The Moderating Effect of Physical Activity on the Association between White Matter Hyperintensities and Gait Characteristics

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Graduate Program in Kinesiology
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Abstract

The objectives of this thesis were; 1) to assess the effect of white matter hyperintensities (WMH) burden on motor outcomes among older individuals in the presence and absence of overt neurological conditions, and 2) to evaluate whether physical activity (PA) moderated the association between WMH and gait velocity and stride time variability (STV), under single and dual-task conditions, in a geriatric clinic sample. Study 1 systematically reviewed the literature demonstrating that greater WMH burden was associated with predefined motor outcomes. Notably, gait velocity emerged as a well-studied characteristic. Study 2 confirmed that WMH negatively affected gait velocity. STV and dual-task gait conditions did not reveal significance. Additionally, PA did not moderate the association between WMH and gait velocity, although conditional effects showed significance for low and moderate levels of PA. This finding extends support for the efficacy of physical activity in attenuating the effects of WMH on mobility.

Keywords

White Matter Hyperintensities, Physical Activity, Gait Velocity, Dual-Task, Older Adults, Stride Time Variability
Acknowledgments

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Chapter 1

1 Literature Review

This thesis aims to evaluate the association between white matter hyperintensities and motor outcome, specifically quantitative gait characteristics, and whether this association is modified by physical activity among older individuals. Chapter 1 will introduce the topic of mobility in aging, focusing on the role of the central nervous system affecting mobility. A brief overview of gait performance in aging will be presented and the inter-relationship with cognitive functions will be explored. In addition, this chapter will discuss the impact white matter hyperintensities detected on magnetic resonance imaging have on quantitative gait characteristics as well the neuroprotective effect of physical activity against cognitive and physical functioning decline in aging. We conclude by providing the study rationale, purpose and hypotheses of the subsequent chapters.

1.1 Mobility in Aging

Mobility is essential for humans as the capacity to move underlies many basic and community functions necessary for independence [1]. Mobility limitations defined as a restriction in an individual’s ability to move around the environment are common in aging, affecting approximately one-third to one-half of adults aged 65 years and older [1]. The consequences of mobility limitations represent a serious health and economic burden as they can render significant impact on overall physical functioning, ultimately leading to loss of independence, future falls, mobility disability and mortality [2-4]. Converging evidence suggests that gait performance is a clinical marker of mobility, in which specific quantitative characteristics (i.e., velocity and variability) are associated with future adverse outcomes in older adults [5-7]. During the last decade, mounting evidence has supported that the central nervous system plays a key role in regulating walking and gait performance, even in older adults without neurological diseases. Specifically, low cognitive functions in attention, executive function, and semantic memory are associated with mobility decline and future falls [8, 9]. Additionally, emerging evidence from neuroimaging studies support that gait performance and cognitive processes share similar
brain networks and regions [10-12]. Therefore, understanding the role of neurological markers in association with quantitative gait characteristics is important in preventing and treating mobility limitations along with potential disabilities.

For the purpose of this chapter, our discussion in the following sections will focus solely on gait as a marker of mobility given the overwhelming evidence in support for this association.

### 1.2 Gait

Gait is a complex clinical entity defined as the pattern of movement of the body during locomotion, which enables humans to move forward [9, 13]. It has a multitude of determinants requiring the integration of the cardiopulmonary, musculoskeletal, nervous and sensory systems [6, 9, 14-18]. Accordingly, alterations to these systems necessary for facilitating gait functions may lead to the manifestation of gait disorders.

The effects of aging on gait performance are commonly recognized. Furthermore, although gait alterations are demonstrated in older adults with specific neurological conditions, they are also reported in otherwise healthy older individuals [19-21]. Hence, studying gait processes beyond disease-based models is crucial for understanding and preventing the onset of clinical impairment.

#### 1.2.1 The Gait Cycle

The gait cycle is used to describe the time from when the heel of one foot makes contact with the ground (heel strike) to the following heel strike of the same foot [22, 23]. The cycle is characterized in two phases: the stance phase and the swing phase (see Figure 1.1). The stance phase represents approximately 60% of the gait cycle, starting and ending with both feet on the ground with one foot maintaining constant contact with the ground. This phase is divided into the initial heel strike, loading response, mid-stance, terminal stance and pre-swing. The remaining 40% of the gait cycle is referred to as the swing phase. The swing phase occurs simultaneously with the stance phase and represents the interval at which the opposing foot is not in contact with the ground. This phase is divided into toe-off, mid-swing, and terminal swing.
1.2.2 Classification of Gait Disorder in Older Adults

As proposed by Nutt, Marsden and Thompson [24], gait disorders can be hierarchically divided into lower, middle and higher levels (see Table 1.1). Lower-level gait disorders refer to deficits in the lower extremity or peripheral dysfunction contributing to changes in gait. Middle-level gait disorders refer to disruptions in motor and sensory modulation of gait affecting the execution of gait while the initiation process remains preserved. Lastly, higher-level gait disorders refer to the deficits not explained by peripheral motor, sensory, pyramidal, cerebellar, or basal ganglia lesions. At this level, categorization of gait characteristics is non-specific, where altered cognitive and attention processes, and behavioral deficits may be present.
Table 1.1 Common cause of gait disorder in older people according to the hierarchic sensorimotor level

<table>
<thead>
<tr>
<th>Level</th>
<th>Deficit/Condition</th>
<th>Gait characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Peripheral sensory ataxia: posterior column, peripheral nerves, vestibular &amp; visual</td>
<td>Unsteady, uncoordinated (especially without visual input)</td>
</tr>
<tr>
<td></td>
<td>ataxia</td>
<td>Avoids weight-bearing on affected side</td>
</tr>
<tr>
<td></td>
<td>Peripheral motor deficit owing to lip problems</td>
<td>Painful knee flexed</td>
</tr>
<tr>
<td></td>
<td>Arthritis (antalgic gait, joint deformity)</td>
<td>Painful spine produces short slow steps and decreased lumbar lordosis, kyphosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and ankylosing spondylitis produce stooped posture</td>
</tr>
<tr>
<td></td>
<td>Peripheral motor deficit owing to myopathic</td>
<td>Proximal motor neuropathy produces waddling and foot slap; distal motor neuropathy</td>
</tr>
<tr>
<td></td>
<td>and neuropathic conditions (weakness)</td>
<td>produces distal weakness</td>
</tr>
<tr>
<td>Middle</td>
<td>Spasticity from hemiplegia, hemiparesis</td>
<td>Leg swings outward and in a semi-circle from hip (circumduction)</td>
</tr>
<tr>
<td></td>
<td>Spasticity from paraplegia, paraparesis</td>
<td>Circumduction of both legs; steps are short, shuffling, and scraping</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td>Small shuffling steps, hesitation, acceleration (pseudoparkinsonian), falling forward</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia</td>
<td>(propulsion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wide-based gait with increased trunk sway, irregular stepping</td>
</tr>
<tr>
<td>High</td>
<td>Cautious gait</td>
<td>Fear of falling with appropriate postural responses, normal to widened gait base,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>shortened stride, slower turning en bloc. Performance improves with assistance or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>evaluator walking on the side</td>
</tr>
<tr>
<td></td>
<td>Ignition failure</td>
<td>Frontal gait disorder; difficulty initiating gait; short, shuffling gait, like</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parkinsonian; but with a wider base, upright posture, and arm swing presence</td>
</tr>
</tbody>
</table>

Adapted with permission from Montero-Odasso M. “Falls as a Geriatric Syndrome: Mecha
nisms and Risk Identification”. Chapter in Osteoporosis in Older Persons: Advances in Pathophysiology and Therapeutic Approaches by Duque & Kiel [25].

