont été prédits par des limitations antérieures de la démarche telles que la vitesse de marche lente. Les mesures de la biomécanique de la marche, qui caractérisent mieux la qualité de la marche, pourraient être des indicateurs précoces de l'invalidité et de la progression de la SEP. Le développement de capteurs portables a rendu l'évaluation de la biomécanique de la marche plus accessible et promet une autosurveillance et une autogestion.

L'objectif de cette thèse est d'apporter des preuves sur la pertinence des mesures de la biomécanique de la marche pour quantifier le handicap dans la SEP. Le travail sur cette thèse a été rendu possible grâce à l'accès aux données de personnes atteintes de SEP dont la qualité de la marche a été évaluée à l'aide d'un nouveau capteur portable : Heel2Toe^{TM} (PhysioBiometrics Inc.). La thèse comprend un manuscrit avec deux objectifs. L'objectif principal est d'estimer dans quelle

mesure les facteurs personnels et les indicateurs fonctionnels sont associés aux paramètres de qualité de la marche (biomécanique de la marche) - mesurés à l'aide du capteur Heel2Toe - chez les personnes ambulatoires atteintes de SEP et l'association des paramètres de qualité de la marche avec des mesures de la capacité physique. L'objectif secondaire est d'estimer dans quelle mesure les paramètres de qualité de la marche - ont changé sur une période de 3 mois chez les personnes atteintes de SEP participant à une intervention d'exercice qui n'incluait pas de traitement ciblé sur la marche.

Une analyse corrélationnelle a été utilisée pour relier les altérations de la SEP liées à la faiblesse des jambes, à la lourdeur des jambes, à la puissance des jambes, à la coordination réduite, à la fatigue, au dysfonctionnement de la vessie et à l'humeur avec des paramètres liés à la biomécanique de la marche. Les relations les plus fortes ($r > 0,4$) ont été observées entre les mesures de la puissance des jambes (saut vertical) et de l'humeur avec les cycles de puissance et d'équilibre du cycle de marche. Parmi les mesures de la capacité physique, les paramètres de qualité de la marche étaient les plus fortement associés ($r > 0,5$) au test de marche en six minutes. Sur une période de 3 mois, sans entraînement spécifique à la marche, les paramètres de la biomécanique de la marche se sont détériorés chez plusieurs participants, améliorés chez d'autres et sont restés les mêmes chez quelques participants, mais ces proportions ne différaient pas de la distribution uniforme. Cependant, certains des paramètres de marche ont changé de manière concordante.

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PREFACE

The work of this thesis is completed by Aeshah Alosaimi under a continuous guidance of Dr. Nancy Mayo. The data used in Manuscript 1 is taken from the Multiple Sclerosis Tailored Exercise Program (MSTEP) trial and was collected by Dr. Kedar Mate and his colleagues. Dr. Ted Hill developed an algorithm that transforms the data collected by a portable sensor. The algorithm applied enabled measuring different gait events that were included in this thesis objectives. Ahmed Abou-Sharkh translated the thesis abstract to French. Data analysis and Manuscript 1 writing was carried out by Aeshah Alosaimi and edited extensively by Dr. Nancy Mayo. Dr. Helen Dawes agreed to be a committee member on this thesis and a co-author of Manuscript 1 of which she will revise and provide feedback.

Thesis Organization:

The global objective of this thesis is to contribute evidence as to the relevance of measures of gait kinematics to quantify disability in MS. This was achieved through answering two questions: 1) to what extent do personal factors and functional indicators associate with gait quality parameters among ambulatory people with multiple sclerosis? 2) to what extent do gait quality parameters change over 3 months period without gait-targeted treatment among people with MS?. Both questions were addressed in one manuscript which will be submitted for a relevant scientific journal. Other chapters were included and organized following the guidelines from McGill Graduate Postdoctoral Studies (GPS). The thesis is thereby composed of:

Chapter1 provides a short introduction to gait science through the definition of gait and the main physiological process needed to produce and control locomotion. A brief history of gait analysis methods was then presented along with the established normal gait components. This chapter then

provides a quick review of parameters used in literature as gait quality measures and highlight angular velocity and its role during the gait cycle which make it a potential measure of gait quality.

Chapter 2 addresses Multiple Sclerosis (MS) definition, types, pathology, and treatment options in a short summary. Common symptoms of MS, including gait limitations, were then reported in more detail. The last part of this chapter describes the challenges in predicting the course of MS and in defining a transition into a progressive form of the disease.

Chapter 3 presents the rationale and objectives of this thesis

Chapter 4 consists of Manuscript 1 titled "Gait Quality in Multiple Sclerosis and Relationship with Functional Indicators"

Chapter 5 provides an overall discussion and conclusion of the thesis work.

Chapter 1: Gait

1.1 Background

Human gait is a unique feature that separates humans from other bipedal animals. Walking was an evolutionary process to maximize distance covered with least usage of energy, therefore it is regular with joint movements optimized for safety and efficiency. These regular automated movements are executed with the aid of multiple high-level brain areas and with the integration of a complex network of muscles and joints. Because most of us started walking long before being able to think, we are inclined to consider walking a simple and innate ability. The truth is that what seems to be simple requires a vigilant and quick interaction of the body parts with the surrounding environment. Take, for example, facing an obstacle, the automatic reaction that happens to avoid the object occurs in a fraction of second, passes through complex planning and commands, and requires the movement of multiple body structures to produce the perfect maneuver.

Vaughan et al. (1992) identified the sequence of events that underpin the process of walking. First, the gait command is activated in the (CNS) which is then transmitted to the muscles through the peripheral nervous system. In response to the gait signal, the muscles contract which generates force and produces movement at the joints. This movement is regulated by the rigid skeletal segment to produce gait recognized as functional which leads to the generation of ground reactional force. During this process, there are sensory feedback signals are constantly sent to the CNS to modify and adapt the walking process to the environment.

Because of the complexity of the interaction between numerous body structures and functions, gait is easily affected if even one of these systems is under threat. Changes due to health conditions are sometimes manifested in gait leading to the application of sophisticated technological gait

assessment in health research to predict, test effectiveness, or monitor the progress of certain diseases.

1.2 A Glance at The Development of Gait Analysis:

Interests in understanding human gait go back to ancient Greece as shown in Aristotle theories about the movement of humans and animals (Baker, 2007); however, Borelli's contribution in 1608-1679 toward describing what we now know as the center of gravity, in addition to the biomechanics of muscles and tendons, are considered the foundation of our modern gait sciences (Steindler, 1953). After Boerelli, different theories arose, but the overall progression of this field was slow. It was until 1804–1891 when the brothers Weber, Wilhelm and Edward, published their major work in 1836, a simple, yet significant experiment. They drew a reliable conclusion regarding the relationships between step length, cadence, and walking speed and measured the stable “stance phase” and the swing phase duration (Steindler, 1953). They also attempted to describe the position of different joints during 14 gait instants, some of which were revoked later by other scientists.

In 1830-1904, Marey, the modern gait analyst, along with his student Carlet, developed the first concept of the force plate. Their primary model of the force plate was a one-dimensional pressure plate embedded in the shoes to detect and record steps taken which helped the accurate description of gait components (Sutherland, 2005). This instrument was later used by Marey on a horse to prove there is an instant where all its hooves are off the ground during the trot. Their work inspired other scientists who used photography and recording techniques to produce more accurate horse shots such as the one taken by Muybridge. These techniques were eventually applied in human gait analysis as in Demeny’s work of using different markers to measure important aspects of gait

(Baker, 2007). The invention of photography and visual recording rapidly advanced the gait analysis field.

The next revolution in gait analysis was the pioneered work established by German mathematician Otto Fischer and his colleague Willhelm Braune which is considered the foundation of kinematic gait measurements. They were the first to apply three-dimensional analysis using multiple cameras while the subject walks in darkness with Geissler tubes attached to his body (Figure 1). Their experiment resulted in providing a more accurate description of different body segments position during the gait cycle. Afterward, Fischer took advantage of the 3-dimensional measurements and calculated different inertial parameters such as the trajectory of the center of mass of the whole body and its separate segments, velocity, acceleration, and force (Baker, 2007).

Further advancement in the force plate took place during the first world war. Jules Amar was the first to develop a three-component (pneumatic) force plate which has gone through multiple enhancements by Wallace Fenn who made the first one-dimensional mechanical force plate, followed by Elftman's contribution in building a three-dimensional mechanical force plate (Baker, 2007). The next evolution in force plate technology made its application in the clinical setting possible. It was developed by Cunningham and Brown using strain gauge; however, their model required a calibration process that was daunting before computers become available. Cunningham and Brown's force plate was improved by different scientists in different countries, produced commercially, and equipped by different gait labs (Sutherland, 2005).

During the mid of the 20th century, interest in gait analysis has shifted toward dynamic gait. A physician named Richard Scherb initiated these efforts by identifying the individual muscle's action during the gait cycle on a treadmill using palpitation (Steindler, 1953). This work was later refined by Inman who studied the action of individual muscles using EMG. The major challenge

was to synchronize the EMG signal with the gait movement which was achieved and improved later by the effort of multiple students of Inman such as Sutherland and Perry. Basmajian, another student of Inman, developed thinner pins which made the experience of inserting EMG electrodes less painful and without the need for anesthesia (Sutherland, 2001). This achievement resulted in rapid and wide studies of different muscles' actions. Inman's name is related to other experiments such as the insertion of pins into the tibia, femur, and pelvis to measure transverse rotation during walking, and with Eberhardt's experiment that used interrupted light to manually measure joint angles. Murray et al. also used reflective strips and interrupted light and contributed to the understanding of normal gait classified based on age and height for men and women and to other studies on pathological gait (Baker, 2007, Sutherland, 2002).

Electrogoniometry came into practice around 1959 and was used to measure joints angles. It had the advantage of recording multiple gait cycles and produce graphs that analog gait motion without any manual calculation; however, due to its multiple drawbacks it was not used at a widespread level (Sutherland, 2002). Photography techniques were more common due to their ability to view all body segments and their inclusiveness for different body sizes and characteristics. A collaboration between the Lockheed Missiles and Space Company, Sutherland and other gait scientists at the Shriners Hospital in San Francisco led to introducing films into gait analysis. Computers helped in performing the mathematical calculation, but the x and y-axes were identified manually using a digitizer, a time and labor-consuming task (Sutherland, 2002).

A few years later, gait analysis became fully automated with the help of engineers and physicists, mainly E.H. Furnee's of the Netherlands who developed a single-camera two-dimensional (2D) automated movement analysis. This method was adopted and further developed by many scientists such as J. Paul, Andrews, and Jarret who built multiple cameras but 2D automated systems. In

1980, the first three-dimensional (3D) automated gait analysis system was shipped to a physician in West Virginia by the VICON team in the Oxford Metrics Ld. lead by Julian Morris (Sutherland, 2002).

1.3 Normal Gait Components:

Gait is a series of repetitive events known as gait cycles. To understand the component of normal gait, one gait cycle is described. The consecutive cycles are assumed to be similar. Each gait cycle extends from the heel contact of one foot to the heel contact of the same foot again and is divided into two phases: stance phase: the period when the foot is on the ground, and swing phase: the period when the foot is moving forward in the air (Whittle, 2014). The traditional nomenclature subdivides the stance phase into 5 events that concern the movement of the foot (Vaughan, 1992). These events are described below with a focus on the ankle movement (Figure 2):

1. Heel strike: Also known as initial contact. It initiates the gait cycle and begins when the heel touches the floor. The ankle is almost neutral at the initial contact
2. Foot Flat: After the heel contact, the ankle moves into plantarflexion and the sole becomes in contact with the floor. This movement is controlled by the eccentric contraction of the dorsiflexors
3. Mid stance: It is when the body is progressing forward over the foot and the contralateral tibia passes the stance leg. The ankle is in a neutral position during this time.
4. Heel-off: As the name reveal, this is marked by the heel losing its contact with the floor. The push-off is initiated by the calf muscle as the ankle moves concentrically into plantarflexion.
5. Toe-off: The end of the stance phase as the foot leaves the ground. The ankle keeps moving into plantarflexion and reaches its peak just after the toe-off.

After the toe-off, the swing phase begins, and it is composed of three events:

1. Acceleration: Start after the toe-off and during which the hip flexion accelerates to swing the foot forward. The ankle starts moving into dorsiflexion to clear the foot from the ground.
2. Mid swing: The foot is progressing forward as the swing leg passes the contralateral leg coincidental with the mid stance of the other leg. The ankle is either in neutral or few degrees of dorsiflexion
3. Deceleration: Describe the muscle action as they act to slow and stabilize the leg in preparation for heel strike of another gait cycle. The ankle is either neutral or in few degrees of dorsiflexion.

In addition to this traditional description, another nomenclature exists to better represent gait events in pathology that alters gait. It was developed by Perry and her associates at Rancho Los Amigos Hospital in California which divides the gait into 8 subsequent events:
Initial contact, Loading response, Midstance, Terminal stance, Preswing, Initial Swing, Midswing and Terminal swing (Cochran, 1982).

1.4 Current Methods Used to Quantify Gait:

Since 1980, tremendous progress in gait analysis systems, speed of data processing and reliability of outcomes have been achieved. Different methods to quantify gait emerged in clinical settings driven by time and price concerns. These different methods use different sources of information to quantify gait deficits. Examples are given below using terminology from Mayo et al., 2017:

1.4.1 Patient-reported measures (PROs):

These are measures filled by the person under study to provide information about their perception of their walking ability. An example of existing measures includes the 12-item walking scale (Bladh et al., 2012).

1.4.2 Self-reported measures (SROs):

These measures differ from Patient-Reported measures in the way that they can be amended by information taken from other measures such as information on intensity and frequencies. The psychometric properties of these measures vary; however, it rarely reports on gait quality or other quantitative aspects of gait (Cameron & Wagner, 2011). An example of these measure is the self-reported gait speed (Syddall et al., 2015)

1.4.3 Clinician-reported (ClinRO) gait analysis measures:

This method is mostly preferred by clinicians and usually aims to assess gait quality and detect major deviations from normal gait by observing the person's walking. It is quick and simple to conduct but its precision, validity and reliability are largely dependent on the examiner's skills and experience (Mirelman et al. 2018, Cameron & Wagner, 2011).

