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Gait Variability Is an Independent Marker of Frailty

Anam Islam, *The University of Western Ontario*

Supervisor: Manuel Montero-Odasso, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Kinesiology

GAIT VARIABILITY IS AN INDEPENDENT MARKER OF FRAILTY

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Anam Islam

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CERTIFICATE OF EXAMINATION

Supervisor	Examiners
Dr. Manuel Montero-Odasso	Dr. Tim Doherty
Supervisory Committee	Dr. Marita Kloseck
Dr. Susan Muir	Dr. Rob Petrella
Dr. Rob Petrella	
Dr. Mark Speechley	

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Anam Islam

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ABSTRACT

The objectives of this study were to 1) determine if high gait variability is associated with frailty; 2) test the inter-rater reliability of the Clinical Frailty Scale (CFS) and its concurrent validity against the Frailty Phenotype Index (FPI) in classifying frailty. Frailty status was determined by applying the FPI and CFS to the sample of 107 community-dwelling older adults. Inter-rater reliability of the CFS was assessed using kappa statistics. Mantel-Haenszel test for trends evaluated concurrent validity of the CFS against the FPI components. Quantitative gait variables were assessed with an electronic walkway. Multivariable linear regression analysis evaluated the outcome of gait variability across CFS levels. The CFS showed substantial reliability and was correlated with FPI components. Increased frailty status was associated with higher variability in stride length, stride width, and stride time. This study demonstrates that high gait variability is associated with frailty, as defined by the CFS.

KEYWORDS: gait, gait variability, frailty

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LIST OF ABBREVIATIONS

FPI- Frailty Phenotype Index

CGS- Comprehensive Geriatric Assessment

ADL- activities of daily living

IADL- instrumental activities of daily living

EMG- electromyography

SD- standard deviation

CoV- coefficient of variation

AD- Alzheimer's disease

PD- Parkinson's disease

EF- executive function

CFS- Clinical Frailty Scale

FMS- Frailty and Mobility Study

NORC- naturally occurring retirement community

CHS- Cardiovascular Health Study

CSHA- Canadian Study of Health and Ageing

ANOVA- analysis of variance

BMI- body mass index

Kw- weighted kappa coefficient

R^2- coefficient of determination

CHAPTER 1- LITERATURE REVIEW

1.1 The frailty syndrome

The term, frail, has been widely used to describe the oldest old in the population, and was once considered to be synonymous with old age and disability (Lang et al., 2009). It has become increasingly recognized that, although, frailty is age-related, it is not caused by old age itself and is not a normal part of aging (Fried et al., 2005). The onset of frailty may be possibly preventable, avoided, or delayed (Morley, 2008). While the definition of "frailty" has evolved over the years, there remains a lack of consensus and is still a topic of controversy (Abellan van Kan et al., 2008). More recently, it has been proposed that frailty is a clinical syndrome, separate from disability and comorbidity with a distinct pathophysiological process (Fried, Ferrucci, Darer, Williamson, & Anderson, 2004). Under this framework frailty reflects subclinical physiological impairment in organ systems, physical function and cognitive capacity (Fried et al., 2001). Consequently, frail adults have a compromised homeostasis and an increased vulnerability to adverse events such as falls, institutionalization and death.

1.1.1 Pathophysiology of frailty

The mechanisms involved in the frailty process are unknown. It has been proposed that frailty is a complex syndrome which results in dysregulation of several systems across molecular, cellular and physiological levels (Halter & Hazzard, 2009). The "frailty cycle" has been proposed to describe the origin and progression of frailty (Fried et al., 2001). Frailty, under this model, is associated with age-related biological and physiological alterations, however frailty is not universal to old age. The etiology of the frailty cycle is associated with low physical activity, inadequate nutrition, negative

environmental impact, injury, disease and genetics, which are compounded by the normal ageing process.

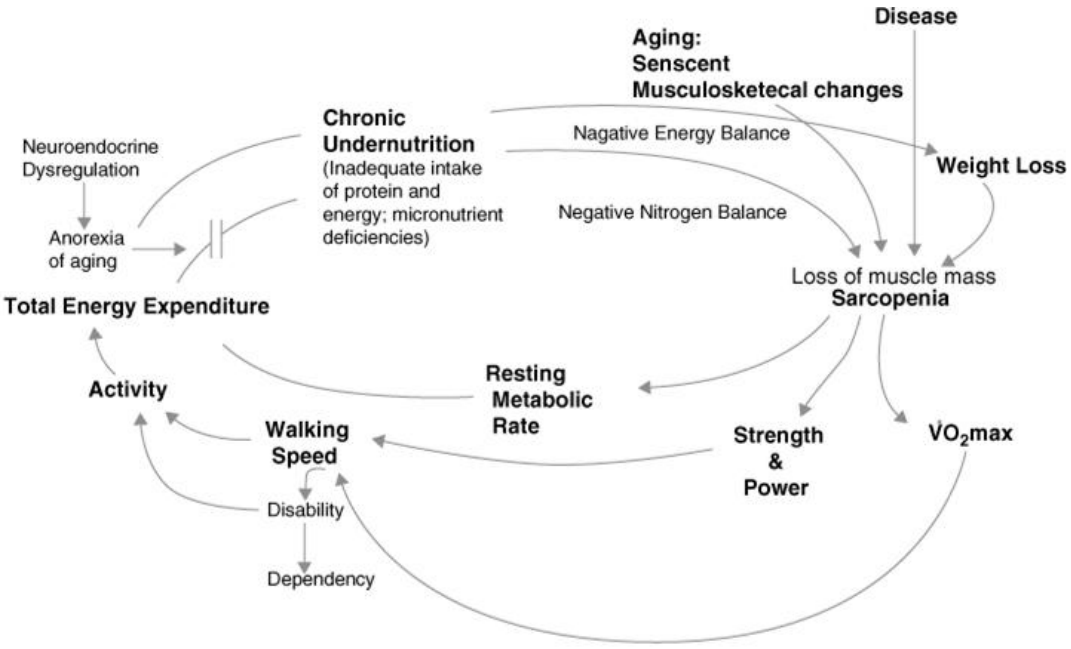
At the molecular and cellular level, these factors produce reactive oxygen species, mitochondrial dysregulation, and damage to mitochondrial DNA (Halter & Hazzard, 2009). Accumulation of these insults result in the alteration of biological mechanisms that regulate energy balance (Fried et al., 2005). Frailty is propagated as these altered energetics over time lead to changes in key physiological systems including the musculoskeletal, immune, hormonal, and inflammatory systems. A dysregulated immune response and activation of inflammatory pathways cause injury to muscle, decrease the rate of muscle repair, and trigger apoptosis (Hubbard, O'Mahony, Calver, & Woodhouse, 2008; Hubbard, O'Mahony, Savva, Calver, & Woodhouse, 2009; Leng et al., 2004). Hormonal changes are associated with diminution of muscle mass, depressed appetite and food intake which affects body composition and nutriture (Mohr et al., 2007; Morley, Kim, & Haren, 2005). Compromised physiological function across these interconnected processes is central to the disruption of homeostatic mechanisms (Halter & Hazzard, 2009).

1.1.2 Clinical symptoms of frailty

The clinical presentations as a result of altered biological and physiological systems are themselves interrelated and feedback into the progression of the frailty cycle (Figure 1.1) (Fried et al., 2001). An increased number of clinical symptoms reflect an increased severity in level of frailty. Sarcopenia, a central clinical manifestation of frailty, is characterised by the loss of lean body tissue, a decline in muscle fibre strength and an infiltration of adipose cells (Halter & Hazzard, 2009). This process ultimately leads to the

degeneration in function of remaining muscle, resulting in an additional decline in muscle strength and an increase in the perceived difficulty for a given exercise intensity (Janssen, Heymsfield, & Ross, 2002; Morley, 2008). This weakness in older adults may lead to avoidance of exercise and a reduced physical activity level which down regulates the resting metabolic rate, and total energy expenditure (Janssen et al., 2002). As a result, frail individuals present signs of decreased physical activity, fatigue, weakness, slowed performance, and in extreme cases, weight loss (Fried et al., 2001).

Figure 1.1: Illustration of the self-perpetuating frailty cycle, resulting from dysregulated and impaired physiologic function.

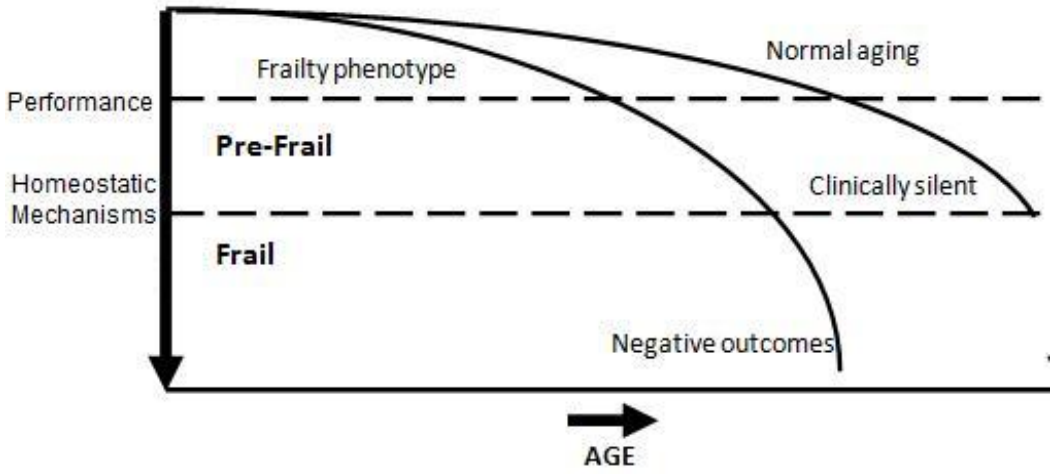


Copyright © The Journals of Gerontology from Fried, L. et al. (2001).

Over time, the combination of a sedentary state, energy dysregulation and homeostatic instability lead to under nutrition and further loss of lean body mass and

physical decline (Fried et al., 2005; Morley, 2001). Consequently, there is a self-perpetuation of the frailty cycle. A pre-frail stage has been identified as a clinically silent stage in which, although there is a decline in performance and homeostatic mechanisms, physiological system are still able generate an adequate response to insults (Fried et al., 2001; Lang et al., 2009). However in frail individuals, these systems are unable to respond and adapt in the face of a stressor, propagating a frail individual into functional decline and increasing the risk of falls, disability, polymedication, increased risk of hospitalization, institutionalization and mortality (Figure 1.2) (Fried et al., 2001).

Figure 1.2: **The decline in performance and homeostatic mechanisms in the frailty process compared to normal aging.**



Adapted from Lang, P.O. et al. (2009).

1.1.3 Assessment of frailty

Currently, the most widely accepted model to identify frailty is the Frailty Phenotype Index (FPI) developed by Fried et al. (2001). The phenotype for frailty is based upon the physiological "frailty cycle" discussed previously. Frailty was defined as a clinical

syndrome in which the presence of the following criteria were explored: unintentional weight loss (≥10 lbs. in a year), self-reported exhaustion, weakness (grip strength in lowest 20% by gender and BMI), slow walking speed (slowest 20% by gender and height), and low physical activity (lowest 20% of kcals expended per week by gender). The presence of three or more of these criteria characterised the individual as "frail", one or two items identified an individual as "pre-frail" or at an intermediate risk, and those with no frailty criteria were categorized as "not-frail".

In a large cohort of older adults the FPI was independently predictive, over three years, of several adverse clinical outcomes, including the incidence of falls, worsening mobility or ADL disability, hospitalization and death (Fried et al., 2001). The prevalence of frailty in the population increased with each five year age group and in each age group prevalence of frailty for women was twice as high then men. Also, those individuals categorized as "pre-frail", showed an intermediate risk of developing poor clinical outcomes and an increased risk of developing frailty compared to those in the "not-frail" category. This study was able to provide a validated and predictive clinical definition of frailty in community dwelling older adults and support for the hypothesis of the "frailty cycle". Furthermore, this study was able to provide evidence for the existence of an intermediate stage of risk between those not at risk, and those that are frail.

1.2 The value of functional assessment in frail older adults

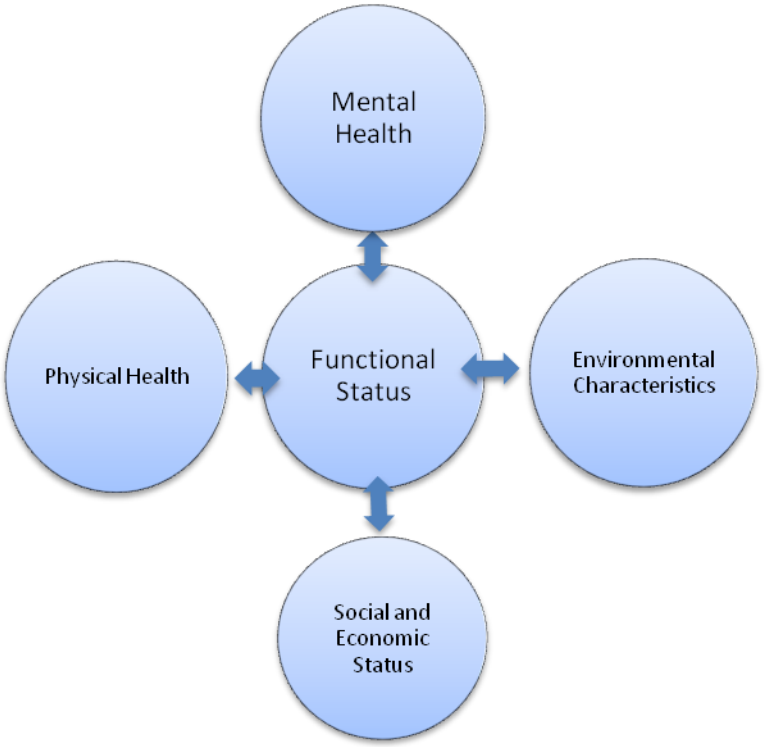
Older adults are a heterogeneous population that present with atypical symptoms to common diseases, exhibit interacting effects of multiple comorbidities, and undergo age-related physiological alterations that are separate from disease (Dharmarajan & Norman, 2003). Assessment and health management of older adults represents a unique challenge

to clinicians. This is particularly evident in frail older adults. Based on recent estimates, almost 20% of people over age 75 are frail and could benefit from effective interventions to identify and minimize frailty (Hogan, MacKnight, & Bergman, 2003). To address the unique needs of frail individuals, the more thorough medical evaluation, termed 'comprehensive geriatric assessment' (CGA), was developed to include the geriatric syndromes that affect the well-being of older adults. The domains of CGA include evaluation of physical heath, psychological health, social and economic support, environmental factors, and functional status (Solomon, 1988).

Key features of frailty syndrome are weakness, lower limb dysfunction, and mobility impairment (Fried et al., 2001; Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995; Walston & Fried, 1999) which may lead to functional decline (Janssen et al., 2002). Functional status can impact upon, and be impacted by, all the previously mentioned domains within the CGA (Figure 1.3) (Dharmarajan & Norman, 2003). Thus, to achieve optimum health status in frail older adults, improvement in function is a crucial objective of the CGA (Gill et al., 2004; Tinetti et al., 1999). Function is measured as the ability to perform routine tasks classified as activities of daily living (ADL) and instrumental activities of daily living (IADL) (Katz, 1983). ADL's include basic physical tasks such as bathing, dressing, toileting, transferring from a bed to a chair, continence, and feeding. IADL's represent behavioural and social activities such as using the telephone, using public transportation, grocery shopping, preparing meals, housework, taking medication, and managing financial responsibilities. Impairment in the ability to perform ADL's and IADL's is predictive of important health outcomes such as subsequent disability (Guralnik et al., 1995; 1989), risk of falls and fractures, and death (Visser, Deeg, Lips,

2003; Guralnik et al., 1994). These are all recognized causes of hospitalization and institutionalization and common adverse events associated with frailty. The capacity to remain independent reflects a high quality of life in older adults (Guralnik et al., 1989), making functional status an essential component of frailty assessment (Gill et al., 2004; Tinetti et al., 1999).

Figure 1.3: Interacting domains of the comprehensive geriatric assessment.



Adapted from Dharmarajan, T. S., & Norman, R. A. (2003).

1.3 Gait and mobility

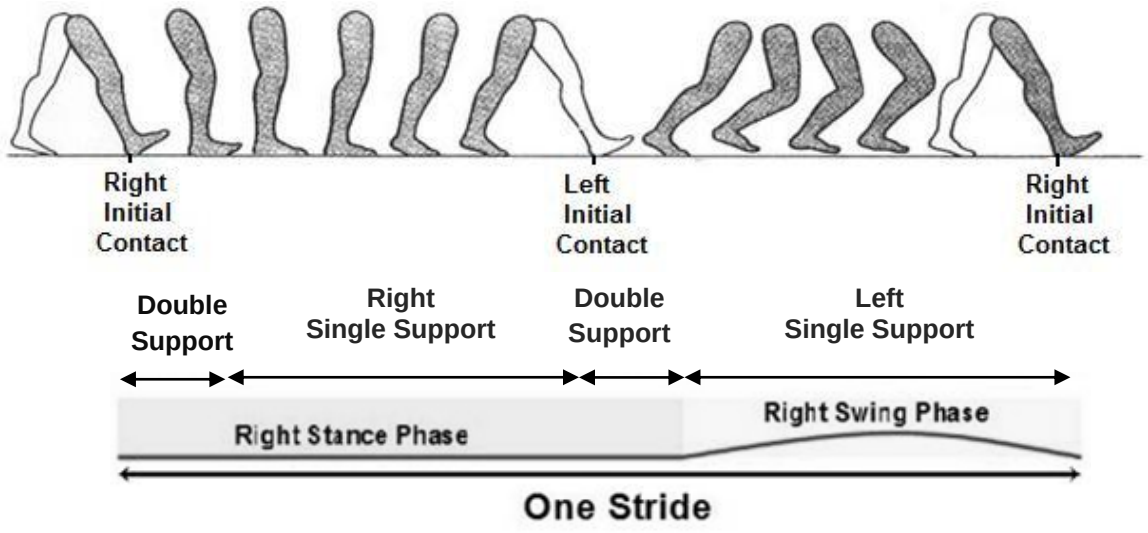
Limitations in mobility, the ability to move one's body, interfere with functioning and are a major cause of loss of independence (Tinetti, Williams, & Mayewski, 1986). Gait is

considered to be one of the most important manifestations of mobility capacity (Hausdorff & Alexander, 2005). Gait, in humans, is the coordinated firing of muscles and limb movement to support the body and move it forward (Hausdorff, 2007). This cyclic pattern of lower limb movement requires input from the central nervous system, as well as sensory feedback to produce these highly coordinated movements for locomotion. In the mobility domain, gait and balance are fundamental markers of function in the lower extremities and the ability to carry out ADL's (Berg & Norman, 1996).