1.2.3 Epidemiology of Gait Disorders

The prevalence and incidence of gait disorders or impairment in older adults varies 
between studies as results of the quantification methods used, as well as the population of 
interest. However, studies including community-dwelling older adults have been 
relatively consistent. For example, the Bruneck Study, a population-based study of older 
individuals between 60–97 years of age, reported that the prevalence of impaired gait 
based on a comprehensive and standardized clinical examination using a three-step model 
for classification was 32.2% (95% confidence interval [CI] = 28.2–36.4) [26]. Similarly, 
the Einstein Aging Study, a prospective cohort study of older adults between 70–99 years 
of age, reported that the prevalence of gait disorder based on clinician observation and 
diagnosis was 35% (95% CI = 28.6–42.1) and the incidence of abnormal gait was 168.6 
per 1,000 person years (95% CI = 117.4–242.0) [27].
In addition, both studies demonstrated that the prevalence of gait disorders increases with age [26, 27]. The Bruneck Study showed that the prevalence of gait disorders for older individuals 60–69 years of age was 10% (95% CI = 7.1–15.8) and increased to 61.7% (95% CI = 52.7–69.9) in those over 80 years of age [26]. The Einstein Study reported that the prevalence of abnormal gait in older adults 70–74 years of age was 24.3% (95% CI = 16.4–34.5) increasing to 45.9% (95% CI = 26.5–66.7) in those 85 years of age and older [27]. The same study reported that the incidence of abnormal gait in those 70–74 years of age was 116.4 per 1,000 person years (95% CI = 62.3–217.5) and in those 85 years of age and older the incidence of abnormal gait was 502.8 per 1,000 person years (95% CI = 284.5–888.6) [27].

1.2.4 Methods of Gait Analysis

Gait analysis refers to the data gathering process of an individual’s walk [23]. There are various methods of gait analysis including: observational gait analysis, timing of the gait cycle, direct motion measurement systems, and electrogoniometers among many others. The applications of gait analysis techniques are dependent on whether it is used for clinical or research purposes [23]. Clinical gait assessment aims to aid in the treatment of patients, whereas gait assessment for research aims to improve our understanding of gait [23].

1.2.4.1 Observational Methods of Gait Analysis

Observational methods of gait analysis can include clinical examinations, or simple timed pencil-and-paper tests using a stop watch and a marked path on the ground. For clinical examinations, an individual is asked to complete a number of walks as an observer, usually a clinician, examines various characteristic of the walk. Parameters evaluated during the clinical examination of gait may include: gait initiation, velocity, turning, arm swing, posture, and many more [18, 23, 28]. On the other hand, simple timed tests typically involve measuring the velocity, number of steps, or cadence (steps per minute) of an individual’s walk over a pre-selected distance. Although both of these approaches demonstrate feasibility within clinical settings, the former is time consuming, relies on
clinician expertise, and can only detect clinically evident gait abnormalities. The latter provides a quantitative measure of gait, which is usually affected before clinically detectable gait impairments.

1.2.4.2 Instrumented Methods of Gait Analysis

Instrumented methods of gait analysis are highly sophisticated techniques with the capacity to provide precise gait parameters. Specifically, quantifiable spatial and temporal characteristics can be acquired through the use of computerized electronic walkway systems (see Table 1.2 and Figure 1.2). These electronic walkways are embedded with pressure sensors that are activated through foot contact (see Figure 1.3). Computerized walkways have gained much acceptance within research as they are feasible, with easy transportation and implementation across a wide-range of settings (e.g., clinic- or community-based). Additionally, they are a valid and reliable tool, providing a quick alternative to observational methods [29, 30]. Furthermore, characteristics of gait velocity and gait variability, which can be acquired through computerized walkways, have emerged as outcomes that may implicate subclinical impairment.

Table 1.2 Definitions of quantitative gait characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity</td>
<td>meters/second</td>
<td>Distance covered by the time to ambulate</td>
</tr>
<tr>
<td>Cadence</td>
<td>steps/minute</td>
<td>Number of steps by the time to ambulate</td>
</tr>
<tr>
<td>Stride length</td>
<td>meters</td>
<td>Distance between heel points of two consecutive footfalls of the same foot.</td>
</tr>
<tr>
<td>Step length</td>
<td>meters</td>
<td>Distance between the heel points of two consecutive footfalls of the opposite foot</td>
</tr>
<tr>
<td>Step width</td>
<td>meters</td>
<td>Distance between the midpoint of the two consecutive footfalls of the opposite foot</td>
</tr>
<tr>
<td>Stride time</td>
<td>seconds</td>
<td>Duration to ambulate one stride length</td>
</tr>
<tr>
<td>Step time</td>
<td>seconds</td>
<td>Duration to ambulate one step length</td>
</tr>
<tr>
<td>Double support</td>
<td>seconds</td>
<td>Duration of when both limbs are in contact with the</td>
</tr>
</tbody>
</table>
Figure 1.2 Basic terminology describing the gait cycle. Adapted from Pirker & Katzenschlager [18].

Figure 1.3 Schematic of GAITRite® electronic walkway. Adapted from CIR Systems, Inc. at http://www.gaitrite.com/WI-02-15_Technical_Reference_T.pdf.
1.2.5 Gait Velocity

Gait velocity, which is the distance covered by the time to ambulate is a simple yet effective measure of mobility [31]. It can be attained both through the use of observational and instrumented methods of gait analysis, demonstrating feasibility within clinical practice. Moreover, gait velocity has demonstrated extensive predictive capabilities for a wide range of outcomes in older adults including limitations in activities of daily living, mobility disability, institutionalization, falls, mortality, and dementia [7, 32-36]. In addition, the responsiveness of gait velocity, that is, the ability to detect real change over time across different settings and in various clinical populations, has led to the designation of this measure as the “6th vital sign” [36-38].

1.2.6 Gait Variability

Gait variability is an emerging quantitative gait parameter that has received considerable attention in recent years. Gait variability refers to the magnitude of the stride-to-stride fluctuations of gait characteristics during the gait cycle [13]. It is obtained by using either the standard deviation (SD) or the coefficient of variation (CoV; SD divided by the mean) of the gait characteristics of interest. Previously, stride-to-stride fluctuations were regarded as “noise” within the data and were dismissed as having little to no relation to the intrinsic mechanisms necessary for normal gait [39]. However, studies now support that the stride-to-stride fluctuations in gait measures (i.e., gait variability) are a clinically relevant feature of gait.