1.4.4 Performance-based measures (PerfROs):

These are widely used measures in clinical as well as research settings. Norms are available for most of these measures, such as in gait speed and 6-minute walking test (6MWT), which provides a better comparison of the resulted outcomes. The availability of testing protocol reduced the need for training. It provides simple gait parameters such as speed and endurance; however, it does not provide information on the underlying mechanism or quality of movement (Mirelman et al. 2018).

1.4.5 Technology-reported measures (TechROs):

- Instrumented Walkways:

These are carpets filled with sensors to detect and analyze footfalls. They come in different sizes, but they are expensive and often require a relatively large space. The data collected by walkways are usually accurate and reliable. Training is required to operate these systems (Cameron & Wagner, 2011).

- Motion analysis systems

This is a three-dimensional device composed of multiple cameras and markers attached to different body parts to record and analyze its movement. It is considered the gold standard to which other methods are usually compared. It is highly accurate and provides rich data on kinetics, kinematics, and muscle activity. However, it is expensive, required large specifically designed spaces and human expertise to operate which makes its application limited to research purposes (Mirelman et al. 2018, Cameron & Wagner, 2011).

- Wearable sensors

These are small and portable devices, worn on one or multiple body parts. Each device can contain an accelerometer, gyroscope, Magnetometer, or all combined. Sensors provide more functional input about gait as they assess gait in real-time, through real situations, and for a longer duration. These advantages might enable sensors to detect subtle changes in gait such as the decline in performance over time. Gait wearable sensors are usually cheap and can be combined with other gait assessment methods; however, in many cases, the data collected by these devices are limited to one or a few segments of the body (Chen et al. 2016, Mirelman et al. 2018).

1.5 Gait Quantity Vs. Gait Quality :

Gait analysis methods provide quantitative data, also called gait parameters, that break down this complex function and measure deviation from normal gait. Mainly, there are three types of data that describe different aspects of gait:

I. Kinematics: gait parameters that describe motion with disregard to the force that caused it. The spatiotemporal parameters, i.e., stride length, swing time, cadence etc., are simple kinematic measures. Other examples include angular kinematics such as joint angles, velocity, and acceleration (Winter, 2009).

II. Kinetics: Gait parameters concerned with the force, power, and energy of the movement. Examples are ground reaction force, joints moments and joints power (Winter, 2009).

III. EMG: These are parameters that identify muscle activity patterns during movement.

Many of these parameters, such as gait variability (Weiss et al., 2013), velocity, step length, percentages of stance and swing phase (Brandes et al., 2008), cadence, step duration, stride duration, percentage of double support (Shah et al., 2020), and gait asymmetry between the two sides (Dewar & Judge 1980), were used in literature to report on gait quality. Although some parameters are simple and provide no more than description, others can explain the underlying mechanism and hence might better describe gait quality.

1.6 Ankle Angular Velocity as An Indicator of Gait Quality:

Angular velocity is defined as the rate of change of joint angle usually expressed in degree/sec. Ankle angular velocity, therefore, describes how fast the ankle moves into dorsiflexion or plantarflexion (Knudson, 2003). Although seems spontaneous, the degree of angular velocity of ankle movement was found to be an important determinant of leg power during the vertical jump (Ibrahim et al., 2020), the speed of forward progression (Winter, 2009) and cadence in people with MS, Parkinson's and older adults (Mate et al., 2019). During walking, ankle angular velocity was found to play an important role in the push-off event in terminal stance (Mentiplay et al., 2018). Power produced at ankle push-off contributes to foot clearance and leg swing acceleration (Zelik &Adamczyk, 2016). With recent development in wearable sensors and algorithms, measuring

angular kinematics data became less complex. Therefore, ankle angular velocity might show great potential to the area of gait quality measures and indicators. In-depth assessment of gait and explanation of the underlying mechanisms of gait deviation could be more accessible for clinical settings.

Figure 1.1 A participant from Fischer and Braune's experiment.

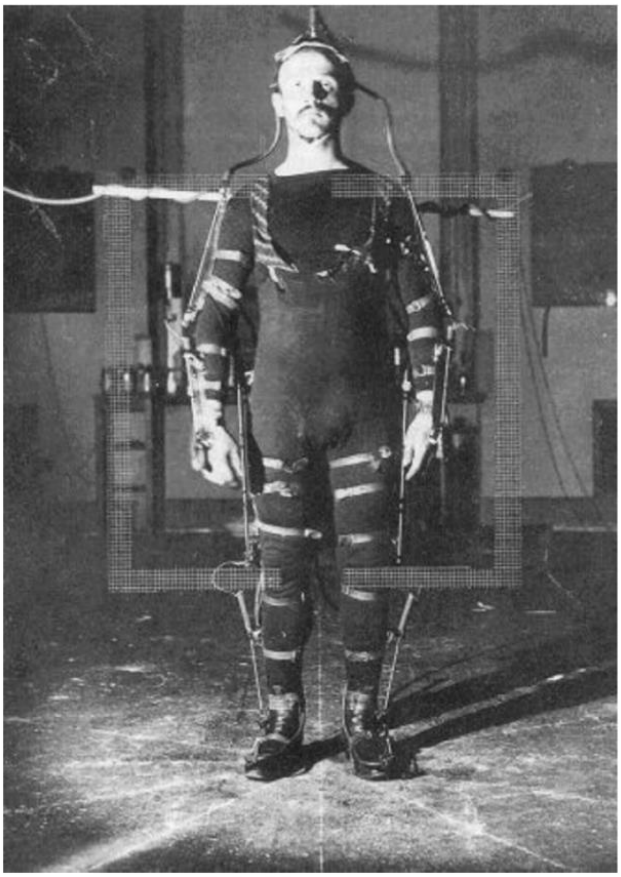
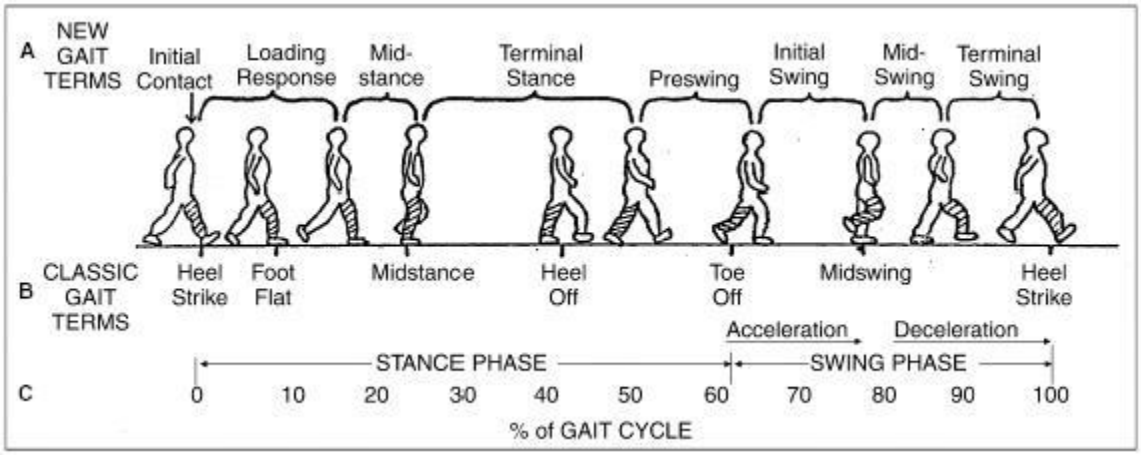


Figure 1.2 Normal gait components



Chapter 2: Multiple sclerosis

2.1 Definition, Types and Pathology

Multiple sclerosis (MS) is a chronic inflammatory neurological disorder that causes damage to the myelin and the axons in the central nervous system. MS is the most common non-traumatic cause of disability in young adults (Dobson & Giovannoni, 2019). Canada has one of the highest rates of MS worldwide. Recent estimate showed that over 77,000 Canadians aged 20+ are diagnosed with the disease, 75% are women (Public Health Agency of Canada, 2019). In the 1900s, MS affected men and women equally, however, the ratio has changed to become 3:1(women to men) (Dobson & Giovannoni, 2019). Although the specific underlying cause of MS is unknown, multiple genetic and environmental factors have been found to play an important role in increasing disease susceptibility with more tendency toward environmental factors as a stronger trigger of the disease (Dobson & Giovannoni, 2019). Factors that have been associated with MS are smoking, obesity, vitamin D, ultraviolet light exposure, and Epstein-Barr virus infection. Migration studies also indicated that moving from a low-risk environment to a high-risk environment increases the risk of developing MS (Dobson & Giovannoni, 2019; Compston & Coles, 2008).

MS is currently diagnosed following McDonald's criteria which consider clinical features and diagnostic testing. McDonald's criteria were developed in 2001 and revised in 2005, 2010 and recently in 2017 (McDonald et al., 2001; Polman et al., 2005; Polman et al., 2010; Thompson et al., 2018). The core concept of MS diagnosis is based on dissemination in time and space. To confirm the diagnosis, a person must have experienced 2 attacks or more and must show objective clinical evidence of 2 lesions (Thompson et al., 2018). Although this can be confirmed by clinical neurological exam alone, conducting MRI testing is recommended for all patients to support these findings (Thompson et al., 2018). Other paraclinical testing such as cerebrospinal fluid might also

be used if necessary. If McDonald's criteria are fulfilled and other potential disorders are excluded, then the diagnosis is definite MS; however, if some criteria are met and it was not possible to find further evidence, the diagnosis is noted as possible MS. If the diagnosis revealed other causes that better explain the clinical feature, the diagnosis said not to be MS (Thompson et al., 2018).

In 1996, the National Multiple Sclerosis Society defined 4 types of MS: 1) Relapsing-Remitting MS (RRMS) which is characterized by periodic acute attacks from which the person either fully recovers or has some residual deficits with lack of disease activity in between, 2) Primary Progressive MS (PPMS) in which the onset of the disease is progressive with no relapses and temporary improvement might occur, 3) Secondary Progressive MS (SPMS) that starts initially as (RRMS) which later turn into more progressive forms with or without relapses, 4) Relapsing-Progressive MS (RPMS), a type that does not have a clear definition, but it usually combines relapses with progressive features. (Lublin & Reingold, 1996). However, with the substantial development in our understanding of MS and its pathology, the previous classifications were later revised and updated as the following: RRMS and PPMS preserved their definition. PRMS was included under PPMS and considered a progressive form with activity. Clinically isolated syndrome (CIS) that was known before as a precursor is now added to MS phenotype and it is defined as the first episodes of MS where signs and symptoms last at least 24h with no associated fever or infection (Lublin, 2014).

There is inflammation in all stages of MS with the difference being quantitative, not qualitative (Frischer et al. 2009). Perivenular inflammation occurs resulting in infiltration of lymphocytes - mainly T-cells but B-cells and plasma cells are also involved in lower numbers - leading to demyelination plaques and loss of oligodendrocytes (Dobson & Giovannoni, 2019). Axons remain intact until the later stage of the disease when the damage becomes irreversible (Lassmann, 2018).

Active lesions with abundant macrophages in the center distinguish RRMS from PPMS which is characterized by an inactive demyelinated center with surrounding activated microglia and some macrophages in addition to the formation of gliotic scars. Although T-cell involvement does not change across all stages of MS, proportions of B-cells and plasma cells increase as the disease progresses (Dendrou et al., 2015).

MS is unpredictable and its clinical features depend on the area affected which varies between individuals. The behavior of MS at the onset could predict the time to enter the progressive stage, however, it has no influence once the progressive phase has started (Lassmann et al., 2007). Plaques are formed in the white matter and the gray matter of the CNS in all stages of MS with more damage to the grey matter in progressive stages (Lassmann, 2018). Treatment options available for MS are either to target the pathological mechanism of the disease or the resulting symptoms. Disease-modifying therapies are currently the main treatment used for MS. They aim to alter the course of the disease by decreasing the number and duration of relapses and slow the overall disease progression. Although it is effective in the early stages, these disease-modifying therapies achieved little success in progressive MS. Symptoms management includes physical therapy and other pharmaceutical drugs that target resulting symptoms such as pain, spasticity, and bladder dysfunction (Goldenberg, 2012).

2.2 Common Impairments in Multiple Sclerosis:

2.2.1 Muscle Weakness and Decrease Muscle Power:

Muscle weakness is frequently reported in MS. A review published in 1998, estimated that weakness affects 80% of MS patients. The most commonly seen pattern was weakness in both lower limbs asymmetrically, or only one lower limb (Joy & Johnston, 2001). Another recent study showed that around 60% (out of 156) reported muscle weakness in any muscle. The highest

percentages of muscle weakness were reported in wrist muscles followed by elbow and shoulder muscles respectively. Their results also showed that muscle weakness highly correlated with the level of disability (Hoang et al., 2014). In the early stages of MS, weakness usually develops after activity performance; however, as the disease progress, it becomes a constant complaint (Joy & Johnston, 2001). Muscle weakness in MS usually results from damage to the spinal cord or the descending motor tracts (Joy & Johnston, 2001). Motor impairment of extremities is not confined to weakness. Cerebellar ataxia and loss of postural sense are common and can contribute to reducing muscle strength.

The term muscle power has been misused interchangeably with muscle strength in literature but in fact, they represent two different phenomena. Power contains kinetic (force) and kinematic (velocity) information and is measured as the product of force and velocity (Sadeghi et al., 2000). Strength on the other hand only measures the maximum force exerted by a muscle (Buchner & Lateur, 1991).

Muscle power has elicited great attention in research of older adults and as a result, it was suggested that muscle power might be a critical determinant of functional impairment in this cohort (Md et al., 2002). In MS, few studies investigated muscle power; however, a recent systematic review concluded that people with MS have impaired muscle power compared to healthy individuals (Jørgensen et al. 2017). Impact of muscle weakness and reduce muscle power extend to other significant functions such as walking and raising from the chair (Jørgensen et al. 2017).

2.2.2 Balance and Coordination

Balance is the result of the integration of sensory, vestibular, and motor signals. Damage to proprioception, vision, vestibular function as well as weakness, and spasticity all lead to impaired balance (Soyuer et al., 2006). In the MS population, 50%-80% develop balance problems

(Cameron & Nilsagard, 2018). People with progressive forms of MS exhibits more impaired balance. When compared to healthy individuals, MS patients with secondary progressive phenotype showed the least favorable balance outcomes followed by primary progressive and relapsing-remitting forms of the disease (Soyuer et al., 2006). Balance issues were also reported as a risk factor of falls among other MS symptoms (Matsuda et al., 2011).