1.3.1 The gait cycle

The gait cycle is defined as the interval from when the heel of one foot makes initial contact with the ground to the next successive heel contact of the same foot (ipsilateral) (Figure 1.2) (Kirtley, 2006). The gait cycle is composed of two phases: the stance and swing phase. The stance phase is the interval between the reference foot making initial contact with the ground and ends when the foot is lifted off the ground. The stance phase makes up 60% of the normal adult gait cycle. The other 40% is represented by the swing phase which is the interval where the foot is off the ground and moving forward and ends just before the foot makes contact with the ground again.

Figure 1.4: Illustration of one stride in the gait cycle.

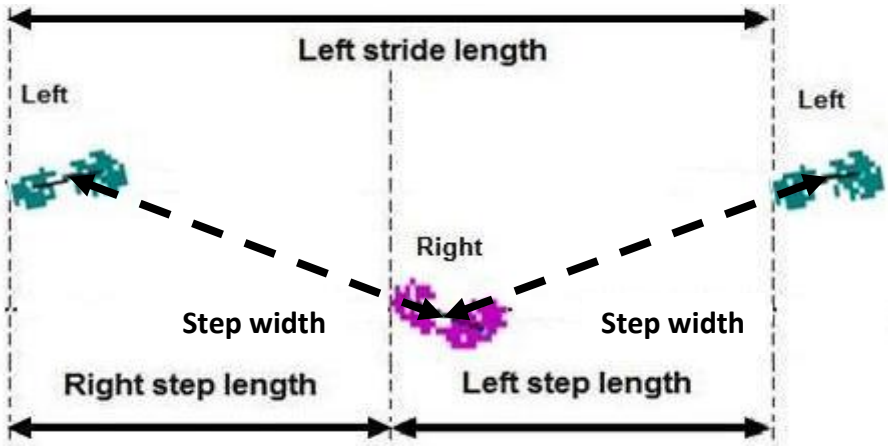


Adapted from Montero-Odasso, M. (2003).

The temporal parameters of the gait cycle include stride time which is the time it takes to complete one full stride measured in seconds (sec); single limb support time is the period of time during a stride when only one limb is in contact with the ground; double limb support time is the overlapping period when both limbs are in contact with the ground (Kirtley, 2006). The spatial parameters of the gait cycle include step length which is the linear distance between the heel of the trailing foot to the heel of the foot in front; stride length is the distance between the heel of one foot to the next successive heel contact of the same foot; step width is the distance from the midpoint of the footstep in front to the midline midpoint of the trailing footstep on the opposite foot (Figure 1.5). Gait velocity measures the speed of a walk on a level surface, quantified as distance covered per unit of time, and is most commonly expressed in meters per second (m/sec). Cadence refers to the rhythm of the walking pattern and is expressed as the number of steps taken in a given time (steps per minute). Cadence, stride length and speed are

related and change together. A subject with a longer stride length and increased cadence will have a shorter cycle time and subsequently a faster gait velocity. In a normal gait pattern, these measurements are symmetrical and equal for both legs.

Figure 1.5: Spatial gait parameters of step length, stride length, and step width.



1.3.2 Methods of gait analysis

1.3.2.1 Observational analysis

The simplest form of gait analysis can be completed with various methods that include paper-and pencil tests (Nelson, 1974; Sekiya, Nagasaki, Ito, & Furuna, 1997), stop watches, and video-based analysis (Perry & Burnfield, 2010). In a clinical setting these methods can provide a way to measure rudimentary gait parameters, such as gait velocity and cadence, in order to assess functional performance. However, this form of gait analysis is subject to human error in manual measurement of spatial and temporal parameters. These strategies are also labour intensive, time consuming and not efficient

for collecting valid and reliable gait data (McDonough et al., 2001; Bilney, Morris, & Webster, 2003; van Uden & Besser, 2004).

1.3.2.2 3D Motion analysis

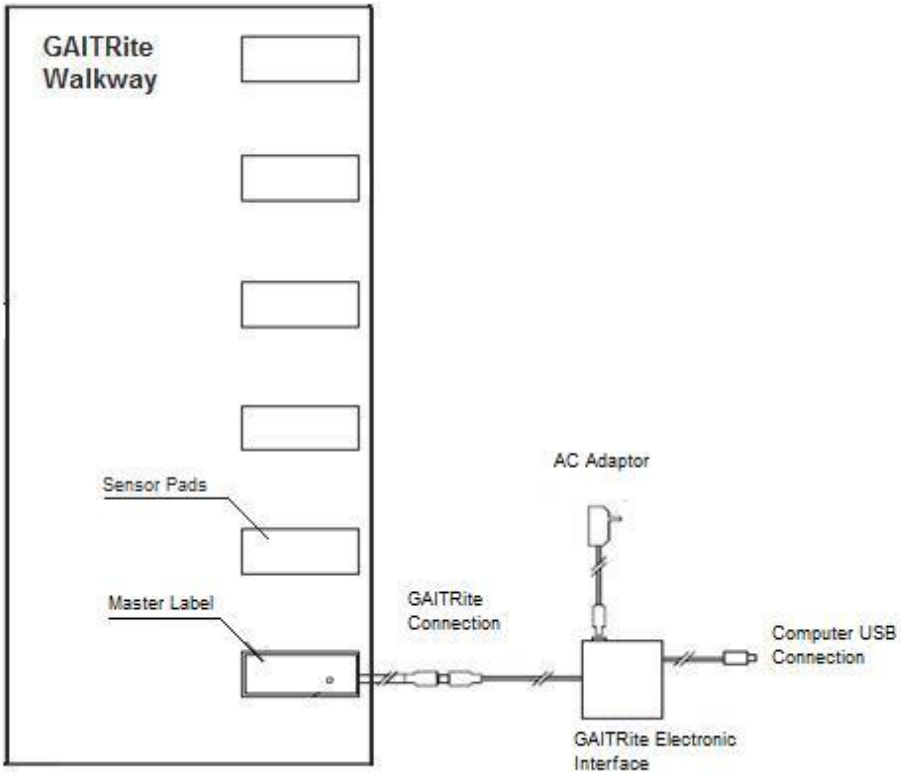
Three-dimensional (3D) motion analysis is a highly sophisticated methodology and the most comprehensive gait analysis system as it allows measurement of both kinetic, kinematic gait parameters, and electromyography (EMG) data of the lower limbs (Perry & Burnfield, 2010). This analysis system utilizes optical, magnetic, or optoelectronic system to track movements of joint segments. A series of cameras, tracking markers placed over predetermined anatomical locations on the subject, and EMG measurement systems are used to determine spatio-temporal characteristics of gait and lower limb muscular activity. Although 3D motion analysis provides a thorough and comprehensive method of gait analysis, it is not a very practical tool in the clinical setting (Bilney et al., 2003; McDonough, Batavia, Chen, Kwon, & Ziai, 2001; van Uden & Besser, 2004). The cost of equipment is expensive, requires a large space and laboratory setting to operate, and data collection is time-consuming and complex.

1.3.2.3 Instrumented walkways

A popular method of gait analysis is the use of computerized walkway systems, such as the GAITRite mat (Figure 1.6) (Bilney et al., 2003; McDonough et al., 2001; van Uden & Besser, 2004). The computerized mat is embedded with grids of pressure sensors to record an electronic imprint of each foot fall as a subject walks over the instrument. Data on gait parameters are calculated and displayed on a computer, connected to the mat and running software, as a subject completes a walk. These instruments have been proven to be highly valid and reliable tool for measuring a range of spatial and temporal

parameters of gait at usual and fast walking speeds in several populations. Advantages of the instrumented walkways over observational and video analysis is that it reduces the labour intensive and time-consuming aspect of measuring gait parameters and does not require extensive training (McDonough et al., 2001). These aspects make computerized instrumented walkways a very practical tool to use in a clinical or research setting and provide clinicians with quick results to objectively diagnose and monitor mobility impairments in patients.

Figure 1.6: The computerised GAITRite walkway.



Adapted from CIR Systems, Inc. at http://www.gaitrite.com/ Downloads/index-new.html.

1.3.3 Gait assessment in older adults

Although gait disorders are not an inevitable part of aging, gait and balance impairment are common in older adults as a result of musculoskeletal, vascular, and neurological disease (Dharmarajan & Norman, 2003). Unlike young adults, gait disorders and mobility disability may be a result of multiple conditions and deficits across a number of physiological systems (Hausdorff & Alexander, 2005). Since multiple processes influence gait, impairment of gait in older adults can be considered a representation of the integrated effects of aging and comorbidities on health and functional status (Studenski et al., 2003). Early detection of gait impairment is effective in identifying those at a subclinical stage of disability (Guralnik et al., 1995), detecting underlying pathologies (Studenski et al., 2003), predictive of future falls (Montero-Odasso et al., 2005; Tinetti, Speechley, & Ginter, 1988), and provides an opportunity to intervene to reduce functional decline (Cesari et al., 2009). A number of temporal and spatial parameters of the gait cycle can be objectively measured to evaluate gait and are associated with future adverse events (Whittle, 2007).

1.4 Gait velocity

Gait velocity is a comprehensive performance measure which captures multiple features of lower limb function (Bendall, Bassey, & Pearson, 1989; Tinetti et al., 1986). Maintaining a stable gait velocity requires the coordination of multiple integrated physiological systems working in a highly regulated manner (Alexander, 1996; Bohannon, 1997), including the nervous system, musculoskeletal system, as well as cardiopulmonary and sensory systems (Studenski et al., 2011). As these systems become altered with age, gait speed has been shown to diminish approximately 10-20% after the

age of 75 compared to younger adults (Alfaro-Acha, Al Snih, Raji, Markides, & Ottenbacher, 2007).

1.4.1 Gait velocity a marker of adverse events

An accelerated decline of gait speed can be an early warning sign for adverse health events and disabling diseases (Cesari et al., 2005; Montero-Odasso et al., 2005; Studenski et al., 2003). Studies across several large cohorts have established that older individuals categorized as slow walkers, walking slower than 1.0 m/s, have been shown to have a higher risk of future falls, hospitalization, institutionalisation (Montero-Odasso et al., 2005), mobility disability (Cesari et al., 2005), cognitive decline (Inzitari et al., 2007), and mortality (Studenski et al., 2011) compared to fast or intermediate walkers. It has been suggested that preclinical conditions, compounded by the effects of aging, affect the physiological domains involved in gait regulation (Studenski et al., 2011). This results in a high energy cost of walking and manifests in the loss of the capacity to maintain normal gait velocity (Bloem et al., 2000; Newman et al., 2001). Reduced gait velocity has been proposed as a "vital sign" which reflects physiological disturbances before they are completely clinically expressed (Studenski et al., 2011).

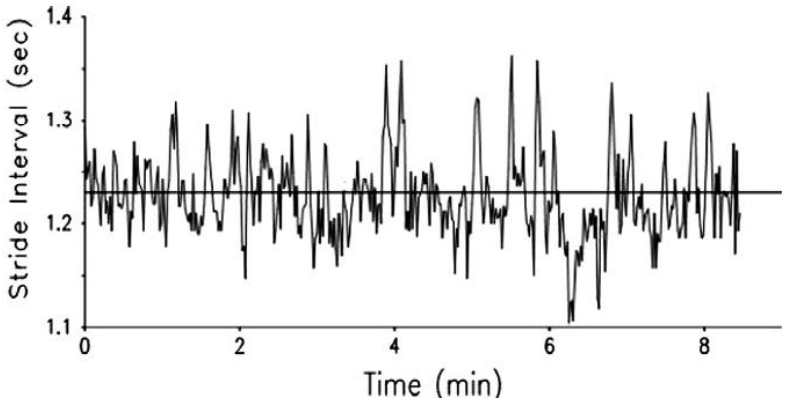
Gait velocity is a test in which individuals walk along a course of a measured distance while being timed. The test is not time consuming and requires very little training to apply in the clinical setting. Furthermore, studies have shown that gait speed, as a single item, does just as well or better than complex performance batteries in predicting important health related outcomes in older adults (Guralnik et al., 2000; Studenski et al., 2003). As a result, gait velocity has become widely adopted as an

assessment tool to measure the onset or predictive risk of adverse outcomes in the process of aging (Abellan van Kan et al., 2009).

1.5 Gait variability

Examination of human gait patterns reveals complex fluctuations between and within strides even under steady environmental conditions (Figure 1.7) (Hausdorff, Peng, Ladin, Wei, & Goldberger, 1995; Beauchet et al., 2009). During a steady state walk, gait variability quantifies the amount of stride-to-stride fluctuation in temporal and spatial parameters of gait (Hausdorff, 2005; 2007). In the past, stride-to-stride fluctuations in gait measures were considered random noise and filtered out of analysis which was focused on average stride values (Newell & Corcos, 1993). Studies in gait dynamics have revealed that these fluctuations actually provide important insight beyond measures of the average stride into the regularity and control of limb-coordinated movements (Hausdorff, 2007). In healthy conditions low stride to stride variability reflects a rhythmic and stable gait, whereas high gait variability reflects an unstable walking pattern (Beauchet et al., 2009; Hausdorff et al., 1997; Hausdorff, Zemany, Peng, & Goldberger, 1999). The magnitude of stride-to-stride fluctuations is critical in understanding the physiology of gait (Lipsitz & Goldberger, 1992; Montero-Odasso et al., 2011), assessing age-related and pathological changes in the locomotor system (Gabell & Nayak, 1984; Hausdorff, Cudkowicz, Firtion, Wei, & Goldberger, 1998), and serves as a measure of function and mobility status in older adults (Callisaya et al., 2011; Hausdorff, Rios, & Edelberg, 2001).

Figure 1.7: Stride-to-stride fluctuations in stride time (sec) about its means (solid line) in a healthy young adult.



1.5.1 Quantification and assessment of gait variability

The variability in gait parameters can be quantified using the standard deviation (SD), a measure of dispersion from the mean value (Brach, Perera, Studenski, & Newman, 2008). However parameters with larger means tend to vary more and changes in the mean value of the parameter being analysed can heavily influence SD measures. SD is also dependent on the unit of measurement being taken (Brach et al., 2008; Hausdorff et al., 1998). To control for this, gait variability can also be quantified using the coefficient of variation (CoV) which is the ratio of the SD to the mean multiplied by 100% (CoV = [(SD/Mean) × 100%]). The CoV is adjusted by the mean and therefore useful for comparing the degree of variation even if means are drastically different and have a range of values (Brach, Studenski, Perera, VanSwearingen, & Newman, 2008). Also, the CoV is a standardized measure which allows for the comparison of temporal and spatial variables in different units (Hausdorff, 2005). Montero-Odasso et al. (2009) showed that in a sample of older adults the test-retest reliability of CoV, measured by

intra class correlation (ICC), was “excellent” for several gait variables under both single task and dual task conditions (ICC=0.80-0.97).

As previously mentioned, a validated method of quantitative gait analysis is the use of the computerized instrumented walkways, such as the GAITRite system (Bilney et al., 2003; McDonough et al., 2001; van Uden & Besser, 2004). The GAITRite mat provides a reliable and valid measure of gait in several populations, including older adults (Beauchet et al., 2011; Brach et al., 2008; Montero-Odasso et al., 2009). The GAITRite mat is able to accurately measure temporal and spatial gait parameters (van Uden & Besser, 2004) and can record several strides which is critical in the investigation of stride-to-stride changes (Hausdorff, 2005; Brach et al., 2008). Brach et al. (2008) showed that gait variability calculated from a limited number of steps (5-6 steps) had “poor” to “good” test-retest reliability (ICC=.22–.48), but reliability was improved when a greater number of steps (10–12 steps) were included (ICC=.40–.63). Too few steps can increase the error in estimating the mean, SD, and CoV values impose limitations in interpreting results of gait variability (Owings & Grabiner, 2003). Also, a fewer number of steps increases the sample size required to ensure sufficient statistical power to detect between-group differences. A greater number of steps provide more data points which allows for a more sensitive assessment of change and more consistent measure of gait variability from stride-to-stride (Brach et al., 2008; Hausdorff, 2005)

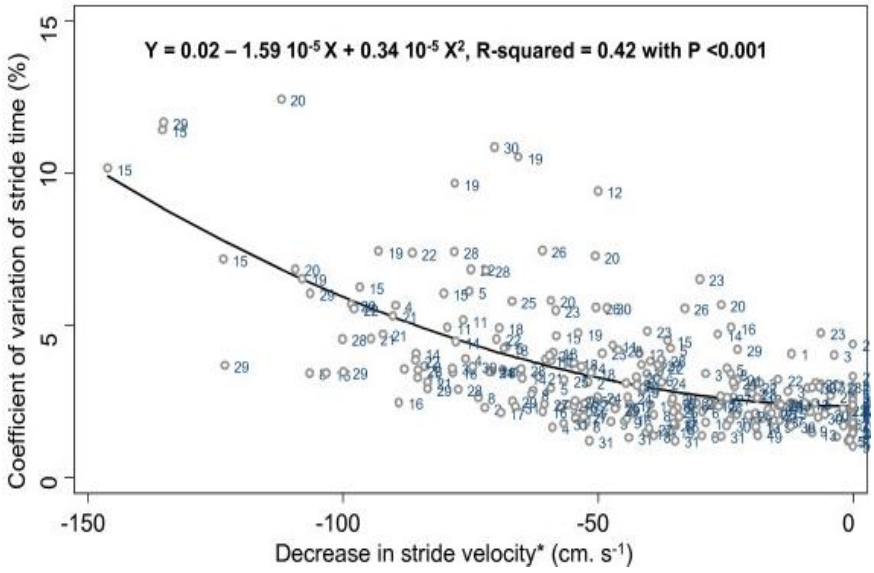
1.5.2 Gait variability and gait velocity

Gait parameters illustrate overlapping features of the locomotor system, hence, various gait parameter measures are strongly related to each other (Kirtley, 2006). In order to evaluate the clinical utility of gait variability in the evaluation of mobility status

in older adults, understanding its relationship with gait speed is essential (Beauchet, Dubost, Herrmann, & Kressig, 2005; Beauchet et al., 2009; Dubost et al., 2006). Biomechanical analysis of gait mechanisms reveals a complex relationship between gait speed and gait variability. Some studies have failed to determine a relationship between the parameters (Frenkel-Toledo et al., 2005; Kang & Dingwell, 2008; Owings & Grabiner, 2004), while others have demonstrated a non-linear relationship (Beauchet et al., 2009; Jordan, Challis, & Newell, 2007; Van Emmerik, Wagenaar, Winogrodzka, & Wolters, 1999).