A prospective cohort study of community-dwelling older adults found that increased stride time variability predicted falls [40]. In fact, there was a 5-fold increased risk for falls in older adults with higher stride time variability [40]. To visualize these effects, Figure 1.4 illustrates the stride-to-stride fluctuations in a faller and a non-faller during the 12-month study follow-up. Moreover, other studies have demonstrated an association between measures of gait variability and mobility disability [5, 41], frailty [42], falls [35, 43] and dementia [44, 45], further emphasizing the clinical utility in this measure. More importantly, several studies have indicated that gait variability may be a more sensitive
measure than gait velocity of assessing mobility impairment [35, 39, 46, 47]. Despite the sensitivity in gait variability to predict impairment, Beauchet and colleagues [48] suggests that gait velocity and gait variability should be explored concurrently, not separately.

![Figure 1.4](image)

**Figure 1.4** Stride time variability at baseline in a 78-year old man who experienced a fall during the 12-month follow up (SD = 66 ms), compared to an 84-year old man who did not fall (SD = 29 ms). Adapted with permission from Hausdorff, Rios and Edelberg [40].

### 1.3 Gait and Cognition

Gait had been considered as an automatic motor task requiring minimal neural input. However, emerging evidence supports that gait performance relies on higher-level cognitive processes. Evidence for this association has been demonstrated indirectly in studies examining cognition. Although there are several definitions, we define cognition as “the intellectual or mental process whereby an organism becomes aware of or obtains knowledge” [49]. As such, it comprises a variety of functions including executive functions, attention, working memory, long-term memory, reasoning, decision making, problem-solving, speech and language, planning in addition to many others [50]. Noteworthy, similar to gait, cognitive functions generally worsen during the aging process and have also been demonstrated in individuals with and without overt neurological conditions.
Additionally, numerous studies suggest that clinical entities of gait impairment and cognitive impairment may coexist in older individuals. For example, the association between low cognition functions and poor gait performance have been demonstrated in general older adults samples and in individuals with mild cognitive impairment (MCI) and dementia [31, 51-53]. One study in particular even demonstrated that slowing gait speed precedes the development of clinically detectable cognitive changes (i.e., onset of MCI) in older adults [54]. Moreover, a recent systematic review and meta-analysis of 37 prospective studies including older adults without overt neurological conditions reported that lower limb motor function was associated with higher risk of incident dementia (pooled hazard ratio \( HR = 1.94, 95\% CI = 1.41–2.65 \)) [32]. Hence, it is postulated that the co-occurrence of these two clinical entities may be a result of shared risk factors and underlying brain networks [55, 56].

1.3.1 Executive Functions

Executive functions refer to a series of mental processes that collectively produce and modulate goal-directed behaviours [57, 58]. This includes mental shifting, information updating and monitoring, and inhibition [57]. Not surprisingly, impairments to executive function subdomains impact an individual’s ability to walk safely. For example, walking in the real-world is a goal-directed action that involves continually attending, integrating, and responding to environmental perturbations to ensure stable movement. In fact, there is substantial evidence in the literature to support that poor performance on tests of executive functions are associated with gait performance [58-60]. While studies have demonstrated an association between general measures of executive functions, specific domains of executive functions (i.e., attention) have also been demonstrated in association with poor gait outcomes [58, 61].

1.3.2 Attention

Attention refers to a specific subdomain of executive functions whereby an organism perceives a stimulus and begins processing this incoming information [58]. There are different forms of attention including focused, sustained, divided and alternating.
Focused attention includes selecting a relevant stimulus while suppressing irrelevant distractors [62]. Sustained attention refers to maintaining focus on a task over an extended period of time [63]. Divided attention is the ability to carry out more than one task simultaneously and alternating attention is the shifting of one task to the next [62]. Walking comprises varying types of attention demands, especially divided attention as walking in the real-world typically involves carrying out multiple tasks as once [58, 61]. Of particular interest, divided attention represents the basis for the dual-task paradigm, which posits that the attention demands of multi-tasking while walking has clinical implications for risk of falls.

### 1.3.3 Dual-Task Paradigm

In a seminal paper by Lundin-Olsson et al. [64], researchers demonstrated in a sample of nursing home residents that the inability to maintain a conversation while walking, or those who ‘stopped walking when talking’ were more likely to fall [64]. Since then, observing gait characteristics of an individual’s walk while performing a secondary attention demanding task has been used to evaluate the relationship between gait and cognition. The underlying hypothesis of the dual-task paradigm suggests that performing more than one task at once will interfere and compete for neural resources required for walking [58]. The resultant gait modifications are interpreted as increased “cost” of involvement of higher level cognitive processes while walking. As such, gait performance under dual-task conditions is dependent on an individual’s ability to adequately allocate the necessary resources for two simultaneously performed tasks.

In general, dual-task performance may impact gait by decreasing velocity and increasing variability [13, 40]. In fact, several studies have provided evidence in support for this association. These studies suggest that the effects of dual-tasking on gait velocity and variability are much higher in individuals with cognitive impairment than in healthy controls [11, 65-67]. Furthermore, a recent prospective cohort study among 112 older individuals with MCI revealed that dual-task cost in gait velocity while counting backwards by one (HR = 3.42, 95% CI = 0.99–11.71, p = 0.05) and naming animals (HR = 2.41, 95% CI = 1.04–5.59, p = 0.003) was associated with progression to dementia.
Interestingly, single-task gait velocity did not show significance [68]. The clinical relevance of dual-tasking is emphasized through its assumed simulation of real-life situations, where falls are more likely to occur, but also its ability to detect subtle brain deficits [69].

There are three main theories to explain the dual-task paradigm, in particular dual-task cost. The first is the capacity-sharing theory, which suggests attentional resources are of finite capacity such that presenting two or more stimuli within close succession of one another will result in deterioration in at least one task if performing both tasks shares capacity [70]. This theory has been applied to tasks that are over-learned and automatic (i.e., walking). The second theory is the bottleneck theory, which suggests that a delay or ‘bottleneck’ is likely to occur if two tasks are processed by the same neural networks [71]. As a result, processing of the second task will occur after the neural networks are free from processing the first task. The last theory is the multiple resource model theory, which suggests that dual-tasking requires a number of resources and if two tasks are not from common resources, dual-task cost will not occur [58]. Alternatively, if the two task share the same resources (i.e., use the same neurons), they will also not disturb each other due to increased activation.