Coordination is the ability to produce accurate, controlled, and smooth movement. A movement is coordinated if was produced at the right time with the right muscle and speed (Desrosiers et al. 2005). In later stages of MS, deterioration of gait coordination is more common (Plotnik et al., 2020). Upper limb coordination was also impaired in a sample of MS patients as manifested by co-contraction of biceps and triceps and incoordination of shoulder muscles with arm movement (Pellegrino et al., 2018).

2.2.3 Fatigue

Fatigue is considered the most common symptom of multiple sclerosis and a center of scientific attention in the last decade. Around 76% - 92% of MS patients struggle with fatigue in their lifetime (Joy & Johnston, 2001), and 28% considered fatigue their most troubling symptoms (Schwid et al., 2002,). MS fatigue is triggered by heat exposure, increases with activity, and insufficiently improves with rest (Kos et al., 2008). Accurate diagnostic tools of fatigue are lacking which leads to inefficient management and unsatisfied outcomes (Manjaly et al. 2019). The concept of fatigue itself is still not yet agreed upon. Previously, most studies on fatigue focused on the subjective perception of the symptom (Manjaly et al. 2019). Lately, a call for a better taxonomy was established and resulted in a more detailed picture. Fatigue, as a result, is now represented under two potentially independent dimensions: “perception of fatigue” and “performance fatiguability” (Kluger et al., 2013). Perception of fatigue is a subjective feeling of

exhaustion that does not necessarily affect performance. Performance fatiguability on the other hand is observed deterioration in physical or cognitive performance over time in relevance to reference value (Kluger et al., 2013). MS fatigue is either primary or secondary, depends on its origin. Primary fatigue results from the disease underlying mechanism and the demyelination process that results in damage to myelin and axons. Secondary fatigue might develop as a consequence of other related issues such as depression, sleep disturbance and medication use (Kluger et al., 2013). Fatigue is treated in MS patients using pharmaceutical drugs and non-pharmaceutical approaches such as aerobic exercise, cooling therapy and cognitive behavioral therapy (Induruwa et al., 2012)

2.2.4 Depression

Depressive symptoms are 2-4 times more prevalent in MS patients compared to the general population. The exact percentage varies widely depending on the study setting and location. In clinical settings, depression affects 20%-40% of MS patients; however, a study conducted in Canada using a population-based household survey showed a prevalence of 26% compared to 8.4% in the general population. A pooled estimate in a recent systematic review showed a prevalence of 23.7% (Patten et al., 2017). The risk of developing depression in MS starts with the disease onset (Arnett et al., 2008). Depression was found to have complex associations with different MS variables at different levels whether related to the disease mechanism (i.e., neurophysiology and neuroimmunology), consequences (for example, physical disability, pain and fatigue) or moderator factors such as social support and conceptions of self and illness (Arnett et al., 2008). Depression is independent of disease severity but might be a side effect of some medications (interferon therapy) (Joy & Johnston, 2001). Few trials studied the effectiveness of antidepressants in the MS population and the available ones are of low or adequate quality.

However, their results favored the use of antidepressants and showed superior results compared to placebo treatment. Other research evaluated the benefit of non-pharmaceutical methods and promising results were seen in cognitive behavioral therapy especially when administered by telephone. The attrition rate of these studies was low, and their benefits were maintained at the 6 months evaluation. Other treatment options include mindfulness-based intervention and electroconvulsive therapy (Feinstein, 2011).

2.2.5 Spasticity

Spasticity is known as velocity-dependent increase in muscle tone and hyperexcitability of stretch reflex resulting in tendon jerk (Joy & Johnston, 2001; Etoom et al., 2018). It is a common phenomenon in neurological disorders with upper motor neuron lesions (Etoom et al., 2018). Spasticity manifestations impact other physical domains, restrict mobility and lead to pain and stiffness (2014). There are also associations between spasticity and other symptoms such as bladder problems and sleep disturbance (Flachenecker et al., 2014). Spasticity can be caused by disruption of normal neurological processes at the spinal or supraspinal levels. At the spinal level, alteration of different components of the stretch reflex arc results in loss of inhibition of alpha motor neurons that is integral to control muscle contraction. Higher levels of the CNS, such as the cortex and the brain stem, also influence the inhibition and facilitation of motor neurons. Any imbalance in these signals contributes to spasticity. Because MS lesions can be scattered across the entire CNS, spasticity is commonly seen in this population (Mukherjee & Chakravarty, 2010). A recent study collected data on 20,969 MS patients and their results showed that 84% have experienced spasticity, among which 34% said that spasticity impacted their activity of daily living. Spasticity is linked to poor quality of life, increased fatigue and a greater risk of falls (Rizzo et al., 2004). Different physiotherapy modalities have been used to reduce spasticity and maintain

normal muscle tone. Shock wave, electrical stimulation, exercise and stretching are some examples. However, two recent reviews found inconclusive (Bovend'Eerdt et al., 2008) or null results for most of these modalities (Rizzo et al., 2004). Antispastic drugs can be used, these include Baclofen, tizanidine and Intramuscular injections of botulinum toxin (Joy & Johnston, 2001).

2.2.6 Bladder Dysfunction

Bladder dysfunction is very common in MS. It affects around 90% of this population at some time during their illness (Joy & Johnston, 2001). Bladder problems mostly result from loss of neural control at the sacral level and are likely to be accompanied by lower limb spasticity (Joy & Johnston, 2001). The burden of bladder problems extends beyond physical well-being to include other aspects of the person's life. MS patients who had bladder dysfunction reported sleep interruption leading to fatigue on the following day. The daily routine such as shopping and driving was also disrupted by the unpredictable need to urinate. Impact on sexual relationships and health-related quality of life have also been reported (Tepavcevic et al., 2017; Browne et al., 2015). A review of literature found strong evidence for two factors that increase the prevalence of bladder problems: duration of the disease, especially after 15 years of onset; and severity of pyramidal symptoms (De Sèze et al., 2007). Complications of bladder dysfunction in MS include lower urinary tract infection and morphological damage to the urinary tract. Bladder cancer was found to be more common in MS patients compared to the general population, especially in those treated with immunosuppressant and are under chronic catheterization (De Sèze et al., 2007).

2.2.7 Gait Abnormality

Gait abnormalities have been widely studied in MS as indicated by the abundant available literature. Gait is produced through different parts of the CNS from cortex to spinal cord and

requires many other functions to be intact such as muscle strength, cognition, and balance, which is rarely the case in MS making gait deterioration a very common feature during the course of the disease. (LaRocca, 2011). Multiple studies tried to characterize gait patterns in MS. Their results were inconsistent; however, one feature was reported repeatedly which is abnormal movement at the ankle joint (Kempen et al., 2016; Kelleher et al., 2010). A recent systematic review and meta-analysis summarized the most affected aspects of gait in MS and found that compared to healthy individuals, people with MS exhibit lower velocity, cadence, stride length, step length, and swing time (Figure 2.1-2.3). Their results also showed an increase in double support time, step width, and stance duration. Regarding other kinematic and kinetic measures, the evidence was not sufficient to draw firm conclusions; however, a trend toward altered joint angles, power and torque, muscle activation pattern and ground reaction force was observed (Comber et al., 2017). Multiple associations between MS symptoms and gait limitations were explored. The most studied relationships were between fatigue, and spasticity and spatiotemporal parameters such as cadence (Kalron, 2015; Newland et al., 2020; Plotnik et al., 2020; Thoumie et al., 2005). Measuring gait in MS might provide information that would be useful to monitor changes in the course of the disease. Different parameters of gait were included in measures of disease progression such as the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) (Cameron & Wagner, 2011).

2.3 Multiple Sclerosis Over Time

MS is a highly variable illness. Its progression over time varies from one individual to the other. The natural history of common symptoms of MS over 30 years showed that fatigue and sensory impairments are commonly reported in early MS in contrast to limitations in mobility which is not usually affected in early stages; however, disability mounts as the years add on (Figure 3.4) (Kister

et al., 2013). Certain features identified at the initial diagnosis might predict the disease behavior. For example, having optic neuritis and at least 3 T2 hyperintense lesions suggest that another relapse might occur within the next 5 years. At the initial diagnosis of CIS, the higher the number of lesions, the greater the risk of long-term disability in the later years. Around 40% of patients diagnosed initially as CIS enter the secondary progressive phase of the disease within 15-20 years (Tullman, 2013). 85% to 90% of people affected by MS develop a RRMS phenotype and 8 in every 10 converts to SPMS within 20 years. To confirm transition to the Secondary Progressive type of MS the patient should show gradual deterioration with or without relapses for ≥ 6 months (Inojosa et al., 2019). Conducting an early and accurate diagnosis of SPMS has significant implications in management and patient care. However, in clinical practice, this is not easily accomplished, and a period of diagnosis uncertainty is likely to exist. One study found that the duration of uncertainty was around 2.8 ± 0.8 years. Clinicians are usually cautious in confirming transition to SPMS due to the lack of treatment options and the stress it can pose on the patient (Katz Sand et al., 2014).

Figure 3.1 Meta- analysis results comparing MS cadence to healthy individuals

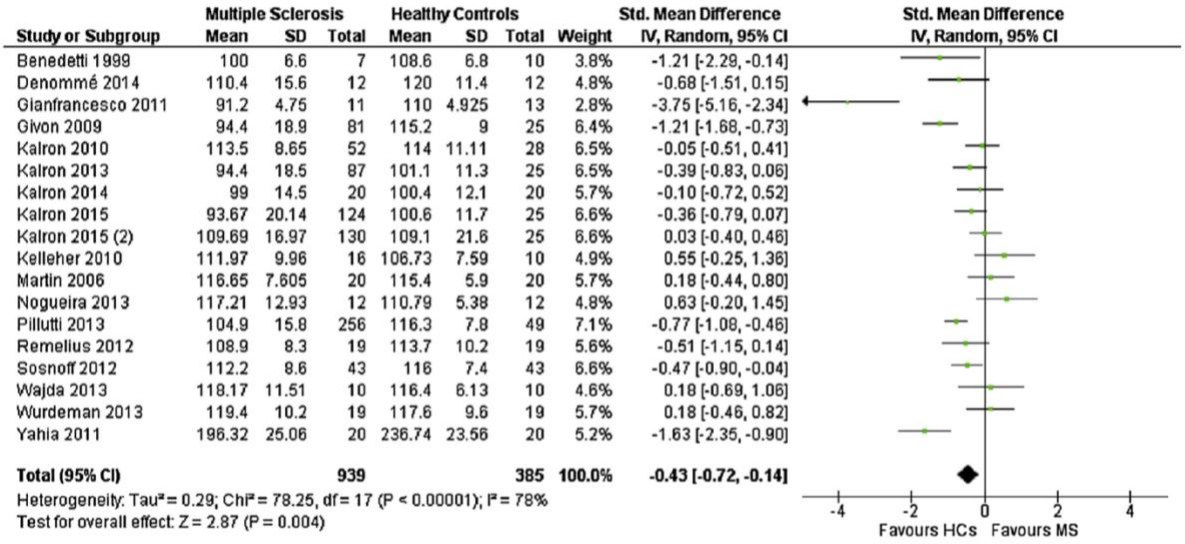


Figure 3.2 Meta- analysis results comparing swing time in MS to healthy individuals

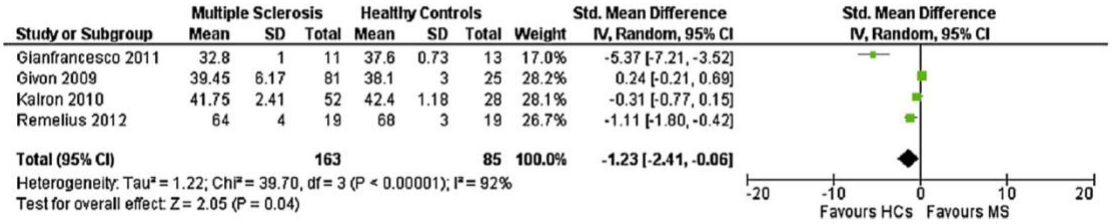


Figure 3.3 Meta- analysis results comparing stride length in MS to healthy individuals