A study of healthy older adult, as well as individuals with Parkinson's disease (PD) revealed that stride time variability increased at slow speeds (0.2-0.6m/s), compared to moderate walking speeds (0.8-1.4m/s) (Van Emmerik et al., 1999). Stride time variability has also been shown to increase at faster walking speeds during the walk-run transition of gait (2.0-2.2m/s) (Brisswalter & Mottet, 1996). Recently, Beauchet et al. (2009) demonstrated that as walking speed is decreased from a normal self-selected pace, stride time variability increased in a curvilinear manner in young adults ($p<0.001$) (Figure 1.8). It has been suggested that in this trend, low variability occurs at speeds which are mechanically optimal and require minimal energy consumption in order to maintain locomotion (Yamasaki et al., 1991; Danion, Varraine, Bonnard, & Pailhous, 2003). As a result of these findings, grouped differences in variability may be observed due to the confounding effects of gait speed (Van Emmerik et al., 1999; Beauchet et al., 2009).

Figure 1.8: Association between stride time variability (CoV %) and self-selected walking speed (cm/sec) in young healthy adults. Normal self-selected walking speed, used as the reference level, is denoted as 0 cm/sec.



However, several studies suggest that alterations in stride variability are a reflection of central nervous system impairment, and not simply a manifestation of slow walking speed (Hausdorff, 2004). Investigations of executive function on locomotor control of Alzheimer's disease (AD) patients demonstrated a significant association between increased stride variability during cognitively challenging tasks, while no difference was noted in gait speed (Sheridan, Solomont, Kowall, & Hausdorff, 2003). Maki et al. (1997) in a cohort of older adult fallers and non-fallers found that while gait speed was associated with a fear of falling it was not associated with fall risk among older adults. In comparison, stride variability was the single best predictor of fall risk but was not associated with fear of falling. Studies comparing gait parameters between healthy young

adults and healthy older adults have shown no significant difference in stride variability between the groups, even though older adults walked at reduced speeds (Gabell & Nayak, 1984; Grabiner, Biswas, & Grabiner, 2001; Hausdorff, Edelberg, Mitchell, Goldberger, & Wei, 1997;).

Taken together these studies demonstrate that gait variability measures may be more sensitive to subtle underlying pathologies, a good marker in discriminating between "vulnerable" and healthy populations, and a better predictor of falls than traditional measures such as gait speed (Gabell & Nayak, 1984; Grabiner et al., 2001; Hausdorff et al., 2001; Maki, 1997). While there is a relationship between variability measures and average speed values, slow gait speed is not a complete explanation of alterations in stride variability (Hausdorff, 2005; 2007). Measures of mean stride time, stride length and gait speed provide a good initial descriptor of a person's mobility and gait (Hausdorff, 2004). However, assessment of the alterations in gait variability provides important information beyond that of average velocity measures in understanding and predicting adverse events in older adults.

1.5.3 Gait variability a marker of adverse events

Walking is highly regulated and a finely tuned activity (Hausdorff, 2007). In healthy young and older adults the magnitude of stride-to-stride variability is relatively low during steady-state conditions, reflecting a rhythmic and more stable gait (Beauchet et al., 2009; Hausdorff et al., 1997; 1999). It has been demonstrated that in the parameters of stride time and stride length, reflecting propulsion in the forward direction, a CoV value equal to or lower than 3% indicates normative variability (Danion et al., 2003; Hausdorff et al., 1997; 1999; Montero-Odasso et al., 2011). In the parameter of stride width and

double support time, which are associated with balance, although some degree of variability is considered adaptive, normative values in healthy older adults have yet to be determined (Brach, Berlin, VanSwearingen, Newman, & Studenski, 2005). The more variable gait is the more uncontrolled and unstable the walking pattern will be, resulting in unsteadiness and loss of balance (Hausdorff, 2005). Increased stride-to-stride variability has been linked to a high risk of falls (Hausdorff et al., 2001), cognitive decline, and neurological diseases such as AD (Sheridan et al., 2003), PD, and Huntington's disease (Hausdorff et al., 1998; 1997).

Regulation of gait variability has been linked with multiple physiological systems including neural control, muscle function, postural control, as well as cardiovascular and cognitive domains (Hausdorff, 2005). It has been postulated that these systems monitoring gait stability may become altered in the face of physiological aging, overt disease, and subclinical conditions (Gabell & Nayak, 1984; Hausdorff et al., 1998; Montero-Odasso et al., 2011). Therefore, measures of gait variability have the potential to be utilized as a clinical tool for functional assessment of aging, disease severity, mobility status, response to therapeutic interventions, and a sensitive marker of risk to adverse health events in older adults (Hausdorff, 2005; 2007).

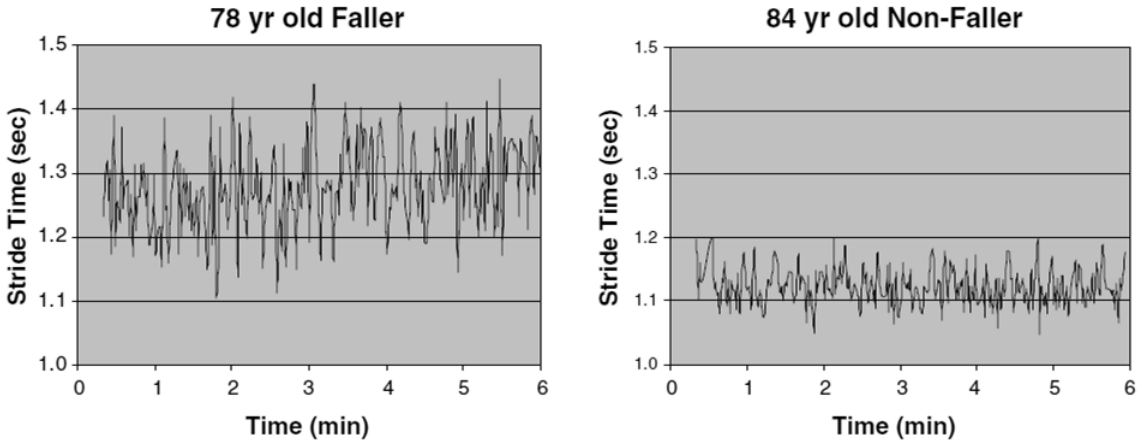
1.5.3.1 Gait variability and fall risk

Falls can have severe health consequences in the elderly due to the resulting injuries, mobility constraints, new disability, loss of independence, and fear of falling (Tinetti, 1987). In order to design targeted interventions for fall prevention, it is critical to determine risk factors for falls and identify sensitive markers for assessing fall risk (Guralnik, Ferrucci, Balfour, Volpato, & Di Iorio, 2001). Quantitative studies looking at

the relationship between fall risk and mobility demonstrate that gait variability measures can be used to prospectively identify older adults at a higher risk of falling (Verghese, Holtzer, Lipton, & Wong, 2009; Callisaya et al., 2011; Hausdorff et al., 2001; Maki, 1997).

Hausdorff et al. (2001) demonstrated that in a group of community-dwelling older adults, future fallers showed significantly increased variability in the parameters of stride time ($p<0.04$) than non-fallers at baseline (Figure 1.8). However, these two groups showed no significant difference at baseline in demographic characteristics, mental health, and ability to perform ADLs or IADLs. Fallers and non-fallers were also similar in measures of lower extremity function, gait speed, and balance, which are associated with fall risk, functional status, and vitality (Gill, Williams, & Tinetti, 1995; Guralnik et al., 1994; 2000; Studenski et al., 2011). Thus, even when other measures of fall risk only show subtle changes in function, gait variability measures may provide a more complete reflection of impairments in gait dynamics which increase instability. These findings highlight the value of utilizing gait variability measures in predicting fall risk in addition to other traditional assessment measures.

Figure 1.9: Illustration of fluctuations in stride time (sec), measured at baseline, in participant who experienced a fall during the 12 month follow-up period (SD= 66ms), compared to a non-faller (SD=29ms).



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1.5.3.2 Gait variability and neurological diseases

Clinically, patients with neurological impairments, such as Huntington's disease, PD and AD show increased gait abnormalities in comparison to age-matched controls (Morris, 2000; Pettersson, Olsson, & Wahlund, 2005). Particularly, these patients have trouble maintaining balance and tend to fall more (Bloem, Grimbergen, Cramer, Willemsen, & Zwinderman, 2001; Schaafsma et al., 2003), leading to serious injuries, disability and effecting the quality of life in these populations (Morris, 2000; Pettersson et al., 2005). As seen in populations of elderly fallers, gait variability can be used as a relevant clinical measure of gait stability and degree of disease severity in those with pathological impairments (Nakamura, Meguro, & Sasaki, 1996).

PD patients have rigid and unstable movement with characteristics symptoms of bradykinesia (slowness of gait), akinesia (cessation of movement) along with rest tremor

(Bond & Morris, 2000). Another feature of PD is the impaired ability to regulate gait rhythm, manifested as increased stride-to-stride variability (Baltadjieva, Giladi, Gruendlinger, Peretz, & Hausdorff, 2006; Blin, Ferrandez, & Serratrice, 1990; Hausdorff et al., 1998). Hausdorff et al. (1998) provided evidence that alteration in gait variability manifest relatively early in the disease process even though dramatic changes in speed may not yet be apparent. Additionally, stride time variability has been shown to be significantly increased in PD patient with a history of falls compared to those that did not fall, while parkinsonian features of bradykinesia, rigidity, and tremor showed no difference between these groups (Hausdorff et al., 2003; Schaafsma et al., 2003). Conferring the potential of gait variability measures, beyond the classic characteristics of PD, as useful indices of fall risk and disease progression in PD patients.

AD patients early in the disease process have also been shown to perform poorly in motor performance assessments and have deteriorating physical ability compared to healthy individuals (Franssen, Souren, Torossian, & Reisberg, 1999; Nadkarni, Mawji, McIlroy, & Black, 2009; Pettersson et al., 2005; Wittwer, Andrews, Webster, & Menz, 2008). Studies of mild to moderate AD patients, showed that stride length variability was significantly greater in the AD group compared to age-matched controls although both groups walked at similar speeds (Webster, Merory, & Wittwer, 2006; Wittwer, Webster, & Menz, 2010). Nakamura et al. (1996) demonstrated that while gait speed was not able to differentiate between AD fallers and non-fallers, stride length variability was significantly higher in AD fallers with mild and moderate disease severity ($p<.01$). Furthermore, changes in gait variability have been demonstrated to precede clinical manifestations of cognitive decline in initially non-demented older adults (Verghese,

Wang, Lipton, Holtzer, & Xue, 2007). Similar to PD patients, measures of gait variability may be an effective index in detecting motor impairments and gait instability in individuals with dementia who are at high risk for falls, even early in the disease process (Nakamura et al., 1996; Webster et al., 2006; Wittwer et al., 2010; Verghese et al., 2007).

1.5.3.3 Gait variability and cognitive decline

Walking is thought to be a "hard-wired" process regulated by subcortical areas of the basal ganglia and spinal regions in healthy young adults, and requires very little attention (Dubost et al., 2006; Woollacott & Shumway-Cook, 2002). However, investigations beyond the biomechanics of walking suggest that higher cortical regions of the prefrontal cortex, which is associated with executive function (EF), play an important role in the performance of learned motor tasks (Perry & Hodges, 1999). EF refers to a network of primary cognitive processes that use cortical and sensory information to produce "goal-directed behaviours involving movement, action planning, working memory, and attention" (Sheridan et al., 2003). Studies of divided attention, an example of an EF, utilize the dual-task paradigm to give insight into the role of attention and EF on gait performance (Bond & Morris, 2000; Camicioli, Howieson, Lehman, & Kaye, 1997; Dubost et al., 2006; Sheridan et al., 2003; Springer et al., 2006).

Walking while performing a secondary task, in the face of limited attentional resources, results in reduced performance in one or both tasks (Springer et al., 2006). Specifically, increased gait variability while dual tasking has been observed in the gait of older adults prone to falling due to limited cognitive resources (Bond & Morris, 2000; Dubost et al., 2006; Springer et al., 2006). Springer et al. (2006) showed that dual-tasking significantly increased stride-to-stride variability in fallers, whereas there was no change

in gait variability of non-fallers and young adults. All three groups had reduced gait velocity under dual-tasking conditions. Memory performance, a general marker of cognitive function, was not significantly different in fallers compared to non-fallers, although fallers did significantly worse on tests of EF. These findings demonstrate that increased gait variability in elderly fallers may be indicative of physiological deficits in cortical regions associated with EF which results in high gait variability and increased risk of falling.

Patient populations at a high risk of falls, such as PD and AD patients, also show evidence that impairment of attention increases gait variability (Camicioli et al., 1997; Perry & Hodges, 1999; Sheridan et al., 2003; Yogev et al., 2005). It has been postulated that due to deficits in the basal ganglia in PD, gait stepping mechanisms recruit regions of the pre-frontal cortex during the execution of movement (Sheridan et al., 2003). Impaired gait stepping mechanisms increasingly rely on cortical pathways to generate a stable walk and put additional demands on attentional resources during multi-tasking (Bond & Morris, 2000). Furthermore, neuroimaging studies of AD show evidence that reduced cerebral blood flow in the pre-frontal lobe regions is associated with increased gait variability (Nakamura et al., 1997). Therefore, impaired cortical networks in the frontal lobe may play a role in reduced EF function and diminished regulation of gait variability.

Recent studies of gait dynamics suggest that the regulation of gait, in healthy young and old adults, utilizes attention (Dubost et al., 2006; Springer et al., 2006). Aggravated gait instability, measured by increased gait variability, and diminished attention resources in PD, AD, and idiopathic fallers explains why these populations are vulnerable to environmental hazards (Woollacott & Shumway-Cook, 2002) and fall more often

(Hausdorff et al., 2003; Yogev et al., 2005). Increased gait variability in older adults indicates a lack of cognitive reserves and, thus, a reduced ability to compensate for gait impairments in challenging conditions (Yogev et al., 2005). This association also underscores the possibility of treating gait disturbances by targeting the cognitive regions through attention-enhancing medications or therapies to improve gait variability and reduce the risk of falls.

1.5.4 Neural control of gait variability

The underlying mechanisms which control stride-to-stride fluctuations of gait variability are unknown. However, in the last decade several studies have tried to elucidate which systems interact during gait dynamics (Beauchet et al., 2009; Rosano, Brach, Studenski, Longstreth, & Newman, 2007; Yogev-Seligmann, Hausdorff, & Giladi, 2008; Zimmerman, Lipton, Pan, Hetherington, & Verghese, 2009). The association between neurological diseases and increased attentional demands with high gait variability suggests a neural control of gait variability beyond the musculoskeletal system (Hausdorff et al., 1998; Sheridan et al., 2003; Springer et al., 2006) . In healthy conditions, the locomotor system produces complex and coordinated movement of limbs and activation of the muscles by integrating signals from the motor cortex, cerebellum, basal ganglia, and sensory feedback from visual, vestibular and proprioceptive systems (Hausdorff et al., 2001). Temporal and spatial parameters of a stride are output measures and a result of these integrated networks of afferent and efferent components of the neuromuscular system (Hausdorff, 2007). It has been hypothesized that separate mechanisms are involved in generating and regulating different gait variables (Beauchet et al., 2009; 2011; Brisswalter & Mottet, 1996; Gabell & Nayak, 1984). Examining

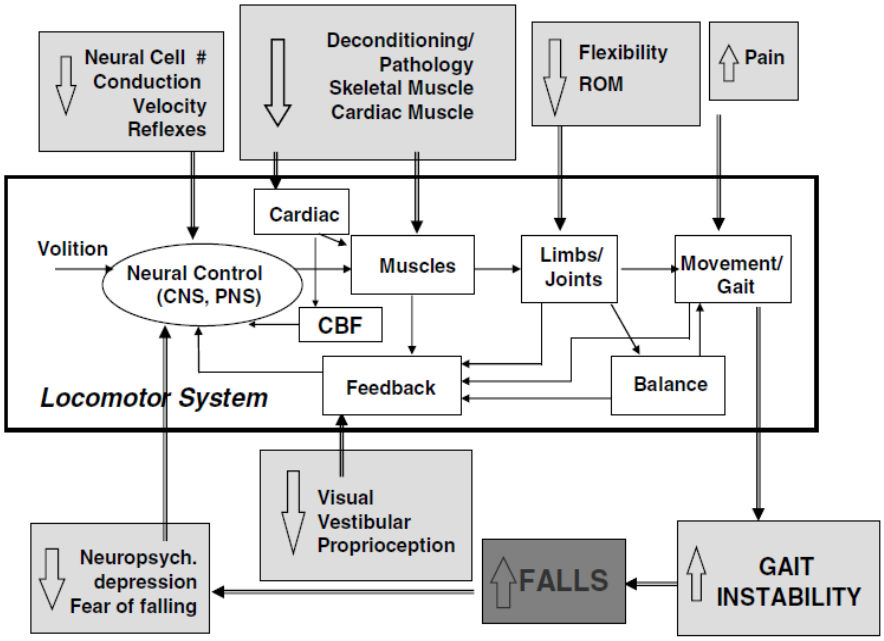
fluctuations in separate stride parameters could therefore provide insight into the organization, regulation, dynamics, and function of the locomotor control system (Hausdorff, 2007).

Gabel and Nayak (1984) proposed that step length and stride time are predominantly controlled by a gait-patterning mechanism, the spinal process which produces the repeated sequence of muscle contraction and relaxation during walking. The regulation of these parameters are predominantly controlled by locomotor centres in the basal ganglia and higher cortical regions of the frontal lobe as reflected in studies of increased gait variability in AD, PD, and Huntington's disease patient populations (Hausdorff et al., 1998; 2003; 2007). High variability in stride time and stride length has thus been suggested to indicate impairment of the automatic stepping mechanism due to degeneration of higher cortical circuits involved in gait regulation (Gabell & Nayak, 1984; Rosano et al., 2007). The parameters of step width and double support time are suggested to be involved in balance control mechanisms and reflect stability (Gabell & Nayak, 1984). Regulation of step width has been associated with muscle strength and the sensorimotor system rather than higher cognitive regions (Brach et al., 2005; Brach, Studenski et al., 2008; Callisaya, Blizzard, McGinley, Schmidt, & Srikanth, 2010). Increased double support time and step width variability could indicate compensation for instability due to impairments in balance control mechanisms (Gabell & Nayak, 1984).

These findings demonstrate that variability in stride parameters provide insight into the multidimensional factors involved in locomotor control beyond the musculoskeletal system (Hausdorff et al., 2001). Below, Figure 1.10 represents the multiple physiological factors which are associated with gait instability. Impairments of these systems, which

can be observed with aging or disease, may be captured by increased variability across different gait parameters. Therefore, gait variability may serve as a marker of underlying deficits in the control mechanisms of gait that predisposes adverse health events.

Figure 1.10: Physiological factors associated with gait instability. Illustration of the locomotor system and certain age-associated physiological changes (shaded boxes) which influence gait instability. CNS, central nervous system; PNS, peripheral nervous system; ROM, range of motion, CBF, cerebral blood flow.