1.3.4 Risk Factors for Gait and Cognitive Decline in Aging

Previously, Pugh and Lipsitz [56] proposed the “Microvascular Frontal-Subcortical Syndrome of Aging” to help explain the “phenotypic” changes of the cognitive and motor systems. This model suggests that the clinical features of aging related to the frontal-subcortical structures may result from age-related neuronal changes in addition to vascular damage resulting from the accumulation of cardiovascular risk factors [56]. Previous research shows robust evidence linking vascular risk factors to cognitive impairment, dementia and Alzheimer’s disease [72-78]. Similar results have also been demonstrated for the association between vascular risk factors and gait outcomes including slowing gait velocity and increased dual-task cost [75, 79-81].
While the relationship between gait and cognition is well-established, converging evidence from neuroimaging studies also supports this association. Specifically, gait and cognitive functions are governed by frontal-subcortical neural networks that are in close proximity to one another [55, 56]. These networks are located within watershed areas of cerebral perfusion that are vulnerable to the effects of vascular risk factors and subsequent formation of white matter hyperintensities (WMH) [55, 56, 82, 83]. Not surprisingly, WMH have been associated with vascular risk factors, cognitive functioning, dementia, and motor outcomes (i.e., slowing gait velocity, balance, and falls) [21, 84-92]. Recently, a more inclusive model including aging, neurodegeneration, vascular brain disease and other factors has been proposed to explain the potential mechanisms affecting the common brain structures and network that govern gait control and cognitive performance (see Figure 1.5). Taken together, interventions aimed at alleviating vascular risk factor burden may also aid in preventing or slowing of motor and cognitive decline, in addition to the formation of WMH, contributing to frontal-subcortical dysfunction.

Figure 1.5 Potential mechanism affecting the common brain structures and networks that regulate gait control and cognitive performance. Adapted from Montero-Odasso, M et al. [93].
1.4 White Matter Hyperintensities

White matter hyperintensities are a common neuroimaging finding among older individuals appearing as hyperintense areas on T2-weighted, proton density-weighted (PD) and fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences [94]. Generally, WMH appear as ‘caps’ on the frontal and/or occipital horns (Figure 1.6A) or as a thin ‘lining’ along the lateral ventricles (Figure 1.6B). Such WMH are referred to as periventricular WMH. Alternatively, WMH can appear within areas of the subcortical white matter, otherwise referred to as deep WMH (Figure 1.6C). With increasing severity or progression of WMH, periventricular WMH may extend into areas of subcortical white matter becoming confluent (Figure 1.6D). Even though these findings of high signal areas were once regarded as a part of the normal aging trajectory and clinically innocuous, numerous studies suggest that WMH are clinically relevant biomarkers and therefore should not be overlooked.
1.4.1 Epidemiology of White Matter Hyperintensities

As mentioned earlier, WMH are a frequent finding on MRI scans of older adults with and without overt neurological conditions. Two large population-based studies, the Cardiovascular Healthy Study and the Rotterdam Scan Study, which included participants of 60 years of age and older, reported a high prevalence of WMH of 95% and 96%, respectively [95, 96]. Additionally, several studies have revealed that the prevalence of WMH increases with the number of vascular risk factors including hypertension, diabetes and history of smoking [97-100].

Aside from investigating overall prevalence, the Rotterdam Scan Study also examined the progression of WMH. Using a semiquantitative visual rating scale (providing a total and
partial regional WMH scores), this study reported progression of WMH in 39% of individuals over a 3-year follow-up period [99]. Predictors of WMH progression included magnitude of baseline WMH severity, and vascular risk factors of blood pressure and current smoking status, although no significant associations were reported for atrial fibrillation, carotid atherosclerosis and homocysteine [99].

1.4.2 Pathogenesis of White Matter Hyperintensities

The pathophysiology of WMH is heterogeneous, however, it is hypothesized that WMH are a result of ischemia and inflammation [101]. The ischaemic mechanism suggests that endothelial damage including loss of smooth muscle cells, lumen restriction, and vessel wall thickening leads to decreased cerebral blood flow and loss of auto-regulation and tissue ischemia [102-104]. Tissue ischemia is characterized as demyelination, loss of oligodendrocytes and axonal damage [102, 104, 105]. Alternatively, endothelial damage can lead to disruption in the brain blood barrier, which allows toxins into the brain causing tissue damage appearing as areas of hyperintensities on MRI [102, 106, 107].

1.4.3 Assessment of White Matter Hyperintensities

Although there is no established ‘gold standard’ for quantifying WMH, numerous methods are available that yield an accurate measure of WMH. Broadly, there are two methods of assessment: semiquantitative visual rating scales and quantitative automated segmentation approaches.

1.4.3.1 Semiquantitative White Matter Hyperintensities

Assessment

Semiquantitative WMH assessment, which uses a visual rating scale that has significant correlation with quantitative volumetric WMH techniques, provides a fast and reliable way for quantifying WMH. Some scales also have the advantage of delineating regional WMH volume, although it must be employed by an experienced rater and is limited to cross-sectional use only [108]. Examples of commonly used visual rating scales include the Fazekas and Scheltens. The Fazekas scale rates WMH on a 0-3-point scale,
combining both periventricular (areas along the lateral ventricles) and subcortical areas [109]. On the other hand, the Scheltens scale yields a score ranging from 0-82-points delineating periventricular and subcortical WMH, in addition to WMH in the basal ganglia and infratentorial regions. [110].

1.4.3.2 Quantitative White Matter Hyperintensities Assessment

Quantitative WMH assessment, such as automated segmentation programs, are capable of providing quick and precise measurement of WMH volume, and often times require minimal human input. As a result, automated segmentation methods eliminate inter-rater bias and can be useful for detecting small volumetric changes longitudinally [111]. While semiquantitative and quantitative methods of analysis can measure visually appreciable WMH, quantitative approaches can also detect subtle structural changes to the white matter integrity derived from diffusion-tensor imaging (DTI) [112].

1.4.4 Clinical Consequences of White Matter Hyperintensities

White matter hyperintensities are increasingly recognized as important neuroimaging biomarkers, particularly in relation to gait and cognition. Gait and cognitive impairments, as previously discussed, are common in aging and can progress to severe stages, manifesting as dementia and falls [8]. Numerous studies including a large meta-analysis demonstrated that WMH are associated with cognitive decline within domains of executive functions and an increased risk of dementia [88, 113-115]. In addition, WMH are also associated with poorer physical functions, resulting in slowing gait, balance instability and falls [19, 20, 87, 115, 116]. Furthermore, strategies aimed at improving risk factors (e.g., hypertension, diabetes) may prove vital to alleviating these consequences of WMH burden.

1.5 Physical Activity

Physical activity is defined as an individual’s daily activity involving bodily movement and the use of skeletal muscles [117]. Physical exercise, is a sub-domain of physical activity that is planned, structured and repetitive movement aimed at improving physical
18

1. Physical activity is an important modifiable lifestyle factor and when prescribed as physical exercise, it has the capacity to maintain and improve areas of an individual’s physical health. The known effects of physical activity have been demonstrated in health conditions of diabetes, osteoarthritic and cardiovascular diseases, through which the effects of these conditions are attenuated [119-121]. More importantly, physical activity has demonstrated a protective effect against cognitive and physical functioning decline, especially in older adulthood.