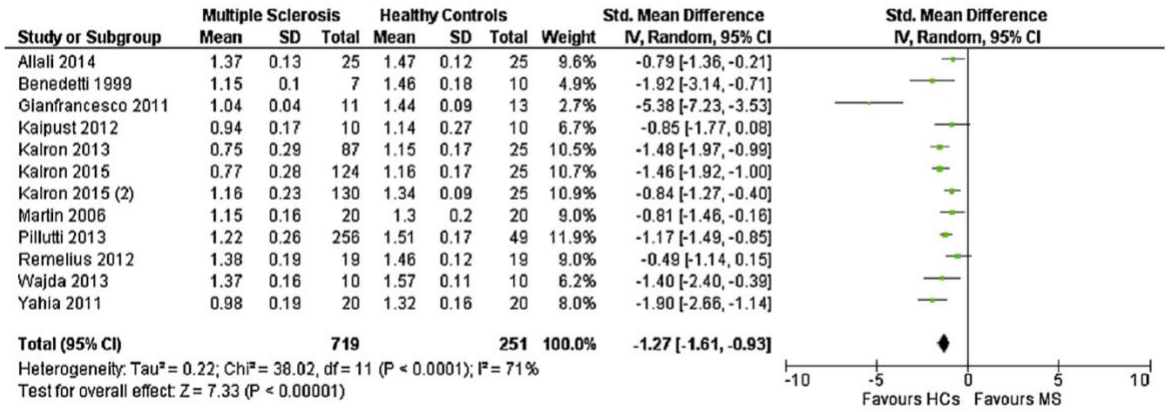
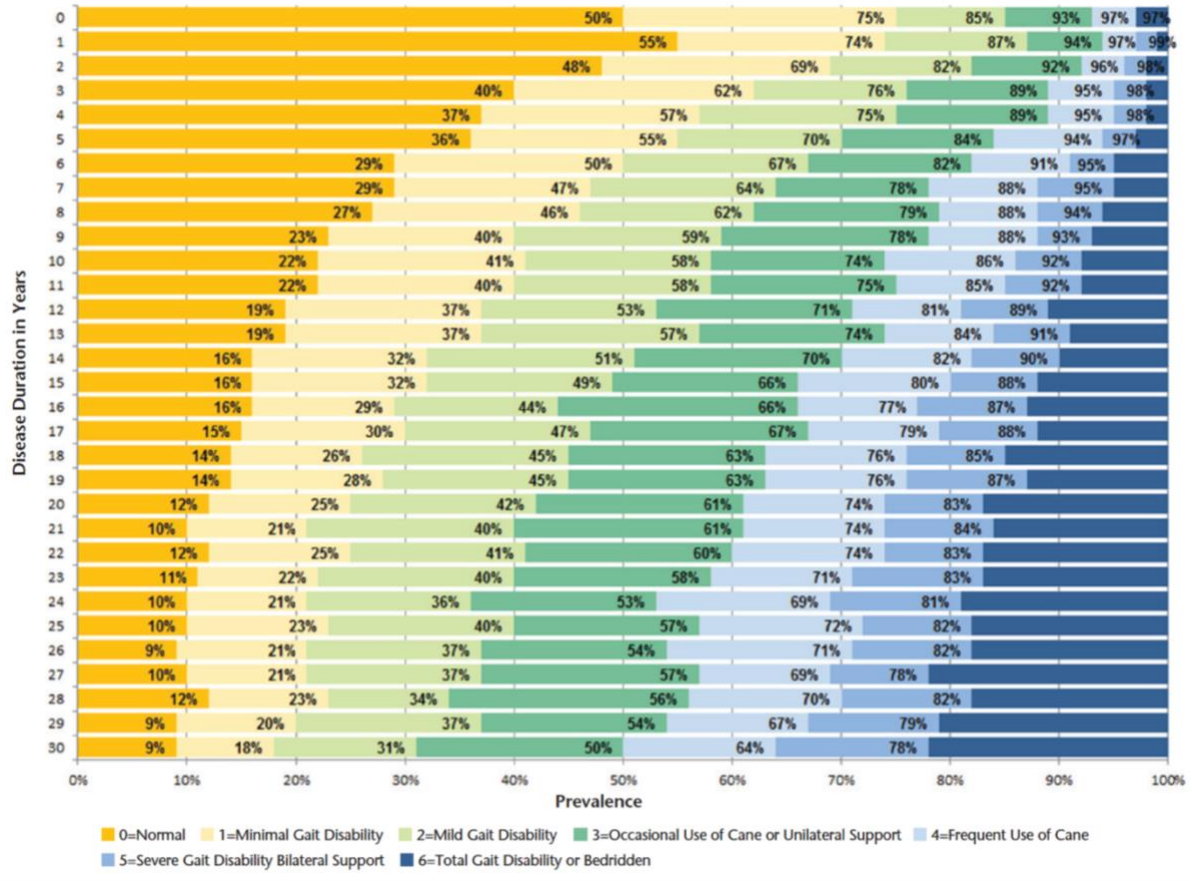


Figure 3.4 Natural history of mobility limitation in 23,860 MS patients.



Chapter 3 Objectives and Rationale

Time matters in MS. Damage to the CNS starts with the disease diagnoses and progresses over time (Lassmann, 2018). To improve the health system's response to the disease, concerted research efforts were directed toward establishing solid criteria for disease diagnosis as well as developing new therapies. As a result, McDonald's criteria were developed and are being used now to confirm MS diagnosis. Different disease modifying therapies (DMT) also emerged and are now available to alter the course of the disease. Multiple studies in RRMS showed that the early usage of DMT resulted in lower mortality rates and slower progression of disability (Goodin et al., 2012; O'Connor et al., 2014). However, less success was gained in the area of progressive MS whether in diagnosis or treatment. Timely diagnosis of the transition into SPMS is also challenging and a gap of uncertainty usually exists before confirming the diagnosis. Clinicians and patients are usually reluctant to declare the transition due to the scarce interventions available for this form of the disease (Katz Sand et al., 2012). Nonetheless, new therapies are emerging (Bhatia & Singh, 2019), and some hold a promising future for SPMS (Gajofatto, 2017; Dumitrescu et al., 2019). Trials published on these medications found that benefits – in form of delaying disability- were maximized when medications were administered early (Kappos et al., 2016), which stresses the need for establishing better diagnostic criteria of SPMS to achieve accurate diagnosis and modify the treatment plan early.

SPMS is defined as deterioration independent of relapses ≥ 6 months. EDSS is the current gold standard of monitoring disease progression (Kurtzke, 1983); however, in SPMS, EDSS has poor responsiveness to changes (Cadavid et al., 2010). Also, gait and balance impairments were observed independent of changes in EDSS (Galea et al., 2017). In response to these critics, EDSS was modified by adding other components (Cadavid et al., 2017), and other measures -such as

MSFC (Fischer et al., 1999)- were used as alternatives in trials of advanced MS (Hyland & Rudick, 2011). In both measures, information is collected on gait, reflecting that gait provides valuable information on the disease status and is an integral part of monitoring disease progression. Therefore, to contribute evidence toward using gait data in monitoring disease progression, we propose using gait kinematics in tracking gait changes in MS and as a result, we approach the gait kinematics topic in MS from a descriptive perspective to lay the foundation and to inform the direction of future studies.

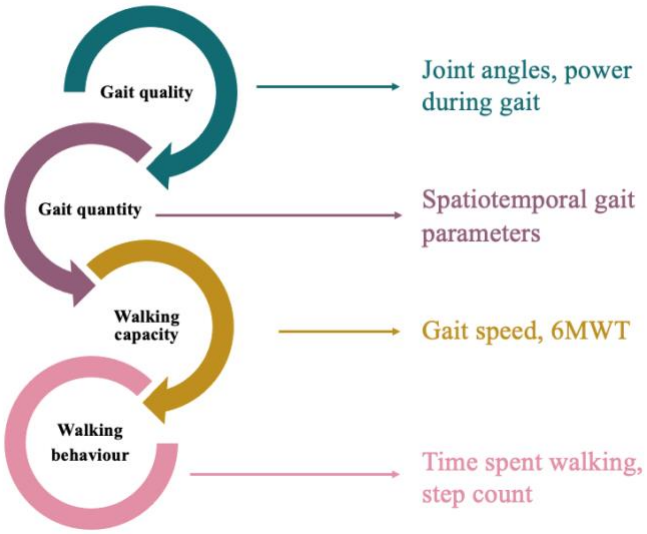
Most gait studies in MS were done at the level of spatiotemporal parameters (step length, swing time, etc.), walking capacity (walking speed or endurance), or walking behavior (step counts). Although these gait outcomes are important, other outcomes such as gait kinematics could have the advantage of detecting early changes. A process through which gait changes develop is proposed in Figure 1. Changes in gait can go un-noticed particularly in gait kinematics such as joint angular velocity. These subtle changes might accumulate and lead to other easily observed gait changes such as gait speed and participation in walking activities. This suggests that gait kinematics might enable early detection of functional deterioration which is of great value in progressive diseases such as MS. Finding associations between MS symptoms and gait kinematics that deteriorate earlier than other gait outcomes might be promising in advancing our knowledge of early triggers of the disease progression. In addition, finding potential relationships helps in developing better interventions that are mechanistically driven.

This thesis is also driven by the possibility of using gait kinematics data obtained from a portable sensor in monitoring disease progression which could have tremendous applications in self-management. Measuring gait kinematics in the past required the use of complex and expensive systems, i.e., 3D motion analysis systems, resulting in sparse studies that investigate and explain

how these gait parameters change due to health conditions. Nowadays portable sensors provided access to some of these gait kinematics and allow data collection for a long duration and in a real environment. Low cost, portability, combined with ease of use and interpretation have favorable implications in research and clinical setting. One of the currently available sensors is “Heel2toe”, a device made of a 3-axis accelerometer and 3-axis gyroscope that can be worn at the side of the foot using an elastic strap or clip (Vadnerkar et al., 2017). It is used to detect heel-to-toe stepping patterns by recording angular velocity at the ankle joint. It can also provide other gait parameters that are important in gait analysis such as cadence and swing time.

The objective of this thesis is to contribute evidence as to the relevance of measures of gait kinematics to quantify disability in MS. The thesis will be manuscript-based built of one manuscript that investigates two objectives. Primary objective is to estimate the extent to which personal factors and functional indicators are associated with gait quality parameters among ambulatory people with MS. Secondary objective is to estimate the extent to which gait quality parameters change over 3 months period without gait-targeted treatment among people with MS.

Figure 3.1 Pathway of gait changes



Chapter 4: Manuscript 1

Gait Quality in Multiple Sclerosis and Relationship with Functional Indicators

Aeshah Alosaimi, B.Sc., PT[1, 3]; Kedar K. V. Mate, PT. Ph.D.[2, 3, 4]; Helen Dawes, Ph.D.[6,7]; Nancy E Mayo, PhD.[1,2, 3]

1. Faculty of Medicine, School of Physical and Occupational Therapy, McGill University, Montreal, Quebec H3G 1Y5, Canada
2. Family Medicine, McGill University, Montreal, Quebec, Canada
3. Center for Outcomes Research and Evaluation, McGill University Health Centre Research Institute, Montreal, Quebec, Canada
4. Department of Orthopedics, Mayo Clinic, Arizona, USA
5. Division of Clinical Epidemiology, McGill University, Montreal, Quebec, Canada
6. Centre for Movement Occupational and Rehabilitation Sciences, Department of Sport, Health Sciences and Social Work, Oxford Brookes University, Headington Rd, Headington, Oxford OX3 0BP, UK
7. NIHR Oxford Health Biomedical Research Centre, Oxford OX3 7JX, UK

The manuscript will be submitted to a scientific journal

Corresponding author:
Aeshah Alosaimi
School of Physical and Occupational Therapy,
McGill University,
Center for Outcome Research and Evaluation,
McGill University Health Centre-Research Institute,
5252 de Maisonneuve,
Montréal, Québec H4A 3S5
aeshah.alosaimi@mail.mcgill.ca

Abstract

Background: The monitoring of gait impairments is promising for detecting progression in people with Multiple Sclerosis (MS). With the recent advancement in portable sensors, comprehensive gait assessment is more accessible. Measuring gait kinematics parameters, such as angular velocity, could provide valuable information regarding gait quality. Linking changes in gait kinematics with MS-impairments and function would be valuable to inform treatment and prognosis.

Objective: The first objective of this study is to estimate the associations between MS-related impairments and gait quality measures. The second objective is to estimate changes over time in gait quality in people with MS participating in an exercise intervention that did not include gait-targeted treatment.

Methods: This is a secondary analysis of gait kinematics data collected using Heel2Toe^{TM} sensor during the Modified Six-Minute Walk Test (m-6MWT). Cross-sectional correlation (first objective) and individual analysis (second objectives) were carried out.

Results: Depression, vertical jump, and modified 6-minute walking distance (m-6MWD) showed the strongest correlation with one or more gait quality measures. Equal numbers of people improved, deteriorated, or did not change in gait quality over time as seen in the individual analysis. Across change categories, the highest concordance was seen between ankle angular velocity at push-off - ankle angular velocity of foot swing and power cycle-balance cycle.

Conclusion: Gait quality is linked to MS impairments and function activities. Wearable sensors can easily be used to measure gait quality and develop personalize interventions.

Introduction:

Multiple sclerosis (MS) is a multifactorial autoimmune disease of the central nervous system (CNS) that is characterized by chronic inflammation, demyelination, and axon and neuronal loss (Pegoretti et al., 2020). Depending on the size and location of the MS lesions, people can experience a wide range of sensory, visual, motor, and cognitive symptoms as well as fatigue, pain, and depression (Pegoretti et al., 2020; Kister et al., 2013). While fatigue and sensory impairments are most common within the first years of the disease, cognitive, visual, pain, and mood symptoms occur throughout the course of MS. Changes in motor impairment (hand function, mobility, spasticity, and bowel/bladder dysfunction) mark the transition from "minimal/mild' to "moderate/severe/ MS (Kister et al., 2013). A consistent decline in motor functions, independent of relapses, is a key feature of progressive MS whether primary (progressive from onset) or secondary (develop following relapsing-remitting MS) (Thompson et al.,2018).

The Expanded Disability Status Scale (EDSS), the clinical measure used to monitor disease progression, relies heavily on changes in ambulation (Kurtzke, 1983). However, in early MS, subtle gait changes have been found independent of changes in EDSS (Martin et al., 2006). Therefore, gait assessment was suggested as a more accurate method of disease monitoring (Cofré Lizama et al., 2016). At a global level, the gait in people with MS differs from healthy individuals in having shorter steps, longer swing time, and slower cadence (Comber et al., 2017). These gait measures, known as spatiotemporal parameters, are the focus of many gait studies in MS. Other gait parameters such as kinematics and kinetics were less commonly studied as they required the use of expensive systems and trained researchers (Kelleher et al., 2010). However, the recent development of wearable sensors has made measuring some of these parameters more accessible.

One such sensors is the “Heel2toe”, a device made of a 3-axis accelerometer and 3-axis gyroscope that can be worn at the side of the foot using an elastic strap or clip to provide data on ankle kinematics (angular velocities) during walking (Vadnerkar et al., 2017). The degree of angular velocity at the ankle joint was found to be an important determinant of leg power during the vertical jump (Ibrahim et al., 2020), the speed of forward progression (Winter, 2009) and the push-off event in terminal stance (Mentiplay et al., 2018). In MS, Parkinson’s, and older adults, every -50 degree/seconds change in ankle angular velocity was found to associate with a difference of ≈3.5 steps per minute (Mate et al., 2019. Therefore, ankle angular velocity might be a good indicator of gait quality. Also, gait quality measured by gait kinematics could precede other tangible changes in gait such as those of step length, cadence, and gait speed; therefore, measuring gait kinematics could flag earlier deterioration in gait and the MS disease, and also enable earlier intervention before impairments accumulate and lead to fall incidence or affect participation in walking activities.

In MS, abnormality in ankle kinematics such as ankle angular velocity has been repeatedly reported (Kempen et al., 2016; Kelleher et al., 2010; Martin et al.,2006). Associations between common MS common impairments and changes in spatiotemporal gait parameters have been observed (Kalron, 2015; Newland et al., 2020; Plotnik et al., 2020). Little is known with regards to gait kinematics. With the recent development in portable sensors and their widespread use in gait assessment, measuring gait kinematics is more accessible and could be used to monitor changes over time. Therefore, the first aim of this study is to characterize gait quality parameters among ambulatory people with MS and to estimate the extent to which personal factors and functional indicators are associated with gait quality. The second aim was to estimate the extent to

which gait quality parameters changed over 3 months period in people with MS participating in an exercise intervention that did not include gait-targeted treatment.