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1.5.5 Gait variability characterizes loss of physiological complexity

In the healthy body, complexity refers to the intricate network of control systems, regulatory mechanisms, structures, and feedback loops which allow an organism to

survive, and carry out its function (Lipsitz & Goldberger, 1992). This intricacy of systems is evident in the assessment of heart rate and blood pressure regulation (Kaplan et al., 1991), respiratory dynamics (Peng et al., 2002), postural balance (Collins, De Luca, Burrows, & Lipsitz, 1995), and gait dynamics (Hausdorff et al., 1997). As a result, the healthy human body is resilient and able to maintain homeostasis, the ability to adapt and respond to stress (Lipsitz, 2002; 2004). It has been suggested by Lipsitz and Goldberger (1992) that the loss of complexity in anatomical structures and physiological systems is part of the normal aging process.

With aging, there is a progressive degeneration of several tissues and organs (Lipsitz & Goldberger, 1992). Although, this loss of complexity threatens functional ability in older individuals, there are many redundancies and plasticity in human biological systems (Lipsitz, 2002). For example, the amount of muscle mass, neuronal circuits, and hormonal stores in the human body far exceed what is needed for usual physiological demands (Lang, Michel, & Zekry, 2009). This "physiological reserve" allows older adults to compensate for age-related physiological systems without negatively impacting their daily life routines (Lipsitz & Goldberger, 1992; Lipsitz, 2002; 2004).

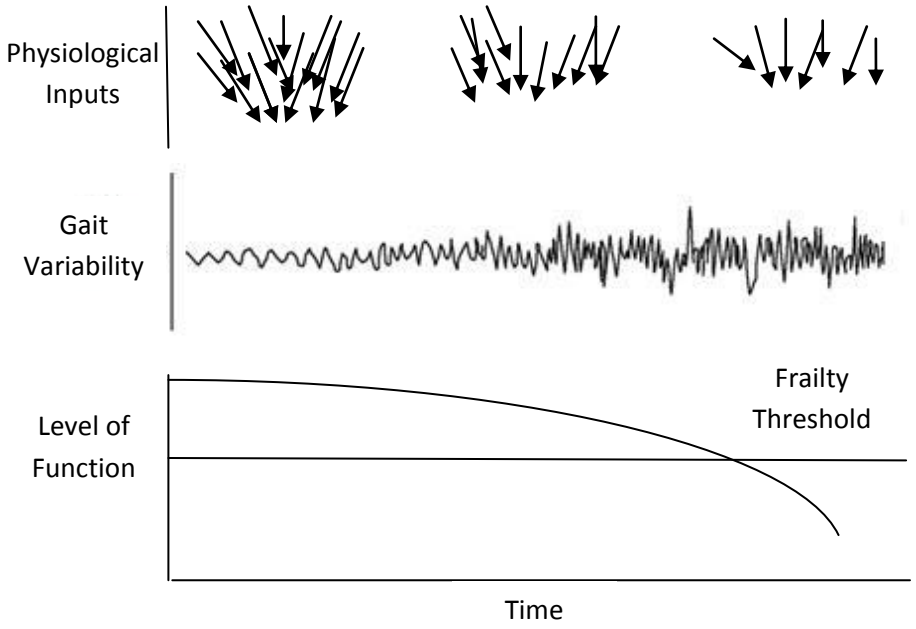
However, the continued loss of complexity disrupts the network of communication pathways between, and within, physiological systems (Lipsitz, 2002). Consequently, the inputs of physiological systems is disturbed and reduced and the resulting output signals become diminished and less complex. For instance, in older adults, reduction in complexity is seen in the breakdown of bone trabecular architecture, which characterizes osteoporosis; there is a diminished ability of the autonomic nervous system to regulate blood pressure, increasing the risk for hypertension (Lipsitz, Mietus, Moody, &

Goldberger, 1990); and decreased proprioception leads to increased postural sway increasing the risk of falls in older adults (Collins et al., 1995). This dysregulation in physiological systems, cause functional capacity of homeostasis to drop below a critical threshold, referred to as the "frailty threshold" (Figure 1.11) (Fried et al., 2005; Lipsitz, 2002). At this point, the decline in functional ability is decreased to the extent that the older adult can no longer adapt and respond to internal or external stressors. This results in a marked increase in vulnerability to disability, disease and mortality (Fried et al., 2005).

As previously mentioned, the regulation of gait involves EF, and impairment of higher cortical regions is associated with increased gait variability (Springer et al., 2006; Woollacott & Shumway-Cook, 2002; Yogev-Seligmann et al., 2008). Additionally, the autonomic nervous system which is involved in the regulation of heart rate dynamics, an indicator of cardiovascular health, has been shown to be associated to gait instability (Hausdorff et al., 1994; Hausdorff, Herman, Baltadjieva, Gurevich, & Giladi, 2003). Increased gait variability has also been associated with low bone mineral density in women which was not detected by typical performance measures or gait speed (Palombaro et al., 2009). Furthermore, older adults demonstrate that diminished sensorimotor functions is associated with high gait variability in several parameters (Callisaya et al., 2010) and resistance training and improvement in muscle strength demonstrates reduced gait instability (Hausdorff et al., 2001). Under the framework of "physiological complexity" these findings demonstrate that gait variability is not only a measure of stability, but is also a sensitive marker of physiologic function. Hence, it has

been hypothesized that high gait variability characterizes the loss of complexity across several physiological parameters (Lipsitz, 2004; Montero-Odasso et al., 2011).

Figure 1.11: Illustration of the loss of physiological complexity with ageing resulting in increased gait variability. Reduction in physiological inputs and connections leads to a decline in functional ability and loss of complexity in output signals, which may manifest as high gait variability. Frailty develops when functional level falls below the "frailty threshold," and the individual can no longer adapt to stressors.



Adapted from Lipsitz, L.A. (2002).

1.6 Gait variability a marker of frailty

As previously discussed, the inability to regulate gait performance and maintain rhythmicity, measured by gait variability, may indicate decreased complexity in several physiological systems (Hausdorff, 2005; 2007). Consequently, high gait variability has been established as an early marker of falls, mobility decline, and cognitive decline

which are also outcomes associated with frailty. Within the framework of a loss of complexity proposed by Lipsitz and Golberger (1992), it has been suggested that gait variability may be associated with frailty (Montero-Odasso et al., 2011). Several studies exploring the relationship between mobility and frailty have shown strong evidence that reduced gait velocity, specifically, is a marker of frailty (Abellan van Kan et al., 2008). However, beyond gait velocity, a limited number of studies have explored the relationship of gait variability and frailty. Recently, Montero-Odasso et al. (2011) investigated the association of frailty, as defined by the FPI, and gait variability in a cross-sectional study of 100 community-dwelling older adults (aged 75 years and older). Results of the study showed that high stride-to-stride variability was significantly associated with frailty status.

1.7 Rationale for study

The previously mentioned study by Montero-Odasso et al. (2011) provides the first set of empirical evidence to further our understanding of mobility and frailty, in the parameter of gait variability. An important limitation of the cited study is that the included participants were categorized as frail using the FPI, a model that includes slow gait velocity as a criterion. Therefore, the high gait variability found in frail older participants may have been confounded by its association with slow gait and not with the participants' frailty status.

In order to examine the true association between gait variability and frailty, a model that does not include gait velocity as a criterion is needed. If high gait variability is found in a sample of older adults with frailty, using a model which does not include gait as a criterion, this will demonstrate the independent association. In addition, this finding will provide support to the theory that frailty is a clinical syndrome with an underlying pathophysiology, characterised by the loss of dynamics in several systems (Fried et al., 2001; Lipsitz, 2004). Examining the association of gait variability and frailty may provide further insight into the underlying mechanisms of this biological syndrome.

1.8 Purpose

The purpose of the study was to determine the association between gait variability and frailty, as defined by the Clinical Frailty Scale (CFS), a model which does not specifically include gait velocity as a criterion. Furthermore, in order to apply the CFS in our sample, this study was designed to test the inter-reliability of the CFS and its concurrent validity against the Frailty Phenotype Index (FPI).

1.9 Hypothesis

We hypothesized that: 1) high gait variability would be associated with increased CFS frailty status; 2) the CFS would be reliable and valid against the FPI in its classification of frailty in our sample of community-dwelling older adults.

CHAPTER 2- METHODOLOGY

2.1 Study design

This study is a secondary analysis of data collected at the baseline assessment of the Frailty and Mobility Study (FMS). The FMS is a prospective cohort study evaluating the relationship between frailty, as defined by the Frailty Phenotype Index (FPI), and mobility in community-dwelling older adults. The current study sample is composed of the FMS participants recruited between the periods of October 2008 to December 2010.

The Clinical Frailty Scale (CFS), an alternative frailty model to the FPI, was applied retrospectively to the dataset by two assessors to determine frailty of individual participants. Next, an analysis of gait data across the CFS frailty groups was performed to evaluate the association between gait variability, as a measure of gait impairment, and CFS frailty status in community-dwelling older adults.

2.2 Study population

Initially, a convenience sample of 109 older adults from the FMS cohort were screened for inclusion in our study; two subjects were excluded from this sample due to missing information of physical activity level and frailty scores bringing the final sample to 107 community-dwelling older adults. This sample was recruited from a naturally occurring retirement community (NORC) and comprise FMS cohort. The Cherryhill NORC is a 13-building apartment complex housing 2,500 older adults (mean age = 79.53 ± 9.53 years) in London, Ontario, Canada (Kloseck, Crilly, & Mannell, 2006). Participants were all community-dwelling older adults and eligible to participate in the study if they were aged 75 years or older, English speaking, and reported being able to

ambulate at least 10 meters independently without the use of a mobility aid. Exclusion criteria were the diagnosis of a terminal illness, life expectancy of less than 12 months, pending nursing home placement, hip or knee joint arthroplasty within the preceding six months, and a diagnosis of dementia.

2.3 Outcome measures

2.3.1 Frailty status

2.3.1.1 Frailty Phenotype Index

Currently, the most widely accepted model of frailty is the FPI (Appendix A) developed by Fried et al. (2001). The FPI was developed and operationalised in a cohort of 5201 older adults (65 years and older) from the Cardiovascular Health Study (CHS). In this sample, the FPI was found to be independently predictive of various adverse clinical outcomes, including the incidence of falls, worsening mobility or ADL disability, hospitalization and death.

At baseline assessment of the FMS, frailty status in the participants was assessed using the five criteria of the FPI (Table 2.1): slow gait velocity, low physical activity, weakness, weight loss, and self-reported exhaustion. The slow gait velocity criterion was met if the participant, at usual pace, walked slower than one meter per second (m/sec). This cut-off was based on evidence from previous studies demonstrating that usual gait velocity below one (m/sec) is indicative of adverse health outcomes in older adults (Cesari et al., 2005; Montero-Odasso et al., 2004; 2005). The low physical activity criterion was assessed by asking the individual to describe their typical activity level as vigorously active, moderately active, or seldom active. A response of "seldom active", defined as preferring sedentary activities, was used to operationalise low physical activity

level (Speechley et al., 2005). The weakness criterion was evaluated with a test of grip strength in the dominant hand using a hand held dynamometer (Jamar, Sammons Preston, Bolingbrook, IL). The weakness criterion was met when the average of three measures of grip strength was less than or equal to the cut-offs outlined in the FPI (Fried et al., 2001). The exhaustion criterion was evaluated using two questions from the Center for Epidemiologic Studies Depression Scale (Orme, Reis, & Herz, 1986): "Do you feel like everything you do takes an effort?" and "Have you ever felt like you could not get going in the previous 2 months?" An affirmative answer to one or both questions categorized participants as exhausted. In addition exhaustion was also evaluated with the question, "how much of the time during the past four weeks did you have a lot of energy?" An answer of a "little or none of the time" classified exhaustion in participants. The weight loss criterion was met if the participant reported losing more than 10 pounds unintentionally in the previous 12 months. A total frailty score was calculated based on the sum of the frailty components present. Individuals were then categorized into one of three frailty categories based on their frailty score as follows: frail, score of ≥3; pre-frail, score of 1–2; and not frail, score of 0.

Table 2.1: Measures of the individual Frailty Phenotype Index components in study participants.

FPI components	Measure of components
Slow Gait Velocity	Gait velocity of ≤ 0.99 m/sec
Low activity	Self-report of sedentary lifestyle Low frequency of physical activity (walking, chores, exercising, and leisure activities)
Weakness	Lowest 20% in grip strength (adjusted by gender and BMI)
Exhaustion/ Poor Endurance	Positive answer from either of: (1) I felt that everything I did was an effort. (2) I could not get going. OR, answer of "A little/none of the time" to the question, "How much of the time during the past 4 weeks did you have a lot of energy?"
Weight loss	Self-report of >10lbs lost unintentionally in the last year

2.3.1.2 Clinical Frailty Scale

The FPI index includes gait velocity as a criterion which is known to be highly correlated with other quantitative gait parameters. In order to avoid a redundancy of the association between gait variability and gait velocity, frailty in our population was also categorized using the CFS (Appendix B), a validated frailty model which does not specifically itemize gait velocity as a criterion in identifying frailty.

The CFS was developed from the Canadian Study of Health and Ageing (CSHA) by Rockwood et al. (2005) in order to provide clinicians with an easily applicable frailty assessment tool. In a sample of 2297 older participants from the CSHA, the CFS predicted mortality during a 5-year follow-up better than individual measures of cognition, functionality and comorbidity. The CFS is based on the clinical evaluation of a patient's status in the following clinical domains: mobility capabilities, level of energy,

physical activity and level of functionality. The scale uses clinical descriptors and figures to stratify older adults according to their level of vulnerability, ranging from CFS-1 (very fit), to CFS-9 (terminally ill). In order to apply the CFS to our sample, self-report measures from questionnaires (Appendix C) completed during baseline FMS assessment were compiled and reviewed for each study participant. Several demographic, clinical, and mobility measures from the FMS questionnaire were selected to represent the different clinical-functional domains included in the CFS.

Two clinicians with expertise in frailty, a Geriatrician and Physiotherapist, independently evaluated each participant's demographic, clinical, and functional mobility information in order to apply the CFS and define frailty in our sample. Each participant was assigned a category of CFS-1(very fit) through CFS-7 (severely frail) on the CFS (Table 2.2). The categories of CFS-8 (very severely frail) and CFS-9 (terminally ill) represent adults who are totally dependent on others to carry out their activities of daily living (ADL) (Rockwood et al., 2005). Since our sample consists of older adults living independently in the community, the categories of CFS-8 and CFS-9 were not applicable. The clinicians were blind to the subjects' FPI frailty score and all quantitative gait parameters measures.

Table 2.2: Categories and descriptors of the Clinical Frailty Scale applied to study sample.

1- Very fit	• robust, active, energetic, motivated, fit
2- Well	• no active disease, less fit than people in category 1
3- Managing Well	• disease symptoms well controlled, not regularly active
4-Vulnerable	• symptoms limit activities, are "slowed up"
5- Mildly frail	• dependence for instrumental activities of daily living
6- Moderately frail	• need help with instrumental and non-instrumental activities of daily living
7- Severely frail	• completely dependent for personal care

Information available to the clinicians to categorize individuals using the CFS is outlined below. Mobility capabilities were evaluated if a subject reported using a mobility aid (cane, walker, or other) to get around, history of falls in the last 6 months, comorbidities, and cognitive impairment. A fall was defined as "unintentionally coming to the ground or onto an object" (Panel on Prevention of Falls in Older Persons, American Geriatrics Society, British Geriatrics Society, 2011; Cumming, Kelsey, & Nevitt, 1990; Lach et al., 1991). Self-report of physician diagnosed comorbidities was collected from a list of chronic medical conditions which included: diabetes, heart failure, hypertension, angina, myocardial function, cancer, previous strokes, osteoarthritis, and lung disease. Cognitive issues were ascertained from a self-report of memory issues, established using a 5-point Likert scale. Participants were asked to rate their memory in comparison to other people their age and to rate how their memory is now compared to five years ago (Speechley et al., 2005). Level of energy was assessed based on two questions. The first asked participants to describe their typical level of energy as low, moderate, or high. The second question asked "How often during the past four weeks did

you have a lot of energy?" for which the possible response options were: (a) all of the time, (b) half of the time, or (c) a little/none of the time (Orme et al., 1986).

The level of physical activity criterion was assessed based on two questions. The first question asked subjects to describe their "typical activity level" as vigorously active, moderately active, or seldom active. The second question was a 5-point Likert scale asking participant to rate their activity level relative to other people their age (Speechley et al., 2005). Finally, functional capacity in basic ADL's was evaluated using a disability scale developed for community-dwelling older adults (Gill et al., 2004; Tinetti et al., 1999). Participants rated their ability to perform the following ADL's: walking inside the house, bathing, upper-body dressing, lower body dressing, moving from a bed to a chair, toileting, feeding, and grooming. Scores for each activity were assigned based on the reported level of difficulty performing the task (no difficulty=0, some difficulty=1, or need assistance=2). The sum of the disability score ranges from 0 to 16, with higher scores representing a greater level of disability. Based on this information, each clinician assigned the participants a score on the CFS. Discrepancy in CFS scores between the two clinicians was resolved by consensus to obtain a single CFS score for each participant. In order to compare agreement of frailty status between the three levels of the FPI and six categories of the CFS, the CFS was collapsed to three levels to match the FPI classifications. CFS scores of one through three were categorized as "not frail", category of CFS-4 was categorized as "pre-frail", and CFS-5 and CFS-6 were categorized as "frail". These cut-offs were created based on the clinical descriptors of the CFS.

2.3.2 Gait function

Quantitative gait parameters were evaluated using the GAITRite system (CIR Systems Inc., Sparta, NJ). The computerized GAITRite mat (6 m × 0.5 m) is embedded with grids of pressure sensors to record an electronic imprint of each foot fall as a subject walks over the instrument. Data on gait parameters are calculated and displayed on a computer which is connected to the mat and running the GAITRite software, as a subject completes a walk. The GAITRite has been proven to be a highly valid and reliable tool for measuring a range of spatial and temporal parameters of gait at usual and fast walking speeds in a range of populations including older adults (Bilney et al., 2003; McDonough et al., 2001; van Uden & Besser, 2004).

Participants were asked to walk across the GAITRite mat at a self-selected usual pace and at a fast pace. In order to limit the effects of acceleration and deceleration, start and stop points were marked on the floor one metre away from the edge of the mat. Three trials were performed at each pace, which allows for the collection of several strides in order to calculate a more reliable measure of stride-to-stride gait variability. Previous studies have shown poor test-retest reliability of gait variability when a limited number of strides are collected (Brach et al., 2008; Hausdorff, 2005). The following five quantitative gait variables were assessed: velocity (cm/s), stride time (ms), step width (cm), double support time (ms) and stride length (cm). These gait variables were chosen for their association with mobility decline, falls, and other adverse events in previously reported studies (Brach et al., 2005; Hausdorff et al., 2001; 2004; Montero-Odasso, 2011).
Gait data of each step from all three walks was pooled to obtain a single mean and standard deviation (SD) value for each gait variability parameter evaluated. Gait velocity

at each pace was calculated as the average from all three trails. Variability in four gait parameters (stride time, stride length, double support time, and step width) was quantified using the coefficient of variation (CoV), which is the ratio of the SD to the mean multiplied by 100% (CoV = [(SD/Mean) × 100%]). The CoV is a standardized measure of variability which allows the comparison of gait variables measured in different units, with different means and having a range of values (Hausdorff, 2005).