1.5.1 Physical Activity and Cognition in Aging

The benefits of physical activity in delaying or offsetting the trajectory of age-related cognitive decline have been long recognized. For example, Yaffe and colleagues in a sample of 5,925 cognitively-healthy community dwelling older women (aged ≥ 65) examined the association between physical activity and cognitive decline over 8 years [122]. Physical activity was measured as the number of city blocks walked (1 block ≈ 160 meters) each day as a part of daily exercise or normal routine and cognitive decline was assessed using the Mini-Mental State Examination (MMSE) at baseline and 6 to 8 years later. The authors reported that compared to the lowest quartile, the odds of developing cognitive decline was 34% lower (OR = 0.66; 95% CI = 0.54–0.82) among women in the highest quartile of blocks walked at baseline after adjusting for relevant covariates [122]. The authors further concluded that the odds of developing cognitive decline was 13% lower (OR = 0.87; 95% confidence interval [CI] = 0.82–0.92) for every 10 blocks per day (~1.6 km [1 mile]) [122].

Similarly, the Nurses’ Health Study investigated the association of physical activity on cognitive decline in 18,766 women aged 70–81 years [123]. Physical activity was measured by asking the women to estimate the amount of time spent partaking in pre-specified activity (e.g., running, walking, racquet sports, lap swimming, dancing etc.) and cognitive function tested domains of global cognition, category fluency, working memory and attention, and verbal memory. Results from this study showed that compared to women in the lowest quintile of physical activity, the risk for cognitive impairment was 20% lower for women in the highest quintile of activity (OR = 0.80; 95% CI = 0.67–
0.95) [123]. Additionally, less cognitive decline over 2 years was seen in women that were more active; women in the fourth and fifth quintile had 0.04 (adjusted mean difference = 0.04; 95% CI = 0.01–0.07) and 0.06 (adjusted mean difference = 0.06; 95% CI = 0.03–0.08) standard units higher for global cognition than those in the lowest quintile [123]. Furthermore, when analysis was restricted to only walking, a significant association for less cognitive decline was detected in those who walked at an easy pace for at least 1.5 hours per week when compared to women that walked <38 minutes per week [123]. It suggests that above a certain threshold, even minimal physical activity time (1.5 hours per week = 13 minutes per day) has a protective effect against cognitive decline.

Other studies with more representative samples show consistent results with aforementioned studies. The Monongahela Valley Independent Elders Survey (MoVIES) study examined the association between levels of physical activity and subsequent cognitive decline in 1,681 community-dwelling older adults (aged ≥ 65) over 2 years [124]. Physical activity was a self-reported composite measure of type, frequency, and duration of level of exercise engagement and cognitive decline was measured using change in the MMSE. It was reported that the odds of engaging in high exercise frequency and duration (≥30 minutes of exercise, ≥3 times per week) was independently associated with a 61% lower (OR = 0.39; 95% CI = 0.19–0.78) risk of cognitive decline (≥3 MMSE points) when compared to no exercise [124].

Moreover, longitudinal studies have also examined the association between levels of physical activity and subsequent cognitive impairment and dementia For example, the Canadian Study of Health and Aging (CSHA) investigated the association between physical activity and occurrence of cognitive impairment and dementia in a sample of 4,615 community-dwelling older adults over a 5-year follow-up [125]. Physical activity was a self-reported composite measure of frequency and intensity of an individual’s regular activity. Cognitive diagnoses (i.e., cognitive impairment-no dementia [CIND], Alzheimer’s disease [AD; probable or possible], vascular dementia, and unclassified dementia) were made by a clinician. It was reported that when compared to no physical activity, high levels of physical activity were independently associated with decreased
risk of CIND (OR = 0.58; 95% CI = 0.41–0.83), AD (OR = 0.50; 95% CI = 0.28–0.90) and any dementia (OR = 0.63; 95% CI = 0.40–0.98) [125].

1.5.2 Physical Activity and Gait in Aging

The protective benefits for physical activity and physical function has also been recognized among the elderly. For example, the Health, Aging and Body Composition (Health ABC) study examined the cross-sectional association between physical activity and physical function in 3,075 high-functioning older individuals aged 70–79 years [126]. Physical activity level was measured using standardized questionnaires from commonly-used physical activity questionnaires and measures of physical functions, which included a 400-meter walk, the Established Populations for the Epidemiologic Studies of the Elderly (EPESE) and the Health ABC battery. Results showed that after adjusting for relevant covariates, the active lifestyle group took significantly less to time complete the 400-meter walk [126].

The Rush Memory and Aging Project investigated the association between physical activity and rate of mobility change in a sample of 886 older adults without dementia [127]. Physical activity was measured using the National Health Interview Survey that yields a value of hours of activity per week and mobility was evaluated as the time and number of steps to walk 8-feet. The findings from this study suggested that higher levels of physical activity were associated with a slower rate of mobility decline [127]. Further interpretations suggested that each 1-hour increase of physical activity was associated with approximately 3% decrease in the rate of mobility decline [127].

Mobility decline was also an outcome of interest in the Longitudinal Aging Study Amsterdam (LASA), a 3-year prospective study of 2,109 adults aged 55 to 85 years [128]. Physical activity was measured using self-reported questionnaires of an individual’s activity including sport participation and total activity time within the last 2 weeks. Mobility performance was assessed using a timed walking test and a chair stand test. It was revealed that higher levels of baseline physical activity were associated with smaller change in mobility performance at 3-year follow up [128]. Additionally, change in physical activity was associated with change in mobility performance such that
individuals reporting stable activity during follow up, experienced smaller decline in performance [128].

1.5.3 Physical Activity and White Matter Hyperintensities

In comparison to the large body of studies examining the effects of physical activity on cognition and gait, far fewer studies have examined the relationship between physical activity and WMH. As a result, the association between physical activity and WMH is less well-established. The Northern Manhattan Study (NOMAS), a population-based study in 1,226 stroke-free older individuals assessed the association between physical activity and WMH volume [129]. Physical activity was measured using a self-reported questionnaire of an individual’s duration and frequency of leisure time and recreational activities for the past two weeks at baseline. Neuroimaging data acquisition occurred 6 (± 3) years after the physical activity assessment, and WMH volume was measured using a semi-automated quantitative approach corrected for total intracranial volume, and log-transformed to achieve normal distribution. No significant association between physical activity and WMH volume was detected [129].

Another study, the Lothian Birth Cohort 1936 (LBC1936), examined the association between physical activity and WMH burden and the integrity of the normal-appearing white matter (NAWM; areas not including WMH) in 691 older adults [130]. Physical activity was measured using a 6-point self-reported questionnaire with items ranging from household chores to exercise and competitive sport. WMH was measured using both the semiquantitative Fazekas scale and semi-automated quantitative volumetric approach accounting for intracranial volume. The results of this study show that higher levels of physical activity independently predicted larger NAWM volume and lower WMH burden (volume and grade) [130]. In the final model, after adjusting for social class and disease, only WMH volume remained significant [130].