Methods:

Study design:

This study is a secondary analysis came from a randomized trial of the Multiple Sclerosis Tailored Exercise Program (MSTEP©). The protocol and results from the trial have been published elsewhere (Mayo et al., 2013; Mayo et al., 2020). Only data from the Montreal site were analyzed as the Heel2Toe sensor was available locally. Both a cross-sectional (Objective 1) and a longitudinal (Objective 2) design were used. Ethics approval for the trial was obtained from the Montreal Neurological Hospital Research Ethics Board.

Participants:

The participants included in the trial were: aged between 19 to 65 years, diagnosed with Multiple Sclerosis after the year 1994, able to walk 100 meters without an assistive device (corresponds to $\leq$ 5.5 on EDSS), self-reported to be sedentary (<60 minutes of exercise in a week), able to communicate in English or French, able to answer simple memory and orientation questions during an interview, no co-morbidity restricting function, and no relapse in the past 30 days. For this study, data from the Heel2Toe^{TM} sensor had to be available as it was added after the trial started and data were obtained depending on the availability of the tester (KM).

Measures:

The measurement framework for this study is shown in Figure 4.1 and is based on The World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF). Theoretically, poor gait quality arises from neuromotor impairments that can be detected as deviations from optimal gait kinematics which subsequently lead to limitations in walking

capacity, limited physical function, and low exercise capacity as a consequence of limited opportunity or desire to exercise. In people with MS the factors that relate to poor gait quality, apart from age, are those also classified as impairments under the ICF: pain, fatigue, mood, muscle weakness, poor co-ordination, and bladder dysfunction as an indicator of spasticity. Data collected used both performance tests (observed or assessed with technology) and self-report measures.

Gait impairments were assessed using the Heel2Toe™ technology. During the 6-minute walking test, participants wore the Heel2Toe™ sensor on the outside of their right shoe using an adjustable elastic strap. The following metrics were extracted: 1) ankle angular velocity (AAV) at heel strike; 2) ankle angular velocity at push-off; 3) ankle angular velocity of foot swing; 4) swing time measured as the time from push-off to heel strike; 5) power cycle (Area Above the Curve – the x-axis: AAC); 6) balance cycle (Area Under the Curve – X-axis: AUC)- so named as its magnitude depend, at least in part, on the capacity for single leg stance on opposite side requiring balance; 7) Coefficient of Variation (CoV = Standard deviation/Mean) of all variables as a measure of gait variability; and 8) cadence (steps per minute). Figure 4.2 provides a visual representation of the metrics obtained by Heel2Toe. Appendix 1 provides a detailed description of these metrics. For cadence, moving from one band to another was considered meaningful (see Appendix 1), while half (½) SD was considered a meaningful change for the other gait quality parameter (Norman et al., 2003).

Functional walking capacity was tested using the modified 6-minute walking test (m-6MWT) (Goldman et al., 2008). People are instructed to walk as fast as they can, and the distance covered in each minute is recorded. Exercise capacity was measured by peak oxygen consumption (VO_{2peak}). Global physical function was self-reported using RAND-36 physical function subscale (Hays et al.,1993).

Other MS-related impairments were: (i) core strength represented by the two variables curl-ups and push-ups (count in 30 seconds); (ii) leg power as measured by the average of 3 trials of maximum vertical jump distance reached; (iii) leg weakness, leg heaviness, coordination, and bladder problem were self-reported as binary (yes/no); (iv) depression item selected from self-report scale EuroQol Index (EQ-5D-3L). Regarding fatigue measures, participants were asked to rate their general and leg fatigue before and after m-6MWT using a 0-10 visual analogue scale where 10 represents worst fatigue. Performance fatiguability was calculated from the m-6MWT (Goldman et al., 2008) using "Fatigability index" (the distance walked in the last minute of 6MWT ÷ distance walked in the first minute). Ratio ≥ 1.0 indicates less fatigability. More details on the measures used are presented in the main study (Mayo et al., 2020).

Data analysis:

All analysis was carried out using R software. Participants' characteristics and gait parameters are presented descriptively for men and women separately. Mean, standard deviation (SD), median, inter-quartile range (IQR) and minimum-maximum are presented. Association between MS-related impairments, gait metrics, and distal outcomes of walking and exercise capacity and physical function were estimated using Pearson, Spearman, and Biserial correlations depending on the measurement scale of the variables. The value of the coefficient is presented with values >0.4 (moderate strength: 0.3 to 0.5) considered to indicate associations worthy of further investigation (Cohen, 1988). Missing data was handled using pairwise deletion.

To estimate changes over time, only a small subset of the included sample had data at two-time points, therefore, an individual analysis was carried out. Chi-square was then applied to compare the observed pattern of change to uniform distribution. Concordance rates were also calculated as a measure of association between changes in different gait metrics.

Sample size:

As these analyses were based on existing data, the available sample size was used to estimate confidence intervals (CI) for the correlation coefficients for the cross-sectional analyses. For a moderate to strong correlation of 0.45; 55 people would yield a 95% CI ranging from 0.21 to 0.64 which excludes trivial correlation.

Results:

A total sample of 55 participants was available for the analysis. Table 4.1 shows the participants characteristics with data on function-related measures according to sex. Women accounted for 70% of the sample and were younger by approximately 2 years with a mean age of 47.3 ± 9.7 years. For both women and men, relapsing-remitting was the most common MS type. Coordination, core strength (push-up, curl-up) and leg power (vertical jump) were all considerably lower than norms for both women and men. Participants rated fatigue more than 2 points higher after the m-6MWT. The women and men showed the same level of performance fatiguability (0.8) during the 6MWT.

Table 4.2 presents the distribution of the sample on gait quality parameters. Cadence for women and men were 94 and 89 steps per minute respectively which is largely below normative values of the healthy similar age group (McKay et al., 2017). Ankle angular velocity was greater during push-off followed by foot swing and lastly heel strike. The coefficient of variation (CoV) describes within-person variability. In general, no difference was observed between men and women in CoV. The highest variability was seen in ankle angular velocity at heel strike (32% women, 34% men) and the least variability was evident in ankle angular velocity of foot swing.

Table 4.3 presents the distribution of the sample on variables related to walking and exercise capacity and physical function. Both women and men were lower than normative values on all these measures.

Table 4.4 presents the correlation between MS-impairments and gait quality measures. Vertical jump was the most highly correlated with almost all gait quality measures. The strongest correlation was with ankle angular velocity of foot swing, ankle angular velocity at push-off, power cycle and balance cycle (0.43, 0.42, 0.40, 0.40 respectively). Depression also showed potential association with multiple gait parameters such as power cycle, balance cycle, and to a lesser degree with ankle angular velocity at push-off and ankle angular velocity of foot swing. Among fatigue measures, only the correlation between performance fatiguability and swing time exceeded the threshold for interest of 0.3

Table 4.5 displays the correlations between gait quality measures and the distal outcomes of walking and exercise capacity and physical function. The strongest correlations (0.5 to 0.7) were seen between all gait quality measures (except swing time) and walking capacity measured by the 6MWT.

To estimate change over time (objective 2), only 17 participants had data at two-time points and were therefore included in the analysis. Figures (4.3-4.9) presents their individual analysis of gait quality parameters. Most deterioration was observed in cadence, ankle angular velocity at push-off and ankle angular velocity of foot swing. Five participants deteriorated in 4 or more gait quality measures (participant 8,11,12,14,17). Interestingly, participant 2, 9, and 15 showed improvement in 5 or more of gait parameters measured. Two participants were stable over the three months period (Subject5 and 10). Table 4.6 showed that the observed distributions did not differ from a uniform distribution indicating no pattern to the changes over time.

Tables (4.7, 4.8, 4.9) presents the concordance between change in ankle angular velocity (AAV) at push-off and change in AAV at heel strike, cadence and AAV of foot swing. Across change categories, the highest concordance was seen between AAV at push-off and AAV of foot swing (82%). Out of the 7 participants (41%) who declined in AAV at push-off, 6 exhibited a decline in AAV of foot swing and one showed no change. Participants who improved or declined in the power cycle showed the same pattern of change in the balance cycle. The concordance was 82% (Table 4.10).

Discussion:

This study shows that leg power and depression correlated with gait quality in people with MS. In return, impaired walking quality was mostly associated with limited walking capacity and showed no relationship with physical function suggesting that people still carry out their function of daily living regardless of their impairment. Our results of the individual analysis of changes over time were in line with the individual variations in the course of MS. Some participants either improved or deteriorated in most of the gait quality measures. Others maintained the same quality for the 3 months period.

The strong correlation between leg power and gait quality measured by ankle angular velocities could stem from the speed component that is common in both quantities. Leg power as measured by vertical jump is the product of force and speed, angular velocity, on the other hand, defines how fast the joint moves in either direction. Speed is essential to produce the power needed to maintain a good quality of walking such as power at push-off to propel the body forward or during foot swing to allow clearance and longer swing. Previous studies found an association between leg power and grey matter in mid-aged females (Steves et al., 2016). It is now recognized that changes in the grey matter could develop in early MS (Haider et al., 2014) which might impact the

performance of vertical jump and therefore gait quality. In older adults, leg power was found to deteriorate earlier and more rapidly compared to strength (Md et al., 2002; Evans, 2000). The possible explanation is the selective atrophy of type II fibers (fast-twitch) in advanced age that is thought to be involved in power output. Loss of these fibers might also contribute to the degree of angular velocity exerted at the ankle joint and therefore explain the association between leg power and gait quality.

Depression also showed significant associations with gait measures specifically, power cycle and balance cycle (AUC and AAC). These values are driven by the height (depth) and width of the measured wave which is formed by angular velocity and the step length respectively. Previous studies found a decrease in stride length in depressed individuals with no other health conditions (Lemke et al., 2000); however, that results were different from those of Kalron & Aloni, 2018 who found no difference in stride length, gait variability, double support time and stance phase between depressed and non-depressed MS patients. Another possible explanation is motor retardation, one of the main features of major depression, which is identified as a slow movement including slow gait speed (Buyukdura et al., 2011). Slow gait speed is known to decrease joint angular velocities and to interfere with other gait parameters (Mentiplay et al., 2018).

The six-minute walking distance (6-MWD) had the strongest correlation with almost all gait quality measures. Alteration in gait spatiotemporal parameters is known to increase the energy cost of walking which in return leads to rapid fatigue (Motl et al., 2012). Changes in joint angular velocities could impact walking efficiency and decrease the amount of distance covered per minute. Our results suggest that impaired walking capacity because of impaired gait quality might extend to interfere with participation in walking activities.

Changes over time in gait quality varied greatly between individuals. Although 3 months is a short period and major changes are not expected, multiple participants deteriorated in more than one aspect of gait quality. Changes over time in gait kinematics could be monitored using these sensors to provide information on physical deterioration needed to flag transition into secondary progressive MS. Future research could explore the benefit of using these sensors as a self-management tool.

Our study explores several MS-impairments that are theoretically expected to be linked with early gait changes. These factors can be targeted in early MS intervention to maintain healthy walking and delay disability. Also, gait was linked to disease deterioration, therefore, studying the mechanism that underlies gait changes attributed to these factors could yield valuable knowledge on the overall disease prognosis. SPMS is defined as deterioration independent of relapses ≥ 6 months, therefore a consistent decline in gait data could be studied in future research parallel to data obtained from EDSS to see whether gait data proceeds and predict EDSS changes or behave the same in order to use it in diagnosing transition to a progressive form of MS. The use of wearable sensors allowed data collection of gait measurement over 6 minutes which improves accuracy and could enable studying performance fatiguability in each of these measures.

There are several limitations in our work. The data arose from an existing study in which the sensor was added after the trial started and not all people were tested. There are missing data on different MS impairments which resulted in using different sample size for each correlation; however, the smallest sample size used was 30 participants which is acceptable in correlation.

Conclusion:

Gait quality in MS patients could be hindered by impairments associated with the disease. Although gait quality is measured by subtle alteration in joints kinematics, the effect of these

changes could extend to include walking capacity and walking behaviour. Changes over time in gait quality of MS patients vary between individuals and thus can be used to monitor disease prognosis.