2.4 Statistical analysis

Means and frequencies of socio-demographic and clinical characteristics were calculated to characterize the sample. Inter-rater reliability of applying the CFS to the study sample was estimated with a weighted kappa. To characterize the sample across CFS categories, means and frequencies of socio-demographic and clinical characteristics were calculated. Differences in descriptive characteristics of participants were evaluated using one-way analysis of variance (ANOVA) for continuous variables and Fisher's Exact test for categorical variables. Statistically significant findings from the one-way ANOVA were followed up by a post-hoc Tukey analysis to identify significant pair-wise associations. Frailty status in the same individual by CFS was compared to the number of FPI components (unintentional weight loss, weakness, exhaustion, slow gait velocity, and decreased physical activity) present using Spearman Rho correlation coefficients. The Mantel-Haenszel test was used to analyse for trend in proportions of each FPI component across CFS categories. Agreement between the FPI and the collapsed 3-level CFS was assessed using weighted kappa statistic. Gait variability parameters (stride time, stride length, stride width, double support time) stratified across the CFS groups, were evaluated using one-way ANOVA for usual and fast pace conditions. This analysis was

then followed with a planned test for trends in means and post-hoc Tukey analysis. Multivariable linear regression analysis was utilized to assess the relationship of categorical CFS levels to each of the gait variability parameters under usual and fast pace conditions with the CFS-1 group as the reference category. The dependent variable was gait variability and the exposure variable of interest was frailty level as identified by the CFS. The regression analyses were adjusted for age and history of falls to control for the effects of confounding. These variables were selected based on evidence from previously established studies that suggest increased age and a history of falls are associated with higher gait variability (Callisaya et al., 2010; Grabiner et al., 2001; Kang & Dingwell, 2008). As a secondary analysis, regression analysis was repeated treating the CFS as a continuous variable to assess the association of gait parameters with increasing CFS frailty status. Statistical analysis for the Kappa coefficient was performed using the software MedCalc (version 12.2, MedCalc Software, Mariakerke, Belgium). All other statistical analyses were performed using PASW (version 18.0, SPSS Inc., Chicago IL). The level of significance for all tests was set at $p < 0.05$.

CHAPTER 3- RESULTS

3.1 Study population and demographics

A total of 107 community-dwelling older adults, aged 75 years and above were included in our initial sample. Three subjects were excluded from further analysis of gait function because clinicians were unable to reach consensus on assigning a CFS frailty score to these participants, yielding a final sample of 104 older adults. The average age of our participants was [Mean (SD)] 82.1 (5.4) years old, 79% of whom were women with an average Body Mass Index (BMI) [Mean (SD)] of 26.4 (4.5). Twenty-nine percent of participants reported having a history of falls in the previous six months, 42% reported having memory problems, and 48% of participants reported being in 'good' health. Characteristics and self-report health measures of the study sample are presented in Table 3.1.

Table 3.1: Demographic characteristics of study participants in total sample.

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Variable	Full Sample (n=107)
Age, mean (SD)	82.1 (5.4)
Women, n (%)	85 (79%)
Body Mass Index, mean (SD)	26.4 (4.5)
Comorbidities, mean (SD)	3.1 (2.2)
Use of Mobility Aid, n (%)	40 (37%)
Number of Medications, mean (SD)	4.2 (3.2)
Disability Score, mean (SD)	2.2 (2.8)
History of Falls in last 6 months, n (%)	32 (29%)
Self-report of memory problems, n (%)	45 (42%)
Self-report of Health Status, n (%)	
Excellent	8 (7%)
Very Good	35 (33%)
Good	51 (48%)
Fair	14 (13%)
Poor	1 (1%)
FPI, n (%)	
Not Frail	13 (12%)
Pre-Frail	60 (56%)
Frail	34 (32%)

Notes: n, group size; SD, standard deviation; BMI, body mass index; FPI, Frailty Phenotype Index

3.2 CFS inter-rater reliability

The inter-rater reliability between clinicians in assessing frailty by applying the CFS in individual participants is outlined in Table 3.2. In the initial independent rating of CFS scores, the clinicians agreed on the exact scoring in 50% (n=54) of cases and disagreed in 50% (n=53) of cases. Of the disagreements, 77% (n=41) were by one category, 21% (n=11) were by two categories, and 2% (n=1) were by three categories on the CFS. The direction of disagreements outlined in Table 3.2 indicates Clinician 2 consistently rated participants higher on the CFS scale than Clinician 1. Calculation of

the weighted kappa coefficient, the measure of agreement reached beyond chance, was K_w=0.76, 95% CI (0.68, 0.85), a value that represents 'substantial agreement' (Sim & Wright, 2005) between raters.

Table 3.2: Assessment of CFS frailty status in study participants by two clinicians.

		Clinician 1						
		1 Very Fit	2 Well	3 Managing Well	4 Vulnerable	5 Mildly Frail	6 Moderately Frail	Total
Clinician 2	1 Very Fit	---	5	1	---	---	---	6
	2 Well	---	14	1	1	1	---	17
	3 Managing Well	---	4	15	2	3	---	24
	4 Vulnerable	---	2	9	12	7	---	30
	5 Mildly Frail	---	---	2	5	5	1	13
	6 Moderately Frail	---	---	---	2	7	8	17
	Total	0	25	28	22	23	9	107

Note: shaded area represents cases of exact agreement between clinicians in CFS frailty classification.

3.3 CFS validity

After reviewing the cases in which there was a disagreement in CFS scores, consensus was reached between clinicians on a single CFS score for each participant. The sample ranged from CFS-1through CFS-6 with a majority of subjects categorized as CFS-3 (n=28). Demographic and clinical characteristics of study participants as a whole and also stratified by CFS frailty status are presented in Table 3.3. No statistically significant differences in age, gender or BMI were noted across the CFS groups. However, participants with a high CFS score showed higher use of mobility aids, increased number of comorbidities, more polypharmacy, poorer functional status, higher history of falls, and greater report of memory problems. Those who were scored as CFS-6

showed a significantly increased disability in ADL's [Mean (SD)] 7.8 (3.1) compared to all other CFS groups. This group also had the highest prevalence for use of mobility aids (83%) and self-report of memory problems (67%). The CFS- 5 group showed a significantly higher number of comorbidities compared to the categories of CFS-1, CFS-2, and CFS-3, and higher number of prescribed medications compared to CFS-2. In the complete sample, 30% of subjects reported a fall within the last 6 months, with the greatest prevalence of falls occurring in the CFS-4 (47%) and CFS-5 groups (45%).

Table 3.3: Characteristics of study participants stratified by Clinical Frailty Scale status.

Variable	Total Sample (n=104)	**1** Very Fit (n=4)	**2** Well (n=19)	**3** Managing Well (n=28)	**4** Vulnerable (n=19)	**5** Mildly Frail (n=22)	**6** Moderately Frail (n=12)	p-value*
Age, mean (SD)	82.1 (5.4)	79.5 (4.7)	81.6 (5.6)	81.6 (6.2)	82.6 (5.4)	83.5 (4.7)	81.3 (4.4)	.643
Women, n (%)	83 (80%)	3 (75%)	18 (95%)	20 (71%)	13 (68%)	19 (86%)	10 (83%)	.249
Body Mass Index, mean (SD)	26.4 (4.6)	27.0 (2.7)	26.1 (4.8)	26.6 (4.5)	25.3 (3.7)	25.3 (3.4)	29.9 (6.6)	.085
Use of Mobility Aid, n (%)	39 (38%)	0 (0%)	0 (0%)	4 (14%)	9 (47%)	16 (73%)	10 (83%)	<.001
Comorbidities, mean (SD)	3.1 (2.2)	1.0 (0.8)[a]	2.1 (1.7)[a]	2.6 (2.2)[a]	3.4 (1.6)	4.6 (2.7)[b]	3.5 (1.6)	.001
Number of Medications, mean (SD)	4.1 (3.2)	1.5 (0.6)	2.5 (2.0)[a]	4.8 (3.7)	3.5 (2.1)	5.9 (3.4)[b]	4.0 (3.6)	.005
Disability Score, mean (SD)	2.1 (2.8)	0 (0%)[a]	0.8 (1.9)[a]	1.0 (1.4)[a]	1.7 (2.0)[a]	2.5 (1.5)[a]	7.8 (3.1)[b]	<.001
History of Falls in last 6 months, n (%)	31 (30%)	1 (25%)	0 (0%)	7 (25%)	9 (47%)	10 (45%)	4 (33%)	.004
Self-report of memory problems, n (%)	44 (42%)	1 (25%)	5 (26%)	14 (50%)	7 (37%)	9 (41%)	8 (67%)	.292

Notes: n, group size; SD, standard deviation; BMI, body mass index; *, One-way ANOVA (Analysis of Variance) or Fisher's Exact test analysis, statistical significance set at $p<0.05$; a, b, denote statistically significant between group differences at $p<0.05$, values with the same letter not significantly different from one another, different letter indicates statistical significance between values.

Participants with higher CFS frailty status also had an increased number of FPI components present (Table 3.4). There was a significant correlation between increasing CFS frailty status and an increased number of FPI components present (r_s= 0.685, p<0.001). Analysis using the Mantel-Haenszel test for trend revealed a significant positive linear trend between increasing CFS frailty status and an increased prevalence of slow gait velocity, low physical activity, low hand grip, unintentional weight loss, and exhaustion (Table 3.5).

Table 3.4: Proportion of the individual Frailty Phenotype Index components present among the stud sample stratified by Clinical Frailty Scale status.

FPI Components, n (%)	Total Sample (n=104)	**1** Very Fit (n=4)	**2** Well (n=19)	**3** Managing Well (n=28)	**4** Vulnerable (n=19)	**5** Mildly Frail (n=22)	**6** Moderately Frail (n=12)	*p-value
Slow Gait Velocity	55 (53%)	1 (25%)	4 (21%)	8 (29%)	12 (63%)	19 (86%)	11 (92%)	<.001
Low Physical Activity	12 (12%)	0 (0%)	1 (5%)	2 (7%)	0 (0%)	3 (18%)	6 (42%)	.003
Low Hand Grip	69 (66%)	0 (0%)	10 (53%)	20 (71%)	14 (74%)	16 (73%)	9 (75%)	.068
Unintentional Weight Loss	7 (7%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	3 (14%)	3 (25%)	.032
Exhaustion	53 (51%)	0 (0%)	3 (16%)	10 (36%)	13 (68%)	18 (82%)	9 (75%)	<.001

Notes: n, group size; *, Fisher's Exact test analysis; statistical significance set at p<0.05.

Table 3.5: Results of Mantel-Haenszel test for trend of proportion of Frailty Phenotype Index components present with increasing Clinical Frailty Scale status.

FPI Components	X^2_{MH}	p-value
Slow Gait Velocity	30.09	<.001
Low Physical Activity	10.46	.001
Low Hand Grip	5.14	.023
Unintentional Weight Loss	9.806	.002
Exhaustion	26.10	<.001

Notes: degrees of freedom=1, statistical significance set at p<0.05.

Agreement between the collapsed CFS and FPI in categorizing participants as "not frail", "pre-frail", or "frail" showed an agreement in 44% (n=46) of cases, and disagreement in 56% (n=58) of cases. Agreement between the scales in classifying frailty yielded a weighted kappa coefficient of Kw=0.51, 95% CI (0.40, 0.63), which represents a "moderate association" (Table 3.6) (Sim & Wright, 2005).

Table 3.6: Agreement in frailty classification between the collapsed Frailty Phenotype Index and Clinical Frailty Scale in study sample.

		CFS			
		Not Frail	**Pre-Frail**	**Frail**	**Total**
FPI	**Not Frail**	**13**	**--**	**--**	**13**
	Pre-Frail	**35**	**11**	**12**	**58**
	Frail	**3**	**8**	**22**	**33**
	Total	**51**	**19**	**34**	**104**

Note: shaded area represents cases of exact agreement between CFS and FPI in frailty classification.

3.4 Gait Variability

Quantitative gait characteristics, stratified by CFS frailty status, are presented in Table 3.7. The parameters of average gait velocity, stride time, stride length, double support time and step width showed significant difference across CFS frailty groups under both usual and fast pace condition ($p<.001$). At usual pace, there was a significant difference in mean gait variability values of stride time, stride length, and step width among CFS frailty groups. Post-hoc Tukey analysis showed no significant associations in stride time and stride length variability. However, CFS-5 was significantly different from CFS-1and CFS-2 in step width variability.

The ANOVA analysis at fast pace revealed significant differences among CFS frailty groups in gait variability parameters of stride length and step width. In the stride length variability parameter, CFS-5 was significantly different from CFS-2 and CFS-4. In the step width variability parameter, groups CFS-1 through CFS-4, although not different from each other, were significantly different from group CFS-5. Gait variability parameters of stride time and double support time were not found to be significant across frailty groups at fast pace. Overall, stride length and step width variability showed a greater difference across CFS frailty groups under fast pace walking condition than usual walking pace conditions.

Analysis of trends in the gait parameter data showed a significant linear trend in certain parameters with increasing CFS frailty status. At usual pace, stride length and stride width showed a significant positive linear trend; at fast pace, stride time, stride length, and stride width showed a significant positive linear trend with increasing frailty level. Results of trend analyses are displayed in Table 3.8.

Table 3.7a: Gait characteristics stratified by Clinical Frailty Scale status at usual pace.

	1 Very Fit	2 Well	3 Managing Well	4 Vulnerable	5 Mildly Frail	6 Moderately Frail	p-value
Mean quantitative gait characteristics at usual walking pace, [Mean±SD]**:**							
Gait Velocity, cm/sec	122.08±22.79[a]	115.83±18.4a	104.57±14.60[a]	100.14±20.95[a]	77.91±20.16[b]	71.77±20.05[b]	<.001
Stride time, msec	1096.20±96.39	1052.51±93.23[a]	1094.85±72.59[a]	1144.86±118.81	1206.77±116.94[b]	1220.62±174.97[b]	<.001
Stride length, cm	132.85±17.85[a]	121.59±16.51[a]	114.40±11.80 [a]	113.32±17.30 [a]	93.24 ±20.83 [b]	86.27±18.59 [b]	<.001
Double support time, sec	0.33±0.04 [ab]	0.31±0.45[a]	0.33±0.06 [a]	0.35 ±0.07 [a]	0.44 ±0.10 [bc]	0.47±0.12 [cd]	<.001
Step width, cm	67.26±8.59 [a]	61.59±7.97 [a]	58.43±5.26[a]	58.23±8.12[a]	49.05±9.70 [b]	45.92±7.76 [b]	<.001
Mean gait variability (CoV%) values at usual walking pace, [CoV±SD]**:**							
Stride time	2.69±0.70	3.67±1.88	3.58±1.34	4.49 ±2.40	5.14±2.52	4.46 ±1.63	.041
Stride length	2.23±0.49	4.10±1.26	5.47±3.06	5.09±2.61	6.14±2.63	5.56 ±2.20	.028
Double support time	11.96±10.04	8.85±3.76	9.32±3.43	8.67±2.42	10.01 ±4.92	8.42 ±1.47	.569
Step width	3.47±0.88[a]	5.15±1.18[a]	6.27±2.15	6.36±2.45	7.71 ±3.23[b]	6.41 ±1.81	.003

Notes: SD, standard deviation; one-way ANOVA (Analysis of Variance), statistical significance set at $p<0.05$; CoV, coefficient of variation, calculated by the formula: [SD/ mean] x100%; a, b, denote statistically significant between group differences at $p<0.05$, values with the same letter not significantly different from one another, different letter indicates statistical significance between values.

Table 3.7.b: Gait characteristics stratified by Clinical Frailty Scale status at fast pace.

	1 Very Fit	2 Well	3 Managing Well	4 Vulnerable	5 Mildly Frail	6 Moderately Frail	p-value
Mean quantitative gait characteristics at fast walking pace, [Mean ± SD]**:**							
Gait Velocity, cm/sec	150.85±31.17 [a]	149.88±23.65 [a]	137.24±18.40 [a]	131.18±20.96 [a]	105.80±26.19 [b]	92.57±18.91 [b]	<.001
Stride time, msec	965.38±78.45	899.42±84.86 [a]	953.57±74.37	972.42±103.14	1025.22±127.38[b]	1052.44±124.84 [b]	<.001
Stride length, cm	144.78±20.09 [a]	134.55±17.89 [a]	130.45±12.38 [a]	127.19±18.71 [a]	107.77±22.61 [b]	97.20±16.95 [b]	<.001
Double support time, sec	0.25±0.04 [ab]	0.23±0.04 [a]	0.26±0.05 [a]	0.27 ±0.05 [a]	0.32 ±0.08 [bc]	0.36±0.08 [cd]	<.001
Step width, cm	72.84±9.64 [a]	67.90±8.71 [a]	66.11±6.07 [a]	64.92±9.01 [a]	55.20±10.90 [b]	48.07±12.71 [b]	<.001
Mean gait variability (CoV%) values at fast walking pace [CoV±SD]**:**							
Stride time	2.39±0.37	2.95±0.94	2.88±1.22	3.23±1.06	3.26±1.24	4.20±2.30	.062
Stride length	2.46±0.66	3.23±0.74[a]	3.97±1.95	3.40±1.45[a]	4.97±2.11[b]	4.98 ±1.81	.002
Double support time	7.15±1.43	8.41±3.12	9.15±5.43	10.58±7.79	8.31±3.04	9.91 ±4.32	.627
Step width	3.68±0.09[a]	4.60±1.06[a]	4.83±2.04[a]	4.92±1.55[a]	7.21±2.91[b]	6.52±1.56	<.001

Notes: SD, standard deviation; one-way ANOVA (Analysis of Variance), statistical significance set at $p<0.05$; CoV, coefficient of variation, calculated by the formula: [SD/ mean] x100%. a, b, denote statistically significant between group differences at $p<0.05$, values with the same letter not significantly different from one another, different letter indicates statistical significance between values.

Table 3.8: Results of trend analysis of gait variability parameters with increasing CFS status.