The conflicting findings from these studies may be a result of the different physical activity measure employed in addition to the WMH methods of assessment. Alternatively, explanations to elucidate the benefits demonstrated in the previous sections
of cognition and gait may highlight the role of physiological mechanism of physical activity.

1.5.4 Physiological Mechanisms Underlying Physical Activity Benefits

The mechanisms underlying physical activity benefits are postulated to occur through central mechanism as well as through the reduction of peripheral risk factors. The central mechanism are facilitated through neurotropic factors, which promotes neurogenesis, central nervous system metabolism and angiogenesis [131-133]. In this regard, physical activity influences the growth, differentiation and maintenance of neurons across the lifespan by up regulating these neurotropic factors. Specific neurotrophins that have been demonstrated in this association include: brain-derived neurotropic factor (BDNF), insulin-like growth factor-1 (IGF-1) and vascular endothelial-derived growth factor (VEGF) [131].

Neurogenesis refers to the production of new neurons in brain regions important for memory, learning and overall performance [134]. Research of animal models has demonstrated that BDNF, which is synthesized and secreted by endothelial cells, is a key mediator for structural and functional plasticity [135, 136]. To support exercise-induced brain plasticity, there is an increase in metabolic demands that subsequently influences angiogenesis, the formation of new blood vessels [131, 137]. More specifically, it is believed that angiogenesis occurs through up regulation of IGF-1 and VEGF on endothelial cell proliferation and vessel growth [131].

In addition, physical activity reduces peripheral risk factors such as; hypertension, hyperglycemia and dyslipidemia [131]. These cardiovascular risk factors denoted as the ‘metabolic syndrome’ have been previously discussed in the “Microvascular Frontal-Subcortical Syndrome of Aging” explaining the phenotypic changes of the cognitive and motor systems [56, 138]. Further, inflammation is a common feature of these conditions and it is also shared in the pathophysiology of WMH [138, 139]. Interestingly, physical activity has been shown to greatly reduce peripheral risk factors and improve overall cardiovascular health [131]. Thus, physical activity represents a modifiable lifestyle
factor with the protective benefits to influence both central mechanism and peripheral risk factors subsequently attenuating the effect of WMH on gait characteristics.

1.6 Overview of Thesis

1.6.1 Study Rationale

The previous section outlines the growing interest in mobility, particularly gait as an early marker of impairment and the role of neurovascular changes in the mobility decline seen in aging. Converging evidence suggests that WMH, an index of vascular burden, are associated with gait decline among older adults [84, 91]. Taken together, modifiable lifestyle strategies such as physical activity, previously demonstrated to improve vascular risk factors burden, may also ameliorate the effect of WMH on gait.

1.6.2 Purpose

The purpose of this thesis was; 1) to systematically review the association between WMH burden and motor outcomes of gait, balance, falls and fractures among older adults from general (absence of neurological disease) and clinical (neurological condition) samples and, 2) to determine whether the association between WMH and gait velocity and stride time variability, under single and dual-task condition, is moderated by physical activity.

1.6.3 Hypotheses

It was hypothesized that; 1) higher WMH burden will be associated with poor gait and balance performance and greater incidence and occurrence of falls and fractures, and 2) the association between WMH and gait characteristics under single and dual-task conditions will be moderated by physical activity, such that higher levels of physical activity will attenuate the effect of WMH on gait.
References


Chapter 2

2 White Matter Abnormalities and Motor Outcomes: A Systematic Review and Meta-Analysis

Brain white matter abnormalities, including white matter hyperintensities (WMH) are a common neuroimaging finding among older individuals [140, 141]. Converging evidence from previous studies suggests that motor performance and adverse motor outcomes including falls and fractures are associated with WMH burden; however, the magnitude of association is less well-established [20, 142, 143]. Noteworthy, because these poor motor outcomes result in serious health and economic burden, identifying the role of WMH burden may point to potentially modifiable factors to reduce falls, mobility disability, and mortality [9, 33, 34, 36, 144, 145].

With the advent of contemporary neuroimaging techniques, studies have demonstrated widespread microstructural alterations in the areas of the normal-appearing white matter (NAWM) that surround these WMH [146]. Specifically, these alterations to the white matter integrity (WMI) quantified using diffusion tensor imaging (DTI) precede the development of WMH and reflect the magnitude of WMH burden [112, 146, 147]. However, the role of WMI in motor outcomes is unknown; and thus, given the continuum of white matter pathology, WMI may be an early marker of future decline in motor outcomes.

Previous systematic reviews have focused solely on WMH, or on a single motor domain, and failed to establish the magnitude of association [84, 91]. Therefore, we conducted a comprehensive systematic review and meta-analysis to assess the associations between white matter abnormalities, both WMH and WMI, and motor outcomes among older adults from general and clinical samples. We included motor performance outcomes of gait, balance, and composite measures, in addition to adverse motor outcomes of falls and fractures.
2.1 Methods

2.1.1 Search Strategy

A comprehensive literature search, without date or language restriction, was conducted using EMBASE, MedLine, and PubMed. The search strategy combined medical subject headings (MeSH) and keywords related to ‘white matter abnormalities’, ‘mobility’, and ‘older adults’. Predefined search terms, syntax, and records yielded are described in Appendix A. Additional records were identified through backwards citation searching from included articles.

2.1.2 Study Eligibility

Studies were included if they met the following criteria: (1) published as an original study examining relationship between white matter changes and motor performance and mobility outcomes of interest, pre-specified below; (2) included a general (absence of neurological disease) or clinical (neurological condition) sample with mean age ≥60; (3) measured white matter changes using either structural MRI (T2-weighted or fluid attenuated inversion recovery [FLAIR]) for WMH or DTI for WMI; and (4) required that assessment and quantification of both white matter changes and motor performance and mobility outcomes were explicitly detailed in methods and/or referenced for validity. Studies using computed tomography were excluded due to lack of sensitivity [148].

All articles identified through database and hand searching were imported into EndNote [149]. Duplicate records were removed and the remaining articles were screened at three levels. One member of the team (NRL) screened the title of remaining articles to identify potentially relevant studies. Two reviewers (NRL and MMO) then independently assessed the abstracts of the articles identified from title screening. The remaining articles were then retrieved and screened on a full-text basis. Any disagreements were resolved by consensus.

For studies with multiple publications, we included articles reporting the most detailed or relevant analysis of variables with the largest dataset. Additionally, articles containing the same study population were included if they presented a different white matter
quantification method, motor outcomes or if they used different sub-samples. This criterion was applied to 6 publications [20, 142, 143, 150-152]. In cases where both cross-sectional and longitudinal data were presented from prospective cohort studies, we included that study in both cross-sectional and longitudinal analyses. The same procedure applied to studies presenting data for both WMH and WMI. Three studies were cross-referenced; 2 studies [153, 154] reported both cross-sectional and longitudinal data, whereas one study reported data on both WMH and WMI [155].