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Figure 4.1 Theoretical Model of the measurement framework

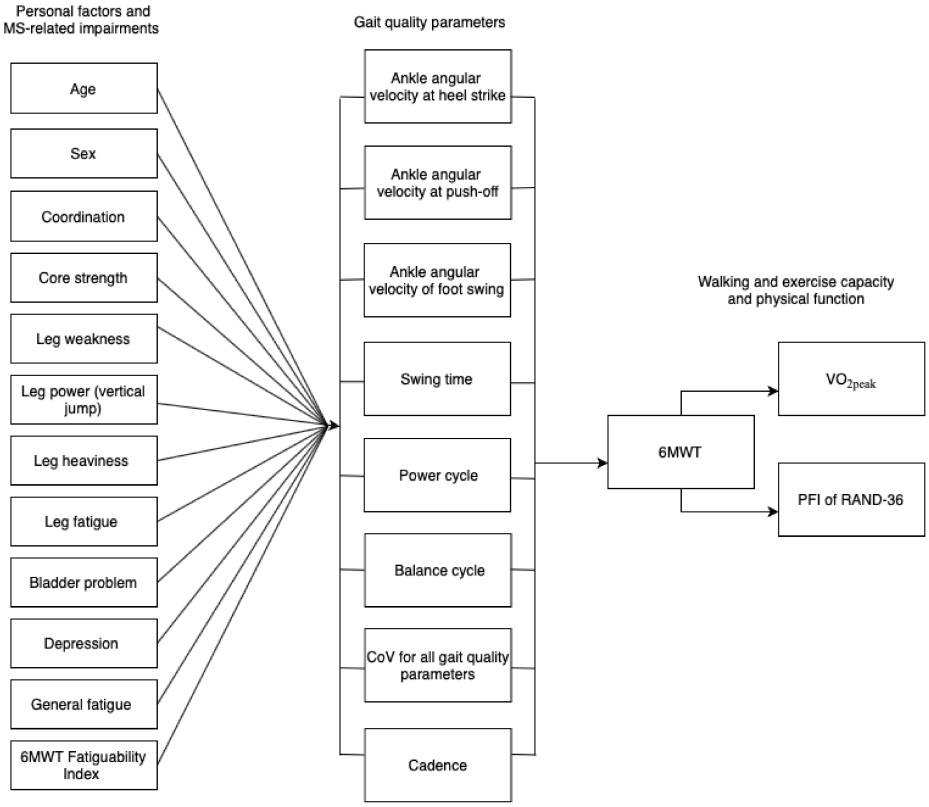
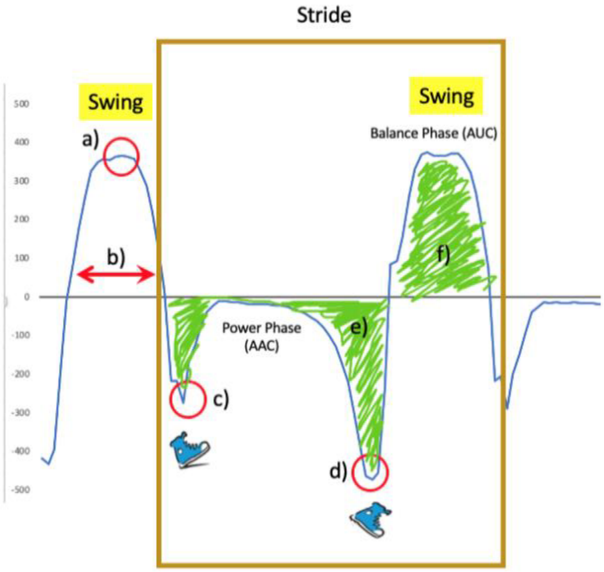


Figure 4.2: Visual representation of the metrics obtained by Heel2Toe. Same title from the text.



a) angular velocity of foot swing. b) swing time. c) angular velocity at heel strike. d) angular velocity at push off. e) power cycle. f) balance cycle

Table 4. 1: Characteristics of the Participants by Age, MS-Type, and Impairment-Relative Factors

Variables	**Women (n=39)**	**Men (n=16)**
	Mean ± SD or n (%)	
Age (years)	47.3 ± 9.7	49.9 ± 9.4
Min – Max	23.1 – 64.1	28 – 61
MS type		
Relapsing Remitting	25 (64.1)	12 (75)
Primary Progressing	1 (2.6)	1 (6.2)
Clinically Isolated Syndrome	1 (2.6)	
Missing	12 (30.8)	3 (18.8)
Coordination impairment		
Yes	9 (23.1)	3 (18.8)
No	13 (33.3)	8 (50)
Missing	17 (43.6)	5 (31.2)
Core strength factors		
Push ups (count in 30 sec)	1.6 ± 3.7	4.4 ± 5.7
Median [IQR]	0 [0.8]	2 [7]
Min – Max	0 – 18	0 –18
Missing	1 (2.6)	-
Curl ups (count in 30 sec) *	8.3 ± 9.6	13.6 ± 11.2
Median [IQR]	2 [15.8]	16.5 [25]
Min – Max	0 – 25	0 – 25
Missing	1 (2.6)	-
% predicted*	31– 40	41–50
Lower limb specific factors		
Vertical jump (cm)*	18.2 ± 6.5	24 ± 11.5
Missing	-	1 (6.2)
% of predicted	21 – 30	11 – 20
Leg weakness		
Yes	11 (28.2)	8 (50)
No	11 (28.2)	3 (18.8)
Missing	17 (43.6)	5 (31.2)
Leg heaviness		
Yes	13 (33.3)	4 (25)
No	9 (23.1)	7 (43.8)
Missing	17 (43.6)	5 (31.2)
Activity-specific factors (from 6MWT)		
Leg Fatigue (scored from 0-10)		
Pre-test	1.8 ± 1.9	2.7 ± 1.9
Median [IQR]	1 [3]	2 [2.5]
Post-test	4.2 ± 2.6	4.3 ± 2
Median [IQR]	5 [4.5]	4 [2.6]
General fatigue (scored from 0-10)		
Pre-test	2.7 ± 2.4	2.8 ± 2.1
Median [IQR]	2 [5]	2.5 [4]
Post-test	4.5 ± 2.4	4.3 ± 2.1
Median [IQR]	5 [3.5]	4.5 [3.4]
Fatigability Index**	0.8 ± 0.1	0.8 ± 0.1
Missing	16 (41)	5 (31.2)
Bladder problems		

Yes	6 (15.4)	2 (12.5)
No	16 (41)	9 (56.2)
Missing	17 (43.6)	5 (31.2)
Psychological status		
Anxious or Depressed		
Not	11 (28.2)	6 (37.5)
Moderately	11 (28.2)	5 (31.2)
Extremely	1 (2.6)	-
Missing	16 (41.0)	5 (31.2)

n= number, SD= standard deviation, IQR= interquartile range, sec= seconds, 6-MWT= 6-minute walking test, min-max= minimum – maximum
*normative data from Payne et al., 2000
**Ratio of distance in last minute of 6MWT to distance in first

Table 4. 2: Gait quality measures

Variables	Women (n=39)	Men (n=16)
	Mean ± SD	
Cadence (steps/min) *	94 ± 16	89 ± 23
Median [IQR]	93 [16]	98 [29]
Min – Max	61 – 129	33 – 124
Ankle angular velocity at heel strike (deg/s)	-332 ± -72	-328 ± -70
Median [IQR]	-343 [-101]	-330 [-85]
Min – Max	-162– (-445)	-185 – (-457)
CoV (%)	32 ± 9	34 ± 10
Ankle angular velocity at push-off (deg/s)	-498 ± -65	-470 ± -131
Median [IQR]	-508 [-93]	-522 [-118]
Min – Max	-328 – (-614)	-175 – (-593)
CoV (%)	23± 10	24 ± 8
Ankle angular velocity of foot swing (deg/s)	422 ± 56.7	375 ± 97
Median [IQR]	398 [85]	389 [83]
Min – Max	332 – 546	130 – 525
CoV (%)	13 ± 4	14 ± 4
Swing time (sec)	0.32 ± 0.04	0. 34 ± 0.04
Median [IQR]	0.3 [0.04]	0.32 [0.03]
Min – Max	0.3 – 0.6	0.29 – 0.48
CoV (%)	20 ± 7	19 ± 8
Power cycle (AUC)	-3735± -443	-3572 ± -814
Median [IQR]	-3649 [593]	-3681 [-1104]
Min – Max	-2662 – (-4687)	-1696 – (-5077)
CoV (%)	24 ± 8	23 ± 7
Balance cycle (AAC)	3956± -542	3702 ± 928
Median [IQR]	3924 [709]	3726 [972]
Min – Max	2373 – 5217	1557 – 5345
CoV (%)	18 ± 7	19 ± 6

SD= standard deviation, min= minute, IQR= interquartile range, min-max= minimum – maximum, deg= degree, s= second, CoV= coefficient of variation, AUC= area under the curve, AAC= area under the curve, *Cadence norms for the same age group: Women 119, Men 112

Table 4. 3: Distribution of the sample on walking and exercise capacity and physical function

Variables	Women (n=39)	Men (n=16)
	Mean ± SD	
6MWD (meters)	515.4 ± 90.8	493.9 ± 148.8
Min – Max	254 – 675	105 – 681
Missing	-	1 (6.2)
Norms*	554.1	608.7
VO_{2peak}	26.61 ± 6.53	26.08 ± 7.02
Median [IQR]	26.7 [9.17]	25.2 [10.1]
Min – Max	13.63 – 41.2	13.6 – 35.57
Missing	4 (10.2)	3 (18.8)
% predicted**	20%	5%
RAND-36 PFI***	77.62 ± 19.91	78.18 ± 10.31
Median [IQR]	80 [25]	75 [15]
Min – Max	35 – 100	65 – 95
Missing	18 (46.2)	5 (31.2)
Norms	89.3	88

6-MWD= 6-minute walking distance, PFI= physical function index, SD= standard deviation, IQR= interquartile range, min-max= minimum – maximum
*Reference man and woman (Snyder et al., 1979) were used in 6MWD calculator
** Reference from Hoffmann et al., 2019
***Reference Hopman et al., 2000

Table 4. 4: Correlations between impairments and gait quality measures

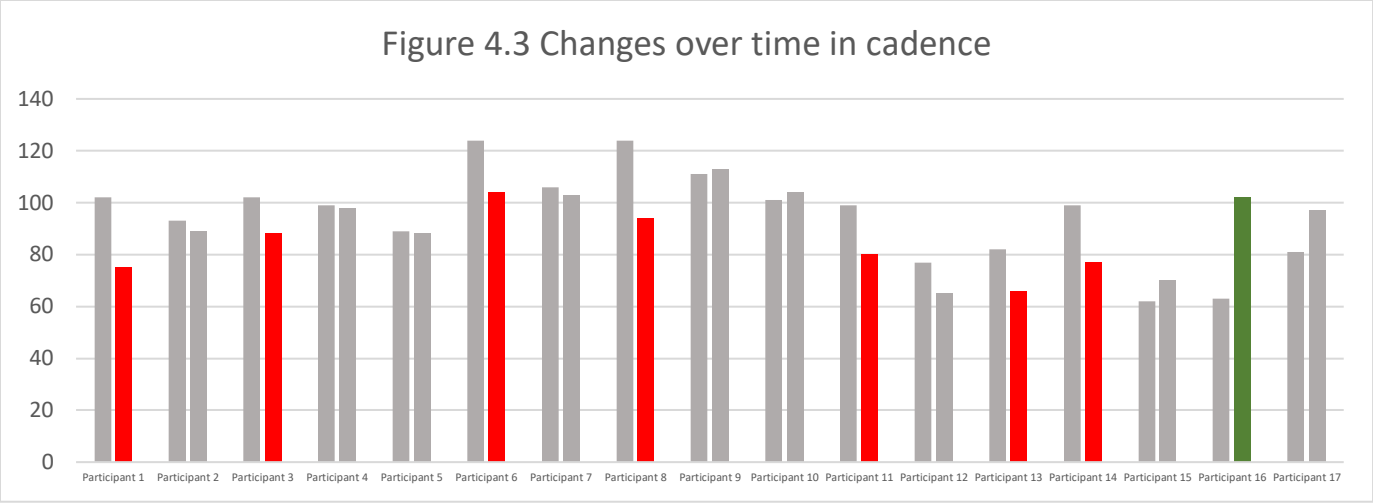
	Cadence	AAV at Heel Strike	AAV at push off	AAV of foot swing	Swing time	Power cycle (AUC)	Balance cycle (AAC)
Age	0.10	0.22	-0.11	-0.19	0.02	-0.06	-0.05
Sex	0.11	-0.02	-0.15	0.29	-0.15	-0.13	0.17
Coordination	0.26	-0.01	-0.20	-0.01	-0.30	-0.09	0.02
Push up	-0.01	-0.07	-0.11	0.13	-0.03	-0.20	0.22
Partial curl up	0.18	-0.24	-0.25	0.22	-0.21	-0.17	0.19
Leg weakness	0.31	-0.16	-0.18	-0.12	-0.13	-0.01	-0.18
Leg heaviness	-0.02	-0.06	-0.18	0.08	0.04	-0.17	0.04
Vertical Jump	0.22	-0.31	**-0.42**	**0.43**	-0.19	**-0.40**	**0.40**
Pre leg fatigue	-0.22	0.21	0.10	-0.19	0.0	0.04	-0.10
Post leg fatigue	-0.19	0.21	0.24	-0.15	-0.02	0.08	-0.17
Bladder Problem	-0.03	-0.004	-0.19	0.07	0.20	-0.27	0.17
Depression	0.10	0.26	0.34	-0.28	-0.06	**0.45**	**-0.44**
Pre general fatigue	0.01	0.05	-0.04	-0.16	-0.08	0.14	-0.08
Post general fatigue	0.21	-0.02	-0.08	-0.05	-0.19	-0.09	-0.12
Fatiguability index	-0.21	-0.11	-0.07	0.19	**0.35**	0.22	0.20

AAV= ankle angular velocity, AUC= area under the curve, AAC= area under the curve

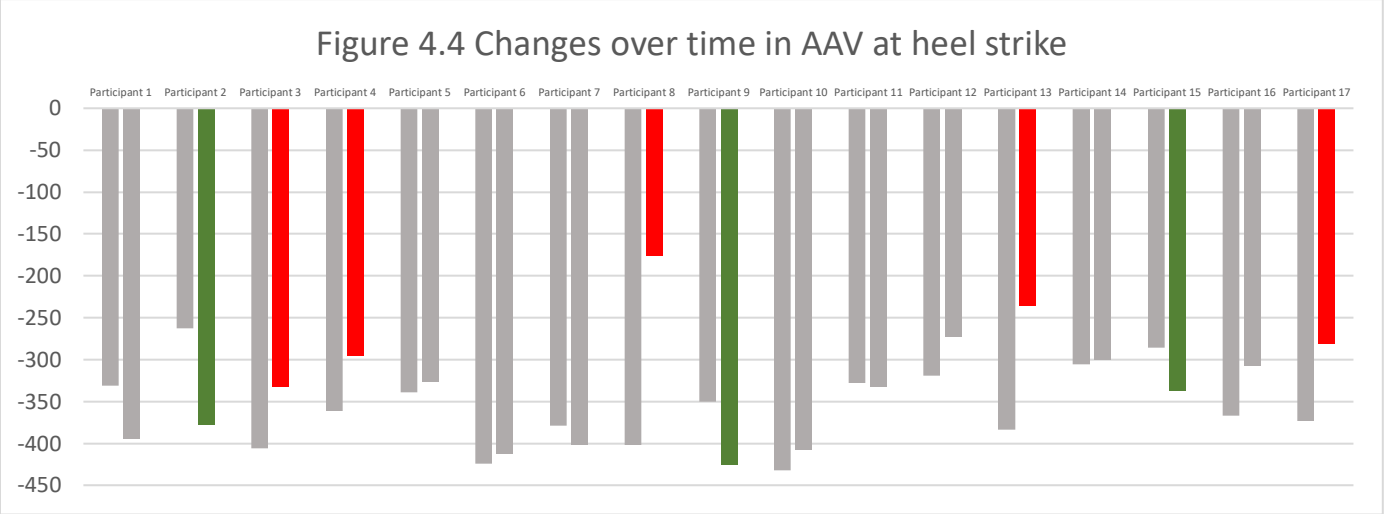
Table 4. 5: Correlations between gait quality measures and walking and exercise capacity and physical function