Variable	F	p-value
Usual gait variability (CoV%) parameters		
Stride time	5.56	.020
Stride length	8.78	.004
Double support time	1.53	.219
Stride Width	10.30	.002
Fast gait variability (CoV%) parameters		
Stride time	6.73	.011
Stride length	11.19	.001
Double support time	0.95	.332
Stride Width	13.56	<.001

Notes: degrees of freedom= 1, statistical significance set at $p<0.05$

Results of the linear regression analysis for the relationship of the CFS frailty status to the gait variability parameters, the dependent variable, are presented in Table 3.9 and Table 3.10. Increased frailty status was significantly associated with several quantitative measures of gait variability at usual and fast pace. In the unadjusted analysis, at usual pace, increased stride time variability was associated with CFS-5; increased stride length variability was significantly associated with frailty categories of CFS-3 through CFS-6; increased step width variability was significantly associated with frailty categories of CFS- 3 through CFS-5. At fast pace, stride length variability was significantly associated with frailty categories of CFS-5 and CFS-6. Under fast pace condition step width variability was significantly associated with frailty categories of CFS-5 and CFS-6. Stride time variability, under fast pace conditions, was associated with the CFS-6 group. Double support time variability was not associated with frailty status under usual or fast pace conditions.

In the adjusted regression analysis, at usual pace, stride length variability remained significantly associated with CFS-3, CFS-5 and CFS-6. Similarly, step width variability was associated with CFS-3, CFS-5 and CFS-6. Double support time and stride time variability was not associated with frailty status in usual pace conditions. At fast pace, stride time variability was associated with frailty category of CFS-6. Stride length variability was significantly associated with CFS-5 and CFS-6 groups. Step with variability was also associated with CFS-5 and CFS-6. Double support time variability was not associated with CFS frailty categories in the fast pace condition.

Table 3.9: Unadjusted multivariable linear regression comparing association of Clinical Frailty Scale status on outcome of gait variability parameters under usual and fast pace conditions.

	Regression Coefficients, (95% CI)				
	2-Well	**3-Managing Well**	**4-Vulnerable**	**5-Mildly Frail**	**6-Moderately Frail**
Gait variability (CoV%) values at usual walking pace:					
Stride Time	0.98 (-1.17, 3.13) p=.369	0.89 (-1.20, 2.98) p=.401	1.80 (-0.35, 3.95) p=.099	**2.45 (0.32, 4.57) p=.024**	1.77 (-0.49, 4.02) p=.123
Stride Length	1.87 (-.84, 4.58) p=.173	**3.24 (0.61, 5.87) p=.016**	**2.86 (0.15, 5.57) p=.039**	**3.91 (1.23, 6.58) p=.005**	**3.33 (0.49, 6.17) p=.022**
Step Width	1.67 (-0.83, 4.18) p=.188	**2.79 (0.36, 5.23) p=.025**	**2.88 (0.38, 5.39) p=.025**	**4.23 (1.76, 6.71) p=.001**	-3.53 (-8.03, 0.97) p=.123
Double Support Time	-3.10 (-7.39, 1.19) p=.154	-2.63 (-6.80, 1.54) p=.213	-3.29 (-7.58, 1.00) p=.131	-1.94 (-6.18, 2.30) p=.366	**2.93 (0.31, 5.56) p=.029**
Gait variability (CoV%) values at fast walking pace:					
Stride Time	0.57 (-0.86, 1.99) p=.433	0.50 (-0.89, 1.89) p=.476	0.85 (-.58, 2.28) p=.240	0.87 (-0.54, 2.28) p=.223	**1.82 (0.32, 3.31) p=.018**
Stride Length	0.77 (-1.08, 2.62) p=.410	1.51 (-0.28, 3.31) p=.098	0.94 (-0.91, 2.78) p=.315	**2.51 (0.68, 4.33) p=.008**	**2.52 (0.58, 4.46) p=.011**
Step Width	.93 (-1.23, 3.08) p=.395	1.15 (-.94, 3.24) p=.277	1.24 (-0.91, 3.40) p=.254	**3.53 (1.41, 5.66) p=.001**	**2.84 (0.59, 5.10) p=.014**
Double Support Time	1.27 (-4.21, 6.75) p=.647	2.01 (-3.32, 7.33) p=.456	3.44 (-2.04, 8.92) p=.216	1.16 (-4.25, 6.57) p=.672	2.77 (-2.98, 8.52) p=.342

Notes: The dependent variable: measure of gait variability; independent variable: CFS frailty; 1 very-fit group is the reference category; CI, confidence interval. Bold values are statistically significant at $p<.05$.

Table 3.10: Adjusted multivariable linear regression comparing association of Clinical Frailty Scale status on the outcome of gait variability parameters under usual and fast pace conditions.

	Regression Coefficients, (95% CI)				
	2 Well	**3 Managing Well**	**4 Vulnerable**	**5 Mildly Frail**	**6 Moderately Frail**
Gait variability (CoV%) values at usual walking pace:					
Stride Time	0.92 (-1.16, 3.00) p= .877	0.65 (-1.36, 2.66) p= .524	1.27 (-0.82, 3.37) p=.231	1.83 (-0.254, 3.91) p=.085	1.50 (-0.67, 3.68) p=.173
Stride Length	1.77 (-0.876, 4.42) p=.187	**2.96 (0.40, 5.53) p=.024**	2.28 (-0.39, 4.95) p=.093	**3.23 (0.58, 5.88) p=.018**	**3.04 (0.27, 5.81) p=.032**
Step Width	1.77 (-0.69, 4.22) p=.156	**2.59 (0.21, 4.96) p=.033**	2.31 (-0.17, 4.78) p=.068	**3.59 (1.13, 6.04) p=.005**	**2.66 (0.95, 5.23) p=.042**
Double Support Time	-3.25 (-7.54, 1.05) p=.137	-2.90 (-7.07, 1.26) p=.169	-3.83 (-8.16, 0.51) p=.083	-2.59 (-6.89, 1.71) p=.235	-3.81 (-8.30,0.69) p=.096
Gait variability (CoV%) values at fast walking pace:					
Stride Time	0.48 (-0.95, 1.91) p=.505	0.41 (-0.97, 1.80) p=.554	0.71 (-0.73, 2.16) p=.328	0.70 (-0.73, 2.13) p=.336	**1.74 (0.24, 3.24) p=.023**
Stride Length	0.77 (-1.06, 2.59) p=.408	1.36 (-0.40, 3.13) p=.131	0.58 (-1.26, 2.42) p=.533	**2.09 (0.27, 3.92) p=.025**	**2.34 (0.43, 4.25) p=.017**
Step Width	0.91 (-1.26, 3.08) p=.407	1.06 (-1.05, 3.16) p=.321	1.02 (-1.16, 3.21) p=.355	**3.28 (1.11, 5.45) p=.003**	**2.73 (0.46, 5.00) p=.019**
Double Support Time	1.22 (-4.35, 6.78) p=.665	1.92 (-3.47, 7.31) p=.481	3.27 (-2.34, 8.89) p=.250	0.96 (-4.61, 6.53) p=.733	2.68 (-0.16, 0.24) p=.676

Notes: The dependent variable: measure of gait variability; independent variable: CFS frailty; 1 very-fit group is the reference category; regression models are adjusted for age and history of falls in the previous 6 months; CI, confidence interval. Bold values are statistically significant at $p<.05$

3.5 Secondary analysis

Linear regression analysis gait variability parameters and gait speed across CFS frailty status repeated with CFS as a continuous variable are presented in Figures 3.1-3.5. The trend line representing the linear regression equation indicates the direction of change in gait parameters with increasing CFS frailty status. The gait variability parameters of stride time, stride length and step width showed a positive linear association with increasing CFS frailty status. Gait velocity showed a negative linear association with increasing CFS frailty status. Double support time showed a negative association at usual pace conditions, and a positive linear association at fast pace conditions with increasing CFS status.

Figure 3.1: Linear regression for the association of CFS status on the outcome of stride time variability (CoV %) in study sample under a) usual pace and b) fast pace conditions.

Figure 3.1.a)

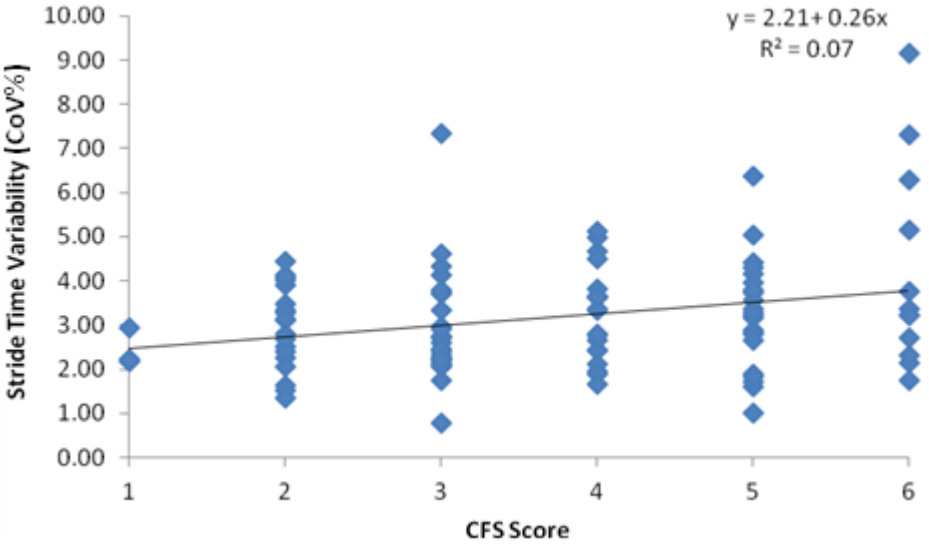
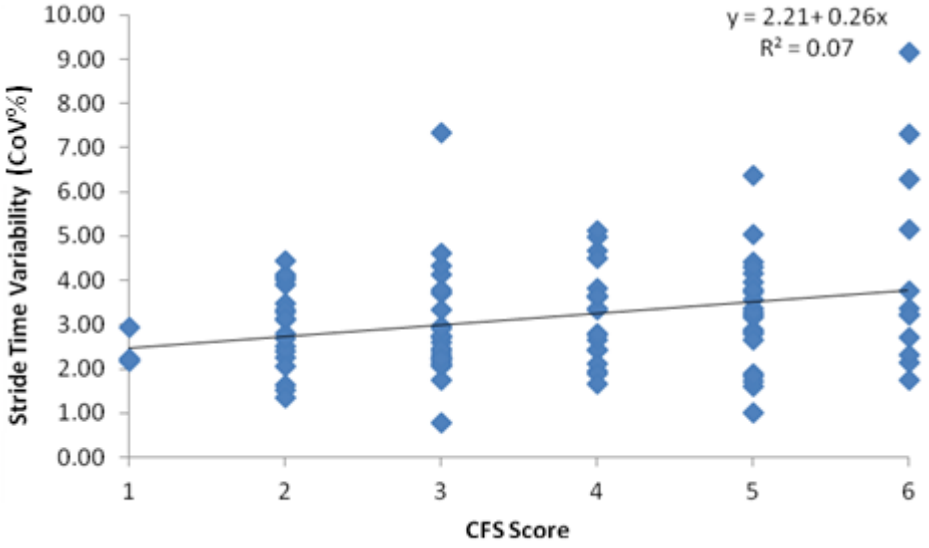


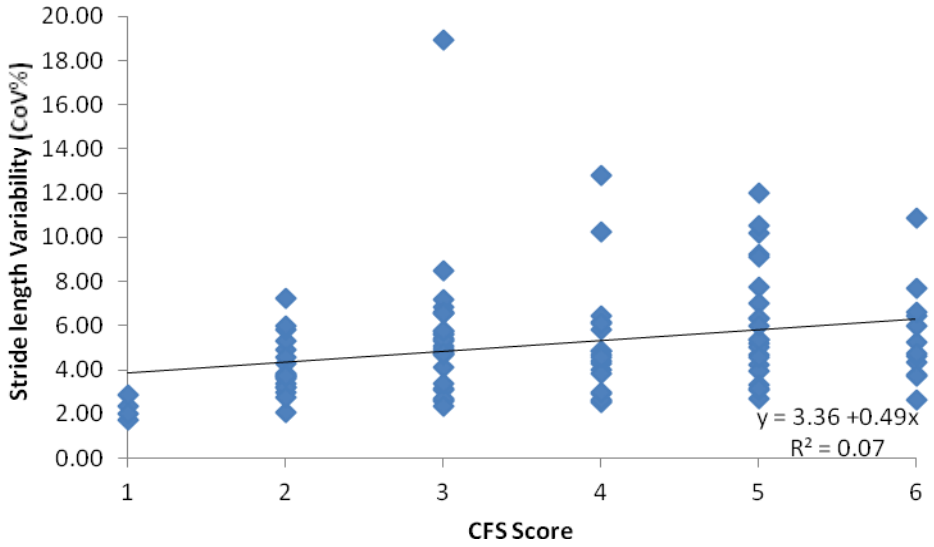
Figure 3.1.b)



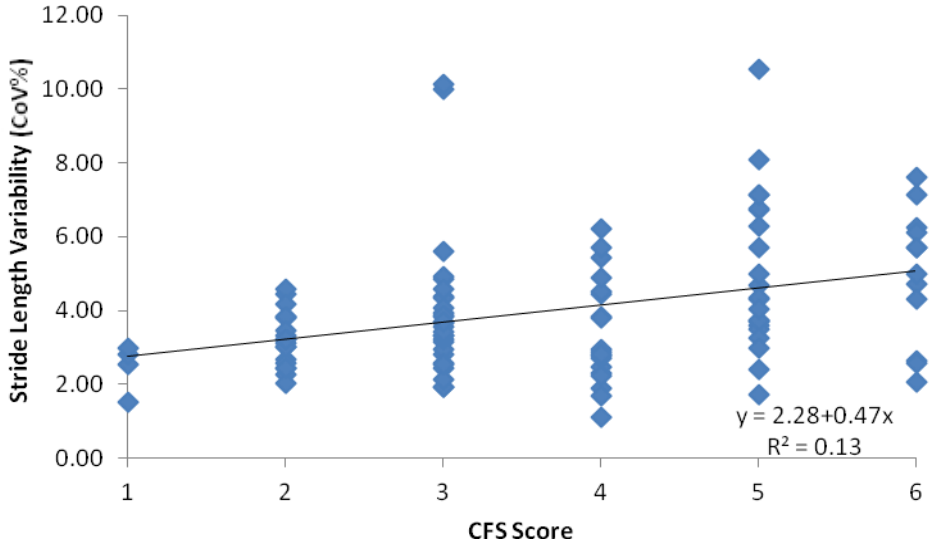
Note: R^2, coefficient of determination, represents amount of variation in stride time variability (CoV%) due to CFS frailty status.

Figure 3.2: Linear regression for the association of CFS status on the outcome of stride length variability (CoV %) in study sample under a) usual pace and b) fast pace conditions.

3.2. a)



3.2. b)



Note: R^2, coefficient of determination, represents amount of variation in stride length variability (CoV%) due to CFS frailty status.

Figure 3.3: Linear regression for the association of CFS status on the outcome of double support time variability (CoV %) in study sample under a) usual pace and b) fast pace conditions.

Figure 3.3.a)

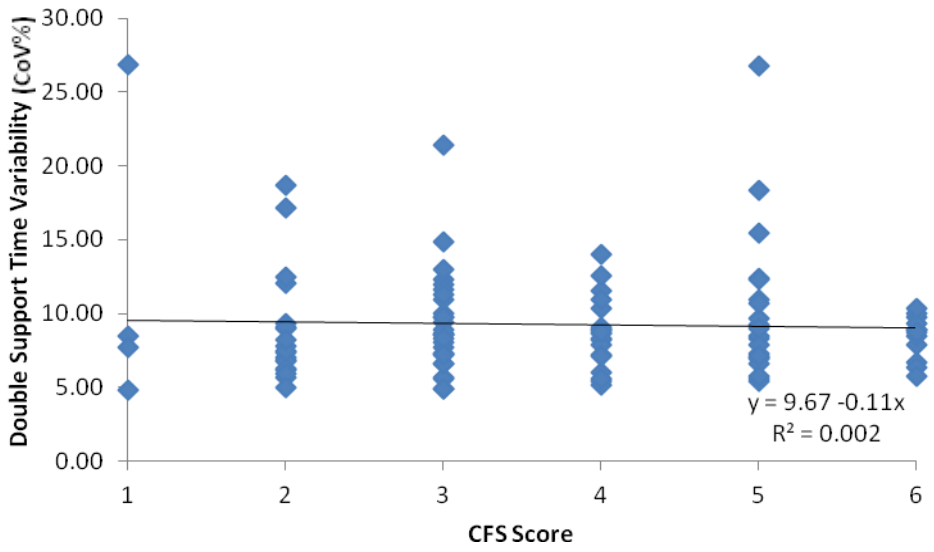
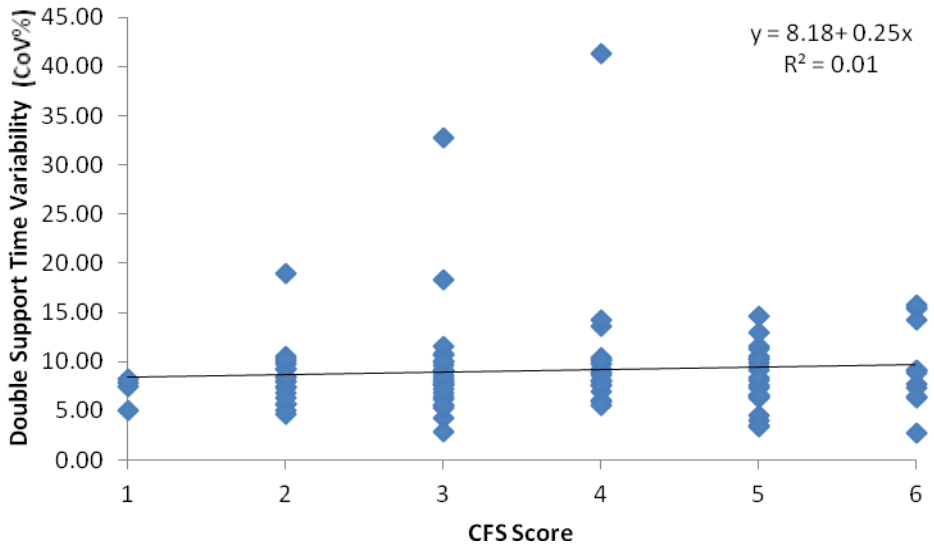


Figure 3.3.b)



Note: R^2, coefficient of determination, represents amount of variation in double support time variability (CoV%) due to CFS frailty status.

Figure 3.4: Linear regression for the association of CFS status on the outcome of step width variability (CoV %) in study sample under a) usual pace and b) fast pace conditions.