2.1.3 Outcomes Measures

The outcome measures of interest were grouped into four categories: motor-gait related, motor-balance related, motor-composite, and adverse motor outcomes. Motor-gait related outcomes included gait velocity and quantitative gait variables. Motor-balance related outcomes included postural sway and single-leg stand time (SLST). Motor-composite outcomes included Short Physical Performance Battery (SPPB), Timed Up and Go (TUG) Test and Tinetti Performance Oriented Mobility Assessment (POMA). Adverse motor outcomes included falls and fractures, modelled as history of falls and fractures for cross-sectional studies and as falls and fracture incidence for longitudinal studies. All of these measures have previously been associated, separately, with WMH [84, 91].

2.1.4 Data Extraction

From eligible full-text articles we extracted first author, year of publication, country, study design, sample characteristics, sample size at baseline and follow-up, inclusion and exclusion criteria, type of measurement methods of white matter changes and motor performance test, and adverse motor outcomes of interest. We also extracted hazard ratios, odds ratios (OR), relative risk, correlation coefficients (Pearson’s and Spearman), and regression slopes when available to evaluate the strength of the association.

2.1.5 Methodological Quality Assessment

The methodological quality was assessed using the Downs and Black Checklist [156], modified for observational studies [157, 158]. High methodological quality was met when >50% of relevant items on checklist were present [158].
2.1.6 Meta-Analysis

We conducted a random-effects meta-analysis and calculated the weighted mean effect size to determine the magnitude of association between total WMH and gait velocity in individuals in absence of overt neurological conditions. Computation of the weighted mean was based on Pearson’s product-moment correlation coefficient \( r \) as the effect size. Sensitivity analysis was further conducted by sequentially excluding studies quantifying WMH through semi-quantitative methods.

We used the \( I^2 \) statistic as a descriptive measure of variability to denote the proportion of true heterogeneity. This implies that larger proportions of variances (i.e. larger \( I^2 \) values) would reflect more heterogeneity. No Egger test analysis using funnel plot asymmetry was conducted as there were fewer than 10 studies. All analyses were conducted using Comprehensive Meta-Analysis software [159].

2.2 Results

2.2.1 Study Selection

The initial search yielded 1,336 articles. After duplicate removal, 855 records were then screened for eligibility and 769 were excluded based on title and abstract. We retrieved and assessed 85 full-text articles, leaving 46 that met inclusion criteria (see Figure 2.1). To facilitate synthesis of data, we separated the studies method of white matter quantifications, either WMH (Table 2.1 and 2.2) or WMI (Table 2.3). Studies examining WMI were classified based on whether they performed whole brain (voxel-based analysis [VBA] or tract-based spatial statistics [TBSS]), or local analyses (region-of-interest [ROI] or tractography).
Figure 2.1 Flow diagram of study selection.
### Table 2.1 Characteristics of cross-sectional studies examining white matter hyperintensities and motor outcomes

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<th>Measure</th>
<th>Gait</th>
<th>Balance</th>
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### Clinical populations

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*=cross-referenced publications; **=same study cohort; N=sample size; NR=not reported; Vis=visual; Vol=volume; ‡=identified region of interests.

3C, Three-City Study; AGES-RS, Age Gene/Environment Susceptibility- Reykjavik Study; CHS, Cardiovascular Health Study; Health ABC, Healthy Aging and Body Composition Study; J-SHIPP, Japan Shimanami Health Promoting Program; LADIS, LeukoAraiosis And DISability Study; MBS, Mobilize Boston Study; NAME, Nutrition, Aging, and Memory in Elders Study; RUN DMC, Radboud University Nijmegan Diffusion Tensor Cohort Study; Sefuri, Sefuri Brain MRI Study; Sunnybrook, Sunnybrook Dementia Study.

*a=single-leg stance time; b=balance/postural sway; c=Short Physical Performance Battery; d=Timed-Up-And-Go; e=Tinetti Performance Oriented Mobility Assessment; f=falls; g=fracture; h=dual-task.
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<td><strong>Clinical populations</strong></td>
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*=cross-referenced publications; **(1,2)=same study cohort; §=progression of WMH; N=sample size; NR=not reported; Vis=visual; Vol=volume; ‡=identified region of interests.
3C, Three-City Study; CHS, Cardiovascular Health Study; LADIS, Leukoaraisosis And DISability Study; TASCOG, TAsmanian Study of COgnition and Gait; MAS, Sydney Memory Aging Study; OBA, Oregon Brain Aging Study; SAM, Stroke Aging Memory Cohort; WHICAP, Washington Heights Inwood Columbia Aging Project.

a=Short Physical Performance Battery; b= Tinetti Performance Oriented Mobility Assessment; c=fall; d=fracture.
## Table 2.3 Characteristics of cross-sectional studies examining white matter integrity and motor outcomes

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<thead>
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<th>Country</th>
<th>N</th>
<th>Age (years)</th>
<th>Males (%)</th>
<th>Measure</th>
<th>Gait</th>
<th>Balance</th>
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**Clinical populations**

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<th>N</th>
<th>Age (years)</th>
<th>Males (%)</th>
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*=cross-referenced publications; **= same study cohort; N= sample size; NR=not reported; ‡=identified region of interests.

Health ABC, Healthy Aging and Body Composition Study; NAME, Nutrition, Aging, and Memory in Elders Study; Rotterdam, Rotterdam Study; RUN DMC, Radboud University Nijmegen Diffusion Tensor Cohort Study; ROI, region of interest; TBSS, tract-based spatial statistics; VBA, voxel-based analysis.
$^a$balance/postural sway; $^b$Short Physical Performance Battery; $^c$Timed-Up-And-Go; $^d$Tinetti Performance Oriented Mobility Assessment
2.2.2 Study Characteristics

The 46 publications retained for inclusion were all observational in design representing data collected from 32 unique study populations. Sample size ranged from 16 to 2,450, mean age ranged from 63.8 to 85.1 years, and proportion of men ranged from 25.4% to 78.5%. Studies were geographically from Western Europe, North America, Japan, Singapore, and Australia. Clinical samples included Alzheimer’s disease (AD), Mild Cognitive Impairment, Frontal-Gait Disorder, Idiopathic Normal Pressure Hydrocephalus, Parkinson’s Disease (PD) and Ischemic Stroke.

2.2.3 White Matter Hyperintensities and Motor-Gait Related Outcomes

2.2.3.1 Cross-sectional Association

Ten studies (n = 4,464) revealed statistically significant associations between greater WMH burden and slower gait velocity [19, 21, 85, 87, 153, 162, 165, 166, 169, 171]. The reported linear regression coefficients ranged from −0.017 to −0.14, and OR ranged from 1.72 to 6.4. Values denoting impaired or abnormal gait velocity ranged from <1.2 to <0.67 meters/second. In contrast, one study including community-dwellers (n = 76) failed to find significant associations [167]. Sample size was a concern for this study.