	Cadence	AAV at Heel Strike	AAV at push off	AAV of foot swing	Swing time	Power cycle (AUC)	Balance cycle (AAC)
RAND-36 PFI	-0.04	-0.02	-0.17	0.12	-0.01	-0.33	0.26
VO_{2peak}	0.15	-0.18	-0.17	0.22	-0.09	-0.14	0.12
6MWD	**0.53**	**-0.51**	**-0.7**	**0.62**	-0.28	**-0.52**	**0.55**

AAV= ankle angular velocity, AUC= area under the curve, AAC= area under the curve, 6-MWD= 6-minute walking distance, PFI= physical function index

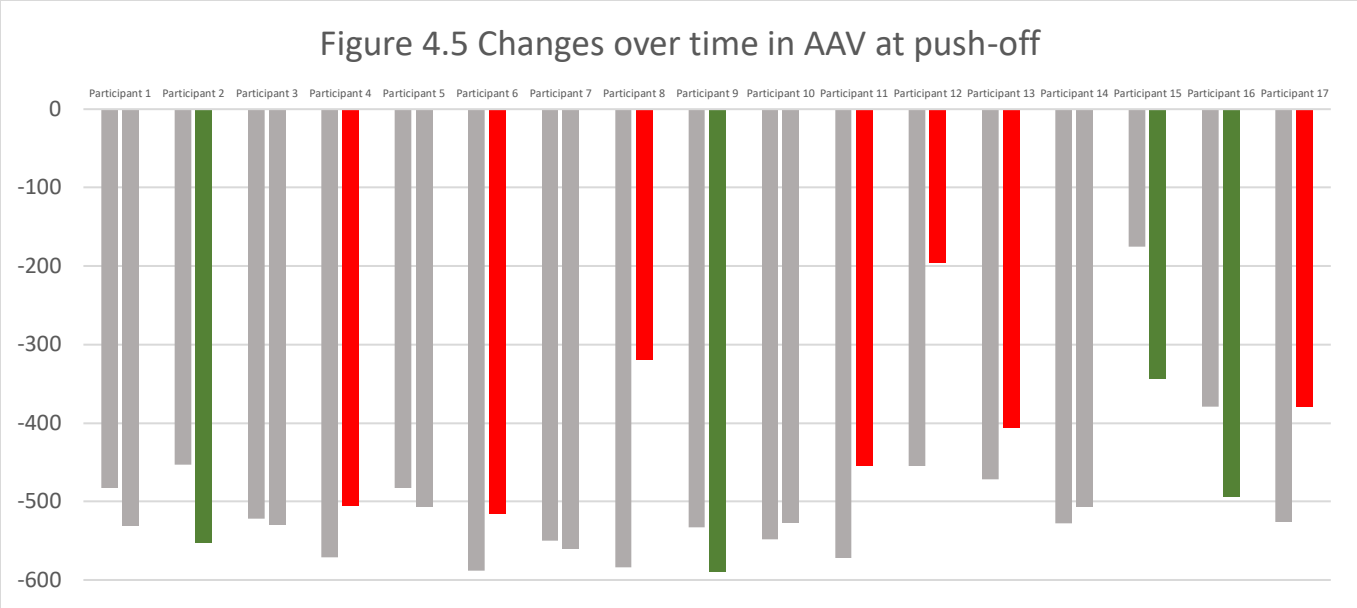


The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.

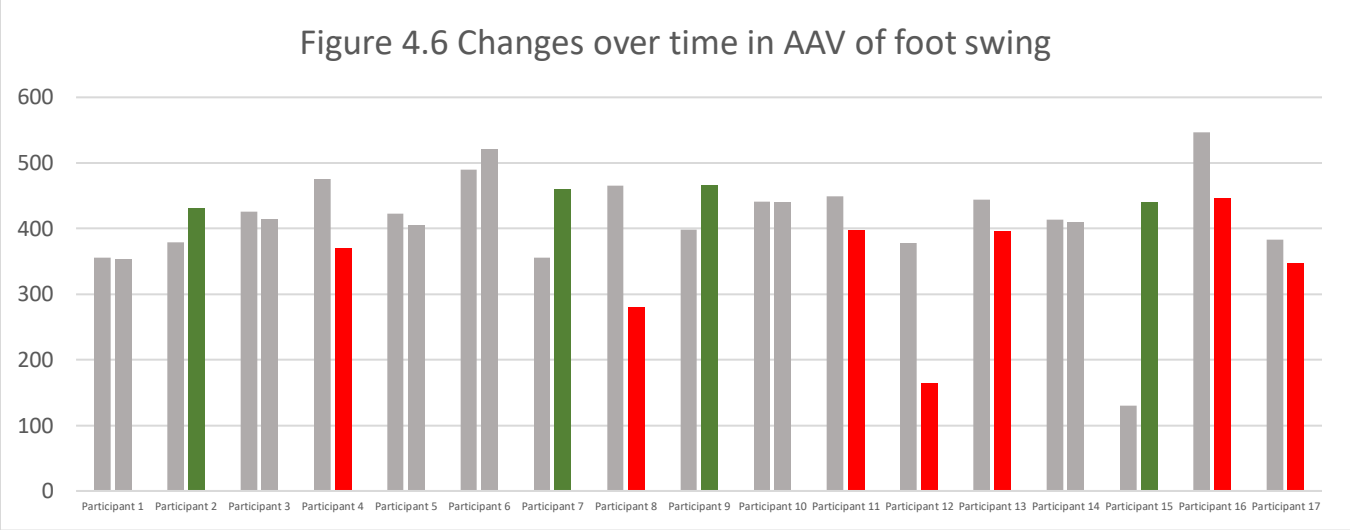


AAV= ankle angular velocity

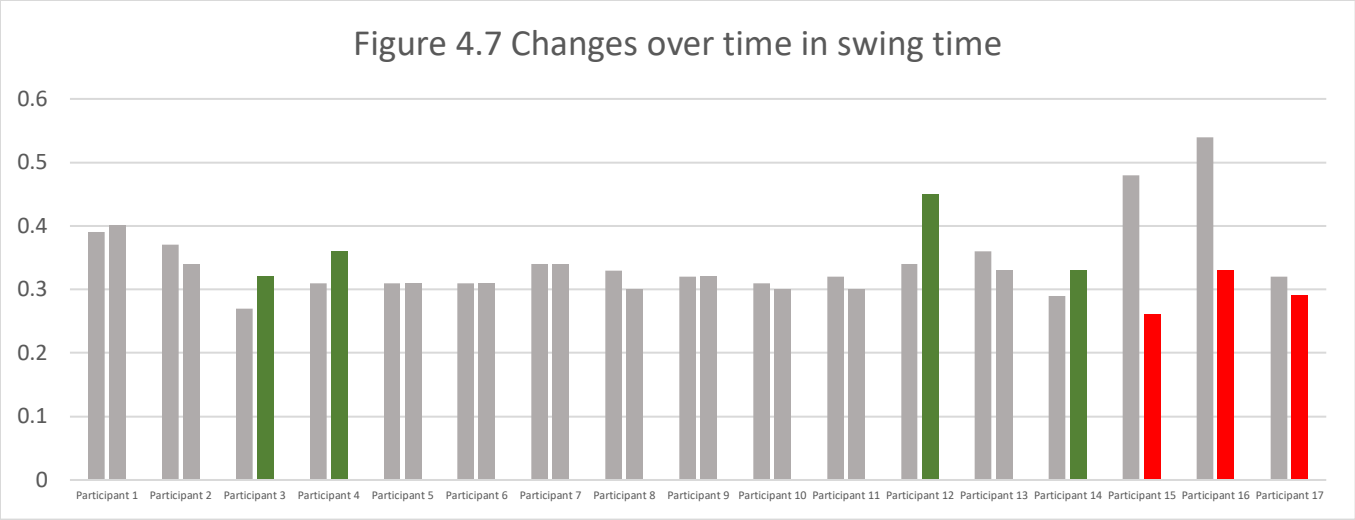
The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.



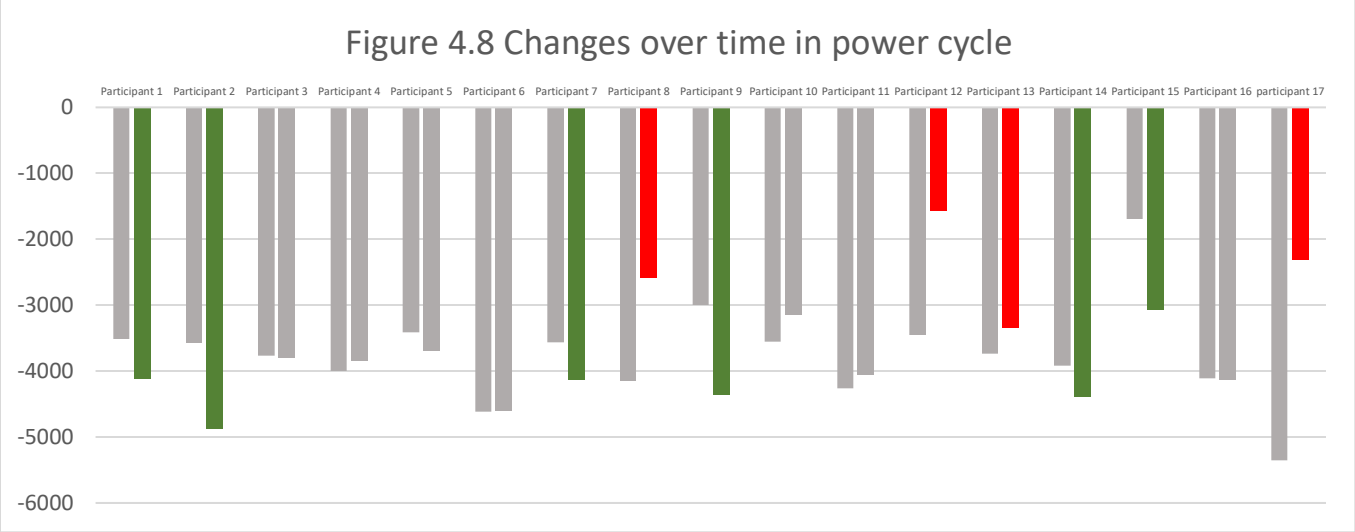
AAV= ankle angular velocity
The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.



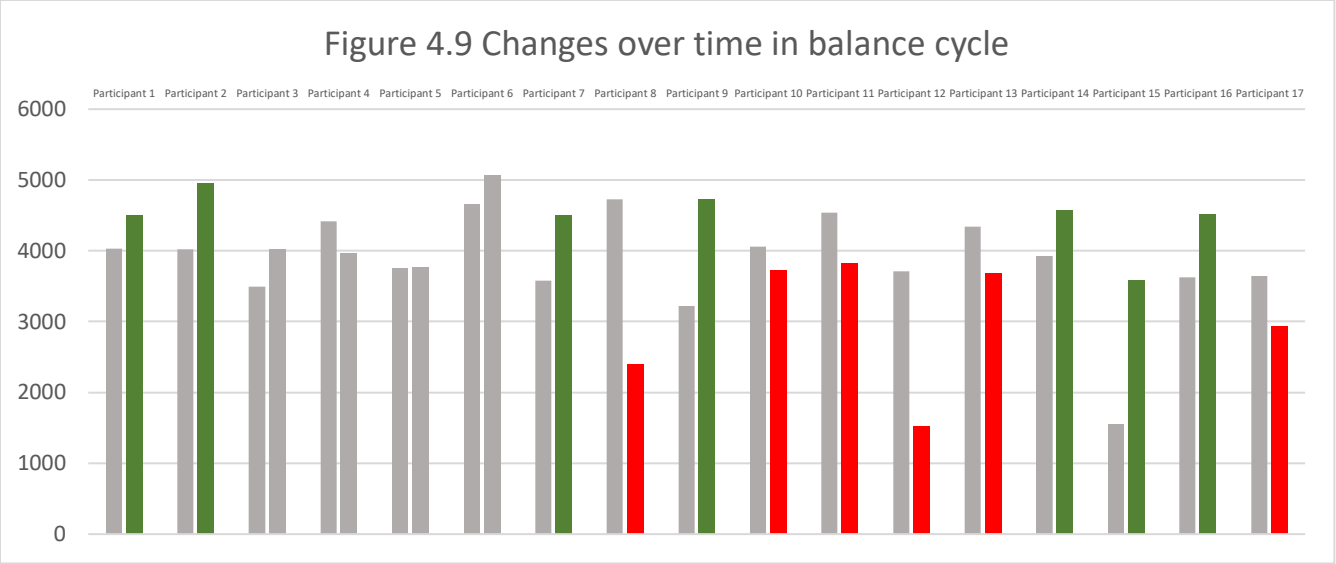
AAV= ankle angular velocity
The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.



The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.



The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.



The two bars of each participant represent time1 and time 2. The second bar for each subject if grey= remained the same, green= improved, red= declined.