Figure 3.4.a)

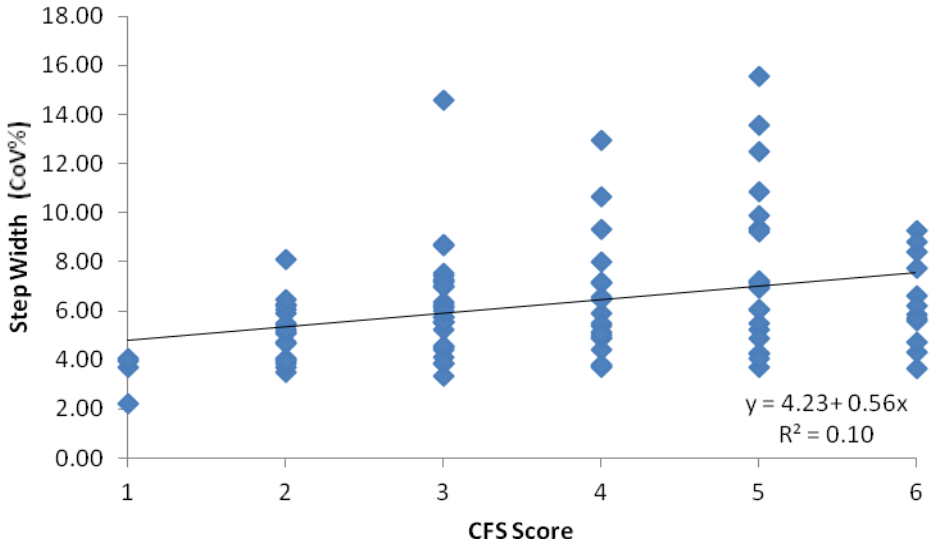
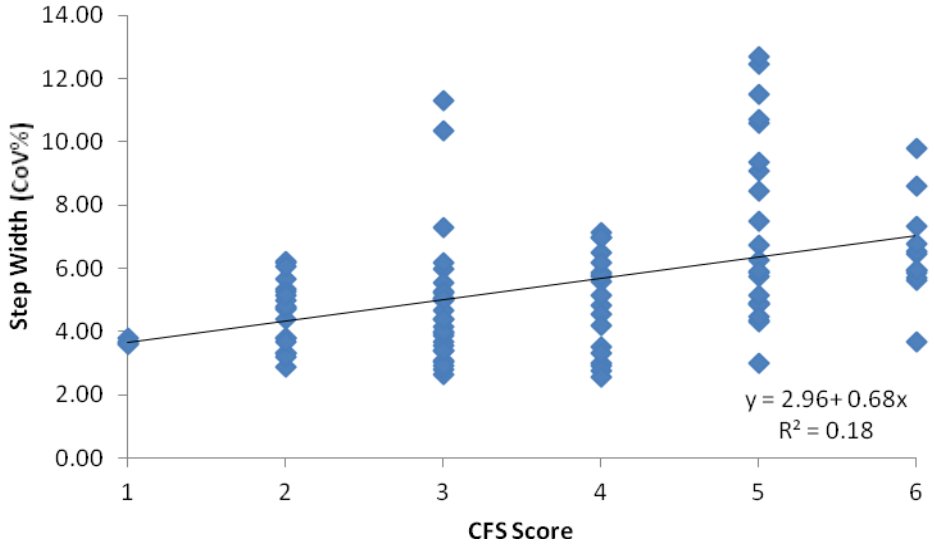


Figure 3.4.b)



Note: R^2, coefficient of determination, represents amount of variation in step width variability (CoV%) due to CFS frailty status.

Figure 3.5: Linear regression for the association of CFS status on the outcome of gait velocity (cm/sec) in study sample under a) usual pace and b) fast pace condition.

Figure 3.5.a)

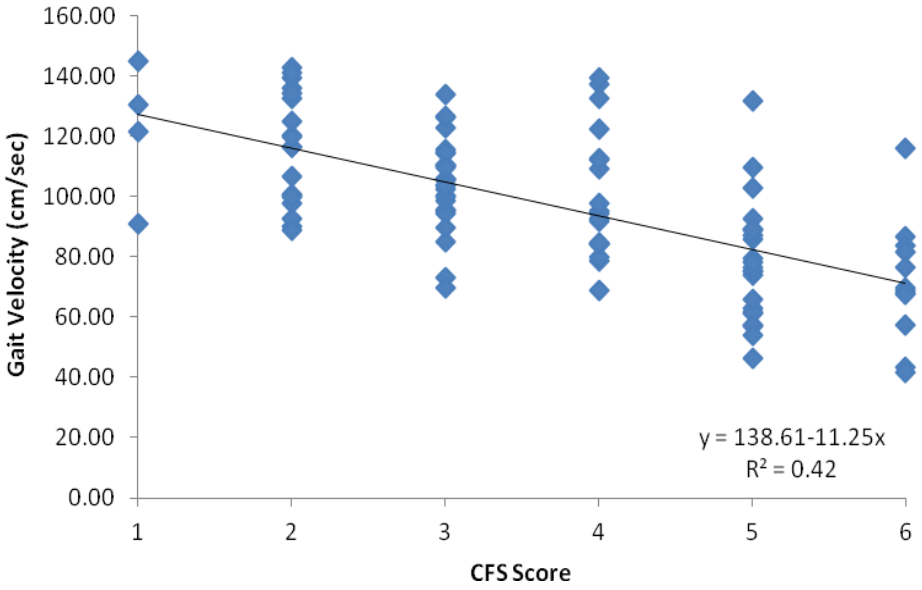
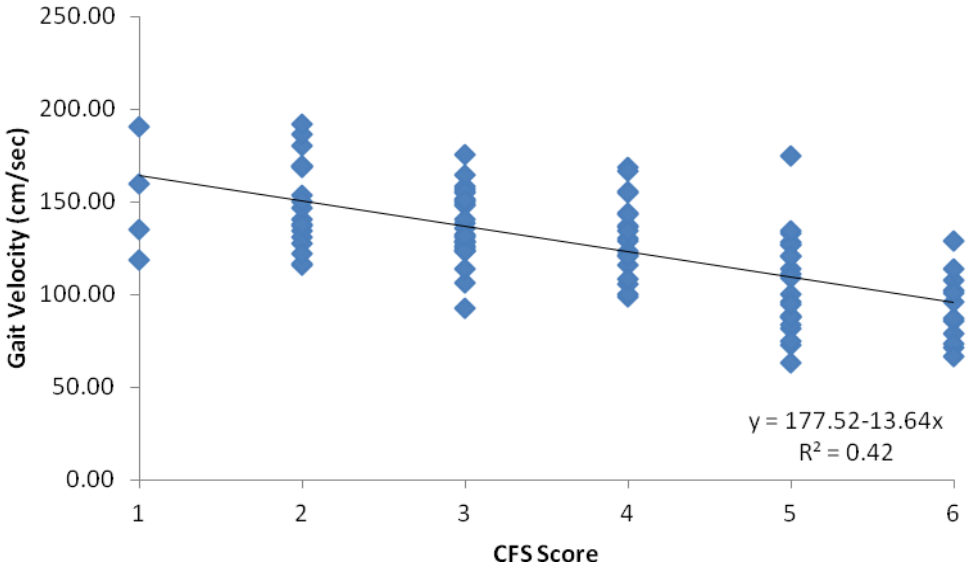


Figure 3.6.b)



Note: R^2, coefficient of determination, represents amount of variation in gait velocity (cm/sec) due to CFS frailty status.

CHAPTER 4- DISCUSSION

This study has demonstrated that low performance in quantitative gait parameters, in addition to gait velocity, are associated with frailty. Specifically, high gait variability is associated with frailty, as defined by the CFS, a model which does not include gait velocity as a criterion in assessing frailty. Specifically, high variability in the parameters of stride length, stride width were associated with frailty at both usual and fast pace; stride time was associated with frailty under the fast pace condition. These results suggest that regulation of gait is impaired in older adults with frailty. Since gait variability is understood to be an expression of gait dynamics, our results provide additional evidence that frailty is a syndrome characterized with loss of dynamic in the regulation of gait. Additionally, the results demonstrate the CFS achieved substantial inter-rater reliability and moderate agreement with the established FPI in assessing frailty in our sample.

4.1 CFS inter-rater reliability

The substantial degree of agreement between clinicians in assessing frailty established the reliability of the CFS scale in our sample of community-dwelling older adults. Consistent with this study's results, Rockwood et al. (2005) found that the application of the CFS to a large cohort of elderly adults demonstrated high inter-rater reliability. In contrast to the previous study, this study included blinded evaluation from two assessors of each participant's CFS status. The current study design may provide a more accurate measure of inter-rater reliability for the application of the CFS in a sample of community-dwelling older adults.

Disagreement between clinicians in participant CFS scores was resolved through a consensus discussion. This process highlighted important disparities in how each clinician

applied and interpreted the CFS. Clinician 2 consistently scored participants higher on the CFS than Clinician 1, suggesting a bias effect between the clinicians in CFS ratings. This bias may account for several of the disagreements by just one CFS category and ultimately resulting in a more conservative kappa value. Discussion between the clinicians also highlighted that this bias was partially due to disagreement on what items in the construct of frailty, as defined by the CFS, should be given importance or considered first. A high rate of disagreement was attributed to how much importance the clinicians gave to the figures included along with the verbal descriptors of the CFS categories. For instance, the figure accompanying category CFS-4 illustrates an individual using a cane, whereas the CFS-5 category illustrates an individual using a walker. Clinicians disagreed on whether an individual who uses a walker should be considered to be frailer than someone who uses a cane as prescription and use of one type of aid over another is influenced by personal choice and not just physical need alone. This difference in how clinicians used the figures resulted in a greater number of disagreements in rating participants as either CFS-4 or CFS-5 than other categories. Another point of discussion, and source of disagreement, surrounded the specific inclusion of 'disability in bathing' as a descriptor of category CFS-6. Clinicians disagreed on whether disability in bathing alone should be a deciding factor in categorizing an individual as CFS-6 or if other functional measures should be taken into consideration in rating this CFS category. In two cases, this difference in judgement accounted for a disagreement by two CFS categories (CFS-4 and CFS-6).

Overall, these disagreements highlight the reliability of the CFS could be further improved by first reaching consensus between clinicians on a standard procedure to apply the scale in a practical setting. As reflected in the discussion above, disagreements in

clinical opinion can lead to a critical difference in classifying someone as frail or not frail. A uniform approach between clinicians in assessing the items included in the CFS construct of frailty would minimize differences and any bias in rating patients' frailty status on the CFS.

4.2 Validity of the CFS

The CFS is a tool that may be readily administered in the clinical setting based on its simplicity for retrieving information from clinical history and physical exams (Rockwood et al., 2005). The CFS provides an advantage from alternative frailty models that require more complex measures and are not easy to use in the clinical setting. Although the established FPI has been demonstrated to be a valid assessment tool of frailty, it requires several tests which may be time consuming, and measures of hand grip strength and gait velocity which may not be readily administered in the clinical setting. To our knowledge, this study is the first of its kind to validate the CFS against the FPI in the same sample.

The CFS demonstrated good construct validity with factors associated with increased vulnerability and frailty in older adults. For instance, our findings showed that high frailty status, represented by CFS-5 and CFS-6, was associated with a higher number of medications, a high prevalence of falls, and self-report of cognitive impairment. The pathophysiology of frailty which leads to inflammation, abnormal immune function, and loss of homeostatic capacity is integral to the progression of several chronic diseases (Hubbard et al., 2008; Hubbard et al., 2009., Lipsitz, 2002) including diabetes, cancer, hypertension, and cardiovascular disease (Roschelle, 2011). The treatment of these diseases in frail individuals is consequently also associated with polypharmacy (Farrell, Szeto, & Shamji, 2011). Furthermore, previous studies have shown that frailty status is

strongly associated with cognitive impairment (Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010; Buchman, Boyle, Wilson, Tang, & Bennett, 2007) and frail individuals with cognitive impairment are significantly more likely to develop disability in activities of daily living (ADL) and instrumental activities daily living (IADL) (Avila-Funes et al., 2009). A previous investigation showed frailty status measured by the CFS and the FPI, were both strongly associated with cognitive decline in frail adults (Mitnitski, Fallah, Rockwood, & Rockwood, 2011). The associations of poor clinical status with an increased CFS frailty status in our sample suggests that the underlying construct of the CFS is able to capture frailty as a state that leaves older adults vulnerable to adverse health outcome.

Furthermore, increasing CFS frailty status showed a positive linear association with the number of FPI components present. The CFS-6 group showed the highest prevalence of all five FPI components (slow gait velocity, low physical activity, low hand grip, and unintentional weight loss). The FPI components are a measure of function and regulation in multiple physiological systems and detect the presence of deficits in homeostasis which may leave an older individual vulnerable to internal or external stressors (Fried et al., 2001). The presence of a linear association between the CFS and FPI components suggest that the CFS shows a similar sensitivity to changes in underlying physiological function which are associated with frailty. Our results support Mitnitski et al. (2011) suggestion of frailty as a valid state that can be measured with different models. In light of the debate on how to define and asses frailty (Abellan van Kan et al., 2008), our findings display evidence that the CFS is comparable to the established FPI in quantifying reduced physiological reserve in older adults, with the advantage of being easy to administer in the clinical setting.

Assessment of concurrent validity of the collapsed CFS scale showed “moderate” agreement to the FPI in classifying frailty in the study sample. Some of the disagreement between the two scales may have been due to the fact that in order to compare the six categories of the CFS to the collapsed three levels of the FPI, the CFS categories also had to be grouped into three categories of “not frail”, “pre-frail”, and “frail”. The multiple levels of the CFS scale, and the increasing number of FPI components present capture the progression of physical decline in an individual as frailty develops. Pooling data from these different categories by creating seemingly arbitrary cut-offs discards important information. For instance, individuals that present two FPI components are evidently in an increased state of vulnerability than those with only one component present. However, in order to make a diagnosis, the FPI pools individuals with either one or two components present into the “pre-frail” category losing any important distinctions between these groups. Although frailty has been theoretically described as a continuous variable (Lipsitz, 2002), cut-offs are created in order to make a clinical diagnosis, and this may add to measurement error.

The greatest disagreement in comparison of the CFS and FPI was seen in 35 cases which were defined as “not frail” by the CFS and “pre-frail” by the FPI. The categories of CFS-1 through CFS-3 were pooled into one “not frail” group in order to draw comparisons to the FPI “not frail” group. Examination of the CFS-3 group showed that although these participants are considered to be “managing well” most participants had at least one FPI component present. This suggests that the CFS may not be as sensitive as the FPI in capturing those that are in a pre-frail stage. The inclusion of CFS-3 in the “not frail” group mixed pre-frail participants into this category and consequently, our

assessment of agreement in frailty classification between the scales may have been more conservative.

4.3 Gait variability

Our results demonstrate that the regulation of gait is impaired in older adults with frailty as indicated by high gait variability in gait performance. In the unadjusted multivariable linear regression analysis, at usual pace, a significant association was found between the spatial parameters of stride length variability and step width variability with frailty. This association remained significant after adjusting for potential confounders. Gabell and Nayak (1984) suggest that step width variability is related to balance control in older adults. Increased step width variability in older adults has been shown to be associated with poorer performance of postural control and reduced proprioceptive visual input (Callisaya et al., 2010) rather than higher cognitive control (Brach, Berlin et al., 2005; Brach, Studenski et al., 2008; Rosano et al., 2007). Increased step width variability in our sample of frail adults may therefore reflect a disruption of balance mechanisms and increased instability while walking (Callisaya et al., 2010; Gabell & Nayak, 1984; Beauchet, Annweiler et al., 2009). Therefore, increased step width variability may serve as a sensitive marker of age or disease related decline in sensory feedback and reduced ability of the vestibular systems ability to maintain postural control (Callisaya et al., 2010). Disruption of balance control, manifested as increased step width variability has been linked to a high history of falls in community-dwelling older adults (Brach, Berlin et al., 2005). Although step width variability as a prospective marker of falls has not been studied, it can be postulated that a disruption of balance control systems may increase the risk of future falls, an outcome also related to frailty (Abellan van Kan et al., 2008; Fried et al., 2001; Fried et al., 2004; Lipsitz, 2004).

Previous investigations have suggested that stride length is controlled by the gait-patterning mechanism which produces the repeated sequence of muscle contraction and relaxation during walking (Gabell & Nayak, 1984). Regulation of this mechanism has been attributed to higher cortical and subcortical regions of the brain (Dubost et al., 2006). Increased stride length variability has been associated with basal ganglia infracts and white matter abnormalities in community dwelling older adults (Rosano et al., 2007) and patients with Parkinson's disease (PD) (Blin et al., 1990) and Alzheimer's disease (AD) (Nakamura et al., 1996; Webster et al., 2006). Consequently, a high degree of variability in stride length may indicate a failure of the automatic stepping mechanism due to impairments in cortical circuits involved in gait regulation (Gabell & Nayak, 1984; Rosano et al., 2007). The association of increased stride length variability in our sample of frail older adults could therefore be a marker of subclinical cognitive impairment. This is supported by studies which have demonstrated that physical frailty is associated with incidence of mild cognitive impairment in community-dwelling older adults (Boyle et al., 2010; Buchman et al., 2007). Increased stride length variability has also been demonstrated to predict risk of future falls in older adults (Maki, 1997), an outcome also related to frailty and increased vulnerability (Abellan van Kan et al., 2008). Under usual pace conditions, stride length and stride width variability also showed increased variability with the category of CFS-3. This may have been due to the fact that although the CFS classifies this group as "managing well", this category appeared to include individuals who were actually pre-frail according to the FPI. The inclusion of pre-frail individuals in this group may have consequently significantly increased the average gait variability values observed in this group.

Double support time variability, thought to be controlled by balance mechanisms, did not show any significant difference among the frailty groups at either pace of walking. In patient populations with neurological diseases such as Huntington's disease, PD (Hausdorff et al., 1997; 1998) and AD (Wittwer et al., 2008), significantly increased double support time variability was observed compared to young healthy controls. In comparison, community-dwelling older adults showed a subtle increase but no significant difference in double support time variability in comparison to young adults (Gabell & Nayak, 1984). Taking these previous findings and our results into considerations, it may be suggested that increased double support time variability is related to the pathology of central nervous system disorders (Brach et al., 2005; Rosano et al., 2007) and may only be seen in advanced stages of frailty. Due to the nature of our sample, our participants were relatively healthy and therefore showed no increase in double support time variability.

Stride time, thought to be influenced by the gait-patterning mechanism, showed no significant difference with frailty status under usual pace. However, stride time was significantly increased in the CFS-6 category under fast pace conditions. Fast walking is a more demanding task and requires additional physical effort than walking at a self-selected pace (Ko, Hausdorff, & Ferrucci, 2010). Fast pace walking may allow for differences in functionality and fitness to emerge that identify older adults with lower physiological reserve and physical frailty (Brisswalter & Mottet, 1996; Fitzpatrick et al., 2007). Stride time variability may not have been sufficiently stressed under usual pace conditions in frail adults. The increased demands imposed on gait patterning mechanisms by fast walking may have allowed for exposure of sub-clinical impairments in stride time variability regulation.

Frailty ensues when there is an aggregate loss of complexity and dysregulation across multiple physiological networks resulting in the loss of homeostatic capacity (Lipsitz, 2004). This loss of complexity in physiological systems can be captured by measuring the variability of physiological output signals (Collins et al., 1995; Kaplan et al., 1991; Montero-Odasso et al., 2011; Peng et al., 2002). Within this framework, measures of gait performance can be seen as a reflection of the functional capacity of systems involved in maintaining a steady gait pattern (Montero-Odasso et al., 2011). As previously mentioned, regulation of gait variability parameters involves several components of the musculoskeletal system, sensorimotor system, and higher cognitive regions. The presence of high gait variability in our sample of older adults with frailty may signify reduced complexity across these physiological systems (Lipsitz & Goldberger, 1992; Lipsitz, 2002; 2004). Our findings of impaired gait performance due to high gait variability support the hypothesis that an aggregate loss of complexity with aging in physiological systems underlies the development frailty. It can be suggested that high gait variability is not only a marker of falls, mobility decline, and cognitive deterioration, but may also be a marker of frailty which leaves older adults vulnerable to the previously mentioned adverse outcomes (Montero-Odasso et al., 2011).

Previous investigations have shown strong evidence that gait velocity is a marker of frailty (Abellan van Kan et al., 2008). Results from our study support these previous findings and indicate that decreased gait velocity is associated with increased CFS frailty status. In comparison to gait variability, gait velocity was more strongly associated with increased CFS frailty status. Although gait velocity is a robust screening tool for frailty, the added value of gait variability as a marker of frailty may lie in detecting frailty in those individuals who walk above the normal gait speed cut-offs and. As it has been

demonstrated in previous studies, gait variability is a predictor of falls even in individual's who walk above 1 m/s (Hausdorff et al., 2001; Verghese et al., 2009).

4.4 Limitations

The findings of the current study need to be interpreted with some caution in light of certain limitations. Firstly, the study is limited by the cross-sectional design. Even though an association between gait variability and frailty status was found, the temporal order of this association cannot be determined. In order to further test this association, prospective studies of frailty status and changes in gait variability need to be conducted. An important factor to consider when performance measures are repeated, particularly over a short time frame, is the possibility of a learning effect. However, in this study the gait tasks performed by participants were not novel activities that would be expected to have changed or improved with repetition over the three trials. Additionally, the GAITRite mat does not impede or obstruct the participants' performance during a gait task so improved comfort with the testing equipment should not be a consideration. Therefore, any learning as a result of performing three trials is expected to have had a negligible impact on measures of gait velocity and gait variability. Furthermore, if there was a learning effect, resulting in improved gait performance and reduced gait variability, this would have biased our results towards the null. As we found a statistically significant association, our findings are a conservative estimate of the change in gait variability expected with increased frailty status. Another potential limitation was the lack of data on fear of falling which can confound values of gait variability. However, gait measures were adjusted for a history of falls which correlates strongly with fear of falling (Friedman, Munoz, West,

Rubin, & Fried, 2002) and the presence of residual confounding by fear of falling is expected to be very small.

This study is also limited by the retrospective application of the CFS. CFS ratings were done by clinicians using data from self-report measures and questionnaires. Assessment of frailty status without the participant present could have resulted in the loss of vital information that can be ascertained by clinicians from the physical examination and interaction with the individual (Gupta, 2008). This could have resulted in an inaccurate judgement of the patients' frailty status leading to an under or overestimation of CFS frailty classification by the clinicians. Furthermore, descriptors included in the CFS for certain categories were limited and there was a lack of instructions in how to apply the CFS. As a result, certain individuals did not seem to fit into one distinct category making frailty classification difficult and led to critical disagreement in frailty rating between clinicians. Also, we were limited by the lack of information on participants' ability to perform IADL's, which the CFS specifies as a specific descriptor in categorizing an individual as CFS-5. Another limitation is the use of a convenience sample of relatively healthy community-dwelling older adults from the Cherryhill community. Most people were categorized as CFS-3, hence our sample represents older adults with relatively good health and functionality. Therefore, our findings are probably a conservative estimate of the magnitude of association between gait variability and frailty and can be only generalized to community-dwelling older adults who are able to live independently. Also, the overall narrow range of frailty statuses and small distribution in some categories could account for the lack of association in the CFS-6 with certain gait variability measures due to insufficient power to detect an association.

Therefore, reproduction of our findings in a larger sample of older adults with a range of frailty statuses is warranted.

4.5 Future directions

This study has established the association between gait variability and frailty, and a prospective study is needed to determine the temporal order of the relationship of gait variability and frailty. This can help determine the clinical utility of gait variability as a predictor of frailty and subsequent adverse event in older adults. Future studies need to be done in order to determine if increased gait variability is a marker for frailty in those who walk at a normal speed and otherwise show no signs of impaired gait. This would be important in determining the value of gait variability as a measure of frailty in addition to gait velocity. The relation of gait variability and frailty status suggests that gait variability may also be used as a potential measure to detect the magnitude of change in older adults undergoing therapies and interventions to improve frailty status. Stride-to-stride fluctuations are critical in understanding the physiology of gait and, therefore, gait variability may serve as a clinical tool in assessing reduced function in physiological systems involved in gait performance, and a predictor frailty status in older adults.

CHAPTER 5- CONCLUSION

This study demonstrated that several gait variability parameters are associated with frailty. Frailty, evaluated with a model which does not include gait velocity as a criterion, is associated with poorer performance on quantitative gait variability parameters.

These findings indicate that measures of gait variability may add valuable information beyond that of traditional measures of gait velocity in the assessment of frailty. The additional value of gait variability in identifying frailty is grounded in the concept that gait variability is an expression of several physiological systems which regulate the dynamics of gait (Lipsitz & Goldberger, 1992; Lipsitz, 2004; Montero-Odasso et al., 2011). High gait variability may therefore be a reflection of diminished homeostatic mechanisms and function across these systems. The association between increased gait variability and frailty contribute to the concept that frailty is a syndrome in which the loss of dynamics across several physiological systems increases vulnerability to suffer adverse events (Fried et al., 2001; Lipsitz, 2002; 2004; Montero-Odasso et al., 2011). This suggests that gait variability may be a potential measure in older adults to assess change in function as a result of interventions targeted at improving frailty status.

Additionally, our study showed that the Clinical Frailty Scale (CFS) can be an effective clinical tool for the identification and measurement of frailty in community-dwelling older adults. The CFS is reliable and comparable to the established Frailty Phenotype Index (FPI) in identifying frailty, with the advantage of being easy to administer in clinical settings. Improved understanding of the causes of frailty and reliable assessment tools to identify frailty in community-dwelling older adult can lead to

earlier and more precise identification of older adults to ameliorate risk of frailty related outcomes such as falls, mobility decline, disability and mortality.

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APPENDICES

Appendix A: Frailty Phenotype Index

FPI components	Measure of components
Slow Gait Velocity	Gait velocity of ≤ 0.99 m/sec
Low activity	Self-report of sedentary lifestyle Low frequency of physical activity (walking, chores, exercising, and leisure activities)
Weakness	Lowest 20% in grip strength (adjusted by gender and BMI) Men — Cut-off forgrip strength kg) BMI ≤ 24 — ≤ 29 BMI 24.1-26 — ≤ 30 BMI 26.1-28 — ≤0 BMI >28 — ≤32 Women — Cut-off for grip strength (kg) BMI ≤ 23 — ≤ 17 BMI 23.1-26 — ≤ 17.3 BMI 26.1-29 — ≤ 18 BMI >29 — ≤ 2
Exhaustion/ Poor Endurance	Positive answer from either of: (1) I felt that everything I did was an effort. (2) I could not get going. OR, answer of "A little/none of the time" to the question, "How much of the time during the past 4 weeks did you have a lot of energy?"
Weight loss	Self-report of >10lbs lost unintentionally in the last year

Adapted from Fried, L. et al. (2001).

Appendix B: Clinical Frailty Scale

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Appendix C: Frailty & Mobility Study Questionnaire

Please note: *This questionnaire and any other information you elect to provide will be kept in a locked filing cabinet in a locked private office at Parkwood Hospital to which only individuals involved in the study will have access. Your answers and contact information will be kept strictly confidential and not be shared with anyone.*

A. General Information:

Date of Birth (dd/mm/yyyy): / / Gender: ▫ Male ▫ Female

Please answer the following questions about any falls you have experienced:

1) Have you **had any falls** in the last 6 months? (By "fall", we mean finding yourself unintentionally on the floor or ground) ▫ Yes ▫ No

   If yes, how many falls have you had in the last **3 months?** _____

2) Have you had a hip fracture? ▫ Yes ▫ No

3) Do you **need a cane or walker** to get around? ▫ Cane ▫ Walker ▫ Neither

Please answer the following questions regarding your general health:

3) In general, how would you **rate your health** compared to others your age? (check one)

▫ Poor ▫ Fair ▫ Good ▫ Very Good ▫ Excellent

4) Are you currently on any **prescription medication**? ▫ Yes ▫ No

   If yes, how many medications? _____

5) Are you currently taking any **over-the-counter** (non-prescription) medications or supplements? ▫ Yes ▫ No

   If yes, are you currently taking any of the following:

Multi-vitamins: ▫ Yes ▫ No Name: _____

Vitamin D: ▫ Yes ▫ No Dose: _____

Calcium: ▫ Yes ▫ No Dose: _____

Please continue to next page ►►

6) Compared to **other people your age**, do you think your memory is:

□ Much worse □ Worse □ About the same □ Better □ Much better

7) Compared to **yourself 5 years ago**, do you think your memory is:

□ Much worse □ Worse □ About the same □ Better □ Much better

8) Are you currently diagnosed with or have experienced any of the following **issues or complaints**: (check all that apply)

Diabetes:	□ Yes	□ No	Osteoporosis:	□ Yes	□ No
Hypertension:	□ Yes	□ No	Cancer:	□ Yes	□ No
Lung disease:	□ Yes	□ No	Depression:	□ Yes	□ No
Congestive Heart Failure	□ Yes	□ No	Parkinson's Disease:	□ Yes	□ No
			Hearing Impairment:	□ Yes	□ No
Heart Attack:	□ Yes	□ No	Visual Impairment:	□ Yes	□ No
Stroke:	□ Yes	□ No	Anemia:	□ Yes	□ No
Osteoarthritis:	□ Yes	□ No	Difficulty sleeping:	□ Yes	□ No

9) Do you have any other **relevant medical or surgical issues** you would like to let us know about? (In particular, issues that might affect your walking: surgery to your hips/legs/feet, back problems, etc.)

_____

_____

_____

_____

_____

Please answer the following questions about your general activity:

10) Which of the following best describes your **typical activity level**? (check one)

- ☐ ***Vigorously active*** for at least 30 minutes, 3 times per week (exercise program, brisk walking, tai chi, swimming, etc.)
- ☐ ***Moderately active*** at least 3 times per week (gardening, walking, housework)
- ☐ ***Seldom active***, prefer more sedentary activities (reading, playing cards, watching television, etc.)

11) Compared to **other people your age**, do you think you are:

☐ Much less active ☐ Less active ☐ About as active ☐ More active ☐ Much more active

12) Thinking about your **usual ability to do the following daily activities**, please circle the most appropriate answer for each activity.

Activity	No difficulty	Some difficulty but no help	Need help (from person OR mobility aid)
Walking inside the house	0	1	2
Bathing *For example, can you get in and out of a bathtub if you wanted to? If you could easily, score 0; if you could with some difficulty, score 1; if you could with the help of a rail or a person, score 3.*	0	1	2
Upper-body dressing *For example, can you hook your bra (woman) or button your shirt (man)? If you could easily, score 0; if you could but with difficulty, score 1; if you could with assistance from another, score 2.*	0	1	2
Lower-body dressing *For example, can you bend and put on shoes? If you can easily, score 0; If you can but it is not easy, score 1; if you need some assistance from a person or a shoehorn, score 2.*	0	1	2
Moving from bed to chair	0	1	2
Toileting	0	1	2
Feeding	0	1	2
Grooming	0	1	2

F. Energy / Weight changes

13) Which of the following best describes your **typical level of energy**? (check one)

☐ Low ☐ Moderate ☐ High

How much of the time **during the past four weeks** did you have **a lot of energy**?

☐ All the time ☐ Half of the time ☐ A little/none of the time

14) During **the last few months**:

Have you felt that everything you did was an effort? ☐ Yes ☐ No

Have you felt that you could not get going? ☐ Yes ☐ No

15) Have you **lost weight unintentionally** in the previous year?

☐ None ☐ 1-5 lbs ☐ 5-10 lbs ☐ More that 10 lbs

Antropometric Information

Height (cm): _____ Weight (kg): _____ B.M.I.: _____

Grip Strength: _____ Leg Length: _____

Current Medications types

Neuroleptics:	Y N	Alpha-blocker:	Y N	Statins:	Y N
Bezodiazapines:	Y N	Vasodilators:	Y N	Multi-vitamins:	Y N
Diuretics:	Y N	Anticoagulant:	Y N	Vitamin D:	Y N
Thyroid (ATD):	Y N	Aspirin:	Y N	Calcium:	Y N
Beta-Blocker:	Y N	SSRI	Y N		

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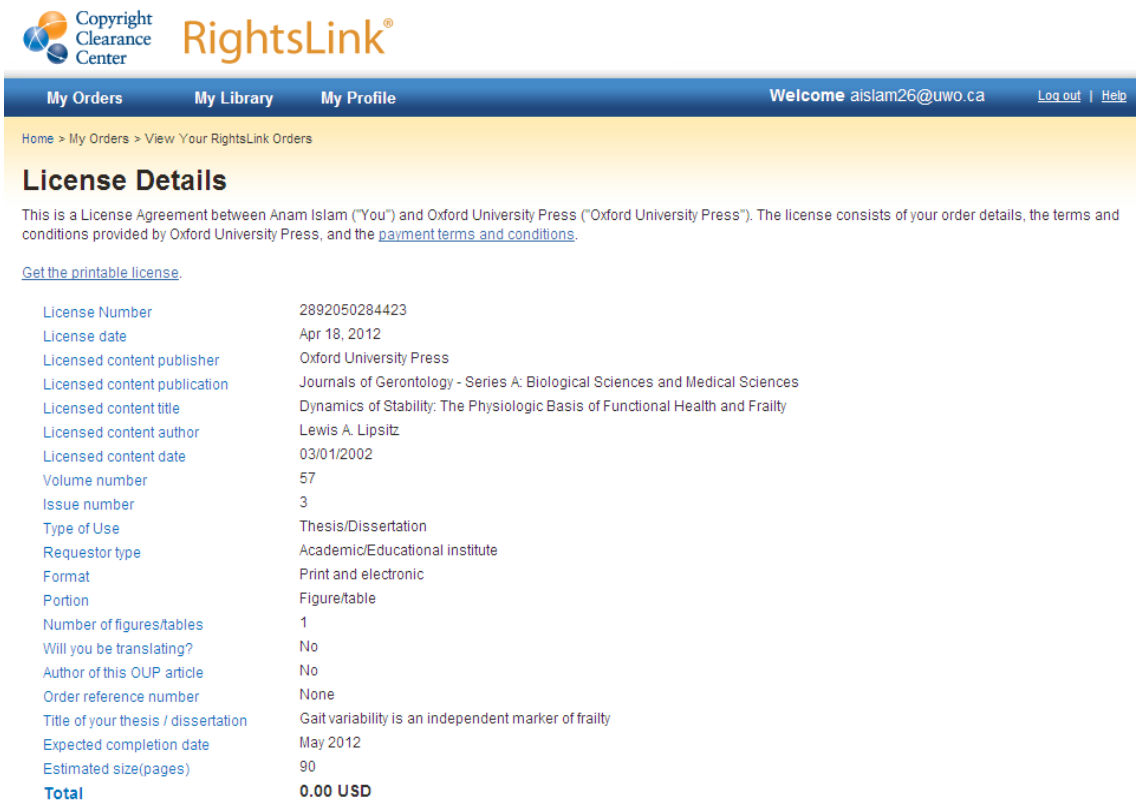

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Curriculum Vitae

Anam Islam

Education

2010-Present	Masters of Science in Kinesiology The University of Western Ontario, London, ON, Canada
2006-2010	Bachelor of Medical Science The University of Western Ontario, London, ON, Canada

MSc Thesis

"Gait Variability is an Independent Marker of Frailty"

Supervisor- Dr. Manuel Montero-Odasso, MD PhD; Department of Geriatric Medicine, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, ON, Canada

Awards and Distinctions

Best Poster Award, Annual Scientific Meeting of the Canadian Geriatric Society, 2012
Top 50 Student Poster, Annual Meeting of the American Geriatric Society, 2012
Canadian Institute of Health Research, Institute of Aging- Travel Award 2012
Canadian Geriatric Society- Canadian Institute of Health Research- Travel Award 2012
Faculty of Health Science Student Conference Travel Award, 2012
Kinesiology Graduate Student Conference Travel Award, 2012
Western Graduate Research Scholarship, 2010/2011, 2011/2012
Western Scholarship of Distinction, 2006

Research Experience

2010- Present	**Research Student** Department of Geriatric Medicine, Parkwood Hospital, London, ON

Refereed Abstracts and/or Papers Presented at Conferences

Islam A, Muir SW, Montero-Odasso M. Gait variability is independently associated with frailty. American Geriatric Society Annual Meeting. May 3-5th, 2012; Seattle, WA. (Poster Presentation)

Islam A, Muir SW, Montero-Odasso M. Facilitating frailty identification in clinical practise: comparison of two methods among community dwelling older adults. 32nd Annual Meeting of the Canadian Geriatric Society. Apr 19-21st, 2012; Quebec City, QC. (Oral Presentation)

Annweiler C, Vasudev A, **Islam A**, Yang N, Montero-Odasso M,. Vascular Risk Factors Predict Gait, Mood, and Executive Function Disturbances in People with Mild Cognitive Impairment. Results from the "Gait and Brain Study". 32nd Annual Meeting of the

Canadian Geriatric Society. Apr 19-21st, 2012; Quebec City, QC. (Oral Presentation)

Islam A, Muir SW, Doherty T, Kloseck M, Speechley M, Montero-Odasso M. Early gait instability as a marker for frailty: the role of gait variability. Aging Rehab and Geriatric Care Conference. February 4th, 2011; London, ON. (Poster Presentation)

Published Abstracts

Islam A, Muir SW, Montero-Odasso M. Facilitating frailty identification in clinical practise: comparison of two methods among community dwelling older adults. J Am Geriatr Soc. 2012;60(s4):S98.

Islam A, Muir SW, Montero-Odasso M. Gait variability is independently associated with frailty. American Geriatric Society Annual Meeting. J Am Geriatr Soc. 2012;60(s4):S160.

Teaching Experience

2011-2012	**Teaching Assistant** KIN 2230A/B, Introductory Exercise Physiology The University of Western Ontario, London, ON, Canada
2010-2011	**Teaching Assistant** KIN 1088A, Introduction to Sport Psychology KIN 1080B, Introduction to Psychomotor Behaviour The University of Western Ontario, London, ON, Canada