Table 4.6 Pattern of change over time compared to uniform distribution

	Better	Worse	Same	chi (2df)	p-value
Cadence	1	7	9	1.079585	>0.05
AAV at heel strike	3	5	9	0.581315	>0.05
AAV at push off	4	7	6	0.145329	>0.05
AAV of foot swing	4	7	6	0.145329	>0.05
Swing time	4	3	10	0.892734	>0.05
Power cycle	6	4	7	0.145329	>0.05
Balance cycle	7	6	4	0.145329	>0.05

AAV= ankle angular velocity

Table 4. 7: Concordance between AAV at push-off and AAV at heel strike

		AAV at push-off			
		Better	Same	Worse	
AAV at heel Strike	Better	3	0	0	3
	Same	1	5	3	9
	Worse	0	1	4	5
		4	6	7	17

AAV= ankle angular velocity

Concordance: 12/17 = 71%

Table 4. 8: Concordance between AAV at push-off and cadence

		AAV at push-off			
		Better	Same	Worse	
Cadence	Better	1	0	0	1
	Same	3	3	3	9
	Worse	0	3	4	7
		4	6	7	17

AAV= ankle angular velocity

Concordance: 8/17 = 47%

Table 4. 9: Concordance between AAV at push-off and AAV of foot swing

		AAV at push-off			
		Better	Same	Worse	
AAV of foot swing	Better	3	1	0	4
	Same	0	5	1	6
	Worse	1	0	6	7
		4	6	7	

AAV= ankle angular velocity

Concordance: 14/17 = 82%

Table 4. 10: Concordance between power cycle and balance cycle

		Power cycle			
		Better	Same	Worse	
Balance cycle	Better	6	1	0	7
	Same	0	4	0	4
	Worse	0	2	4	6
		6	7	4	

AAV= ankle angular velocity

Concordance: 14/17 = 82%

Table 4. 11 Appendix 1: Glossary of gait outcomes

Gait kinematics (Quality) Metrics	**Explanation**
Cadence bands[1]	1-19--incidental movement; 20-39--sporadic movement; 40-59--purposeful movement; 60-79--slow walking; 80-99--medium walking, 100-119--brisk walking; >120--fast walking)
Ankle angular velocity at heel strike	This is the speed at which the foot moves from dorsiflexion when the heel strikes the ground to neutral when the foot is flat on the floor. It is measured in degrees per second. This is a clockwise movement with the ankle at the pivot. The sensor shows clockwise movement as negative. The more negative the value the greater is the angular velocity.
Ankle angular velocity at push-off	This is the speed at which the heel lifts off the floor to propel the body forward. As this is a clockwise movement around the pivot point of the ankle, it shows as negative. The more negative the value the greater is the angular velocity.
Power cycle	This is the phase of the gait cycle from heel strike to push off that essentially generates the power to propel the body forward. It is calculated by summing the areas under that are below the 0 line on the graph. The value is negative and the more negative the value the greater is the power generated. It is measured in degrees per second.
Ankle angular velocity of foot swing	This is the speed at which the foot pivots around the ankle joint from plantarflexion at push-off to dorsi-flexion when the leg is preparing to position the foot to make a heel strike. A certain angular speed is needed to clear the toes from the ground, or the person can stumble and fall. As the movement is counter-clockwise, the value is positive. The greater the value, the greater is the angular velocity.
Balance cycle	This is the phase of the gait cycle when one foot is in the air, swinging forward, and the other foot is on the ground. The height and duration of the swing creates an area measured in which is degrees per second. The magnitude of this area depends on the person being able to stand on one leg, termed single leg stance. For this reason, the area above the zero axis is dependent to a large extent on balance.
[CoV] Coefficient of variation	Heel2Toe generates gait metrics for each step. When the person takes many steps, as in a walking test, the average value is one summary metric as well as the variability (standard deviation) around the mean. The coefficient of variation is the ratio of the standard deviation of angular velocity to the average value. This is an indicator of how consistently the person walks. Optimally, the coefficient of variation is about 10% to 15%. People with a high

	coefficient of variation do not walk with a regular gait pattern. This can be fatiguing and can increase the risk of falls. Reducing the coefficient of variation can be a treatment target. Use of external cues such as walking to a beat have been shown to be effective for reducing variability in gait (Ford et al., 2010; Gini et al., 2017) Each of the metrics described above has an associated coefficient of variation.

Chapter 5 Discussion and conclusion

The objective of this thesis is to describe gait kinematics in MS, estimate associations with MS-related impairments and identify changes over a short-term period without gait-targeted treatment, and using a portable sensor to measure these parameters. The objective was achieved through one manuscript that tested two objectives.

In the manuscript, associations between gait kinematics and multiple MS-related impairments were estimated in the first objective using a cross-sectional design of existing data. Different types of correlation were applied based on the measurement scale of the variables under study and because it is a novel relationship and no prior expectation exists, 0.3 – 0.5 was considered a moderate relationship, and >0.5 was considered a strong relationship. Theoretically, our model assumes that MS-related impairment could affect gait kinematics. In return, altered kinematics might impact walking capacity, physical function, and exercise capacity. Associations between these measures were tested. Moderate associations (around 0.4) were found between leg power, depression, and multiple gait kinematics measures. All gait kinematics except swing time correlated strongly (0.5-0.7) with walking capacity measured by the Six-Minute Walking Distance (6-MWD). This result highlights the complexity of MS and the interaction of its impairments. Subtle changes in gait could be driven by leg power, that is rarely tested, leading to lower walking capacity. Depression is another common symptom in MS that is usually not linked to walking impairment in clinical practice. Different MS impairments seem to impose different effects on gait which could have several implications in gait classification or impairment detection from gait pattern. Gait interventions could be enhanced when several factors are taken into consideration through managing related MS symptoms.

The second objective estimated changes over time in gait kinematics in a subgroup of 17 participants who had data on two-time points. Due to the small size of the available sample, an individual analysis was applied. Meaningful change in these parameters is unknown, therefore the rule of ½ SD of each participant was used to identify the meaningful change in all gait kinematics except cadence in which moving from one cadence band to another was considered meaningful. Of the 7 gait kinematics measures, most deterioration was seen in cadence, ankle angular velocity at push-off, and ankle angular velocity of foot swing. Swing time and balance cycle were the most improved measures over time. Several of participants deteriorated in more than one gait parameter. However, these changes did not differ significantly from a uniform distribution. A high agreement rate in change was observed between ankle angular velocity at push-off and ankle angular velocity of foot swing suggesting that these two aspects of gait could be related. The power cycle and balance cycle also showed a high concordance rate suggesting that stance and swing phase of the gait change with the same pattern. The inconsistent changes in gait over time observed between individuals could be the result of the "time since onset", especially after knowing that mobility impairment progress rapidly at the later stages of the disease. This result emphasizes the role that gait changes could play in disease monitoring. Using a portable sensor to measure changes over time also suggests applying these technologies in self-management programs used in MS.

This thesis provides a starting point for understanding gait kinematics in the MS population. Different aspects of gait have been explored descriptively due to the abundant data we received from the Hee2Toe sensor. The results revealed multiple potential directions of future research and the possibility of further uses of these sensors to answer other related questions. However, there are some inevitable limitations in this project. Not all MS impairments were tested in this thesis. Although gait kinematics were measured, normative data of these parameters, that enable

interpretation of these values, are lacking. Measuring change over a period longer than 3 months might provide a more accurate conclusion, however, because data used in this thesis are existing data it was not possible to analyze a longer follow-up.

Conclusion:

This thesis explores different gait kinematics and associations with MS impairments which can be easily targeted during treatment. The concordance rate calculated suggests that changes in one of these gait measures drive changes in other gait changes. More research is needed to confirm these findings. Changes over time might have potentials for MS prognosis.

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Supplementary document:

Table 4. 12: Individual analysis of cadence, AAV at heel strike and AAV at push-off

Participants	Cadence (steps/min)			AAV at heel Strike (deg/s) Mean ± SD			AAV at push-off (deg/s) Mean ± SD		
	Time 1	Time2	Differ	Time1	Time2	Differ	Time1	Time2	Differ
Participant1	102	75	27	-331±175	-394±147	63	-483±160	-531±134	-48
CoV	-	-		53	37	16	33	25	8
Participant2	93	89	4	-263±142	-378±133	115	-453±145	-553±137	-100
CoV	-	-		54	35	19	32	25	7
Participant3	102	88	14	-406±131	-333±89	73	-522±102	-529±101	23
CoV	-	-		32	27	5	20	19	1
Participant4	99	98	1	-361±117	-295±121	66	-571±132	-505±171	66
CoV	-	-		32	41	-9	23	34	-11
Participant5	89	88	1	-339±130	-327±119	12	-483±97	-507±107	-24
CoV	-	-		38	36	2	20	21	-1
Participant6	124	104	20	-424±121	-413±132	11	-588±102	-515±96	73
CoV	-	-		28	32	4	17	19	-2
Participant7	106	103	3	-379±105	-402±114	-23	-550±111	-560±160	-10
CoV	-	-		28	28	0	20	29	-9
Participant8	124	94	30	-402±133	-176±61	226	-584±127	-319±41	265
CoV	-	-		33	53	-20	22	13	9
Participant9	111	113	-4	-350±136	-426±118	-76	-533±112	-590±93	-57
CoV	-	-		39	28	11	21	16	5
Participant10	101	104	-3	-432±148	-408±118	24	-548±153	-527±111	21
CoV	-	-		34	29	5	28	21	7
Participant11	99	80	19	-328±100	-332±128	-4	-572±103	-454±99	118
CoV	-	-		30	39	-9	18	22	4
Participant12	77	65	12	-319±118	-273±78	46	-455±121	-195±34	260

CoV	-	-		37	28	9	27	18	9
Participant13	82	66	16	-384±157	-236±94	148	-472±76	-406±196	66
CoV	-	-		41	40	1	16	48	-32
Participant14	99	77	22	-306±53	-300±100	6	-528±95	-507±120	21
CoV	-	-		17	33	-16	18	24	6
Participant15	62	70	-8	-286±67	-337±100	-51	-175±25	-343±171	-168
CoV	-	-		23	30	7	15	50	-35
Participant16	63	102	-39	-367±142	-307±78	60	-379±89	-494±125	-115
CoV	-	-		39	25	14	23	25	-2
Participant17	81	97	-16	-373±62	-281±99	92	-526±86	-379±77	147
CoV	-	-		17	35	-18	16	20	-4

SD= standard deviation, deg= degree, s= second, CoV= coefficient of variation, AAV= ankle angular velocity, Differ = difference, min = minute. Green highlights improvement, Red indicates deterioration

Table 4. 13: Individual analysis of AAV of foot swing and swing time

Participants	AAV of foot swing (deg/s) Mean ± SD			Swing time (sec) Mean ± SD		
	Time1	Time2	Differ	Time1	Time2	Differ
Participant1	356±78	353±52	3	0.39±0.04	0.4±0.05	0.01
CoV	22	15	7	11	13	-2
Participant2	379±54	431±80	-52	0.37±0.08	0.34±0.05	0.03
CoV	14	18	4	21	15	6
Participant3	426±74	414±49	12	0.27±0.07	0.32±0.08	-0.05
CoV	17	12	5	28	26	2
Participant4	476±73	370±53	106	0.31±0.07	0.36±0.05	-0.05
CoV	15	14	1	22	15	7
Participant5	423±50	404±67	19	0.31±0.07	0.31±0.08	0
CoV	12	17	-5	24	26	-2
Participant6	490±70	521±81	-31	0.31±0.04	0.31±0.06	0
CoV	14	16	-2	12	21	-9
Participant7	356±34	459±79	-103	0.34±0.04	0.34±0.05	0
CoV	9	17	-8	13	14	-1
Participant8	465±71	279±38	186	0.33±0.08	0.3±0.05	0.03
CoV	15	14	1	24	17	7
Participant9	398±49	465±48	-67	0.32±0.13	0.32±0.04	0
CoV	12	10	2	40	13	27
Participant10	441±58	439±51	2	0.31±0.04	0.3±0.03	0.01
CoV	13	12	1	14	10	4
Participant11	449±59	397±52	52	0.32±0.06	0.3±0.03	0.02
CoV	13	13	0	19	10	9
Participant12	378±48	164±26	214	0.34±0.08	0.45±0.06	-0.11
CoV	13	16	-3	23	13	10

Participant13	444±61	395±88	49	0.36±0.11	0.33±0.06	0.03
CoV	14	22	-8	32	18	14
Participant14	414±47	409±61	5	0.29±0.03	0.33±0.05	-0.04
CoV	11	15	-4	9	14	-5
Participant15	130±14	439±58	-309	0.48 ±0.07	0.26±0.09	0.22
CoV	11	13	-2	15	36	-21
Participant16	547±90	446±48	101	0.54±0.2	0.33±0.04	0.21
CoV	16	11	5	37	11	26
Participant17	383±36	347±57	36	0.32±0.06	0.29±0.07	0.03
CoV	9	16	-7	20	24	-4

SD= standard deviation, deg= degree, s= second, CoV= coefficient of variation, AAV= ankle angular velocity, Differ = difference, sec= second, Differ= Difference. Green highlights improvement, Red indicates deterioration

Table 4. 14: Individual analysis of power cycle and balance cycle

Participants	Power cycle (AUC) Mean ± SD			Balance cycle (AAC) Mean ± SD		
	Time1	Time2	Differ	Time1	Time2	Differ
Participant1	-3517±790	-4122±920	605	4035±916	4507±574	-472
COV	22	22	0	23	13	10
Participant2	-3577±1085	-4873±1141	1296	4017±899	4949±1248	-932
COV	30	23	7	22	25	-3
Participant3	-3763±982	-3796±836	33	3495±1205	4024±644	-529
COV	26	22	4	34	16	18
Participant4	-3996±996	-3844±794	152	4413±954	3960±795	453
COV	25	21	4	22	20	2
Participant5	-3412±788	-3699±918	-287	3755±544	3770±872	15
COV	23	25	-2	14	23	-9
Participant6	-4620±835	-4601±869	19	4660±896	5069±1020	-409
COV	18	19	-1	19	20	-1
Participant7	-3559±741	-4128±1157	-569	3582±546	4504±821	-922
COV	21	28	-7	15	18	-3
Participant8	-4148±1212	-2581±966	1567	4728±712	2392±545	2336
COV	29	37	-8	15	23	-8
Participant9	-3001±941	-4356±927	-1355	3221±497	4729±422	-1508
COV	31	21	10	15	9	6
Participant10	-3557±1331	-3144±1232	413	4058±636	3726±541	332
COV	37	39	-2	16	15	1
Participant11	-4260±842	-4062±734	198	4535±664	3830±570	705
COV	20	18	2	15	15	0
Participant12	-3452±894	-1569±356	1883	3715±528	1518±227	2197
COV	26	23	3	14	15	-1

Participant13	-3737±734	-3343±1311	394	4341±477	3680±1023	661
COV	20	39	-19	11	28	17
Participant14	-3915±369	-4385±858	-470	3925±537	4576±850	-651
COV	9	20	-11	14	19	-5
Participant15	-1696±499	-3073±1319	-1377	1557±323	3579±1285	-2022
COV	29	43	-14	21	36	-15
Participant16	-4110±1678	-4129±1174	-19	3625±1310	4513±523	-888
COV	41	28	13	36	12	24
Participant17	-5354±660	-2308±861	3046	3647±456	2934±592	713
COV	19	37	18	13	20	-7

SD= standard deviation, AUC= area under the curve, AAC= area above the curve, Differ= difference. Green highlights improvement, Red indicates deterioration