Studies assessing WMH and quantitative gait characteristics show mixed results. A population-based study reported in two publications (Cardiovascular Health Study; n = 321 [21] and n = 331 [168]) found significant associations for double-support time and stride length variability but failed to find associations for stride length, stance time variability or step width variability [21, 168]. Conversely, two studies (n = 579) reported significant associations for stride length [87, 166]. Additionally, one of these studies (n = 431) reported significant findings for stride width but not for double-support time, stride length variability, stride time variability or stride width variability [87].
One study examining dual-task cost on cadence, reported a significant decrease in performance in individuals with Alzheimer’s disease and higher WMH when compared to individuals with lower WMH [90].

2.2.3.1.1 Meta-Analysis

The correlation coefficients of 5 studies examining total WMH on gait velocity yielded a highly significant overall effect of $r = -0.29$ (95% CI -0.40, -0.16; $p < 0.01$). Sensitivity analysis revealed that omitting studies on the basis of WMH quantification, either semi-quantitative or quantitative, did not have an effect on association. See Figures 2.2 and 2.3.

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Figure 2.2 Forest plot for association between white matter hyperintensities and gait velocity.
Figure 2.3 Forest plot of sensitivity analysis for association between white matter hyperintensities and gait velocity.
2.2.3.2 Longitudinal Association

Four studies included community-dwelling older adults demonstrated significant associations between greater magnitude of baseline WMH and change in gait velocity ($n = 2,450$, follow-up = 4 years [116], $n = 1,702$, follow-up = 8 years [153], $n = 67$, follow-up = 4 years [182], and $n = 104$, follow-up = 9.1 years [183]). In contrast, a population-based study did not find significant results for transition from normal to abnormal gait velocity ($n = 701$, follow-up = 4.7 years) [184]. Moreover, two studies showed that the progression of WMH volume was associated with change in gait velocity ($n = 225$, follow-up = 2.5 years [179] and $n = 77$, follow-up = 4 years [182]).

Aside from gait velocity, a population-based study (Tasmanian Study of Cognition and Gait; $n = 225$, follow-up = 30.6 months) revealed that WMH progression was associated with change in step length but not step width [179].

2.2.4 White Matter Hyperintensities and Motor-Balance Related Outcomes

2.2.4.1 Cross-sectional Association

Three studies from four publications ($n = 836$) quantified balance outcomes using the SLST test. Two studies ($n = 673$) reported significant associations for higher WMH burden and shorter stance times [19, 162]. In particular, a prospective cohort study (Leukoaraiosis and Disability Study [LADIS]; $n = 639$) in community-dwelling older adults reported that when compared to mild WMH, severe WMH was independently associated with increased risk of SLST <15 seconds (OR = 2.05; 95% CI = 1.30–3.25) [19]. The remaining two studies showed significant associations for regional WMH burden and shorter SLST test [160, 175].

Five studies ($n = 2,290$) quantified balance outcomes using measures of postural sway [154, 167, 172, 174, 175]. Significant associations for greater WMH burden and increased postural sway (decreased postural stability) were found in a MCI sample ($n = 560$ [174]) and in a study of community-dwelling older adults ($n = 1,387$ [172]).
remaining three studies identified significant regional WMH burden in association for decreased postural sway [154, 167, 175].

2.2.5 White Matter Hyperintensities and Motor-Composite Outcomes

2.2.5.1 Cross-sectional Association

Three studies from 4 publications (n = 772) examined WMH on SPPB outcomes [19, 162, 164, 165]. Significant associations were found in two studies (n = 738) of community-dwelling older adults [19, 165]. The reported OR ranged from 1.75 to 2.29 after adjusting for relevant covariates. In contrast, a study comprised a healthy older adult sample (n = 34) found no association for greater WMH burden and SPPB score [162]. Sample size may have contributed to lack of significant findings. The remaining study examined regional WMH burden and SPPB outcomes [164].

Three studies (n = 795) investigated WMH on TUG scores [87, 163, 175]. A prospective cohort study (Radboud University Nijmegen Diffusion Tensor and MRI Cohort Study [RUN-DMC]; n = 431) detected that those with severe WMH volume (i.e., fifth quintile [20.6–139.7 mL]) were four times more likely to have an abnormal TUG score >12 after adjusting for relevant covariates (OR = 4.4; 95% CI = 1.2-15.8) [87]. No association was found for TUG number of steps [87]. The other two studies found regional WMH correlated with longer TUG time [163, 175]. Another study, examining dual-tasking using the TUG did not report significant associations for higher WMH and TUG under dual-task condition, however, regional areas were identified in association for TUG (single-task) alone [163].

Four studies (n = 757) looked at WMH on total Tinetti scores [87, 155, 161, 165]. Significant associations between higher WMH and lower Tinetti scores were reported in three studies (n = 326) of community-dwelling older individuals [155, 161, 165]. A prospective cohort study reported that for each 1% increase in WMH, individuals were almost two times more likely to have a Tinetti score ≤24 (OR = 1.98; 95% CI = 1.17–3.38) [165]. Significant association was not found in a previously mentioned prospective
cohort study for Tinetti scores after adjusting for lacunar infarcts (RUN-DMC; n = 431) [87].

2.2.5.2 Longitudinal Association

Two studies (n = 706) examined WMH and motor-composite SPPB outcomes [178, 182]. Significant association was found in a study of community-dwelling older individuals between greater WMH burden at baseline and decline in SPPB score (LADIS; n = 639, follow-up = 3 years) [178]. In contrast, another study of community-dwelling older individuals failed to find statistically significant associations with baseline WMH and WMH progression and change in SPPB score (n = 67, follow-up = 4 years) [182].

One study evaluating WMH and motor-composite Tinetti outcomes reported that the progression of WMH volume was significantly associated with >4 point change on the Tinetti score (n = 70, follow-up = 4 years) [177].

2.2.6 White Matter Hyperintensities and Adverse Motor Outcomes

2.2.6.1 Cross-sectional Association

Two studies (n = 802) examined WMH and falls, retrospectively [160, 175]. Significant associations were reported for higher regional WMH burden and falls from the year prior [160, 175].

One study investigating adverse events of fractures found WMH to be significantly higher in those with traumatic hip-fractures compared with age-matched controls (n = 81) [170]. Regional correlates of WMH differentiating groups were also identified.

2.2.6.2 Longitudinal Associations

Four studies evaluated WMH and fall incidence [154, 176, 180, 181]. Two population-based studies reported in one publication revealed significant association for greater magnitude of baseline WMH and falls (n = 655, follow-up = 1 year) [181]. Furthermore, in one of the aforementioned population-based study a significant associations was detected for WMH progression and greater risk for multiple falls after controlling for
relevant covariates ($n = 187$, follow-up = 2.5 years [180]). Contrary to the previous studies, one failed to report significant association ($n = 54$, follow-up = range 8-10 years) [176]. The remaining study examined baseline regional WMH and falls during a one year follow-up period [154].

An ischemic stroke cohort found that when comparing patients with none-to-mild WMH to those with severe WMH there was an increased risk for hip fractures ($n = 383$, follow-up = 12 years) [185].

2.2.7 White Matter Integrity and Motor-Gait Related Outcomes

2.2.7.1 Cross-sectional Associations

Four studies from five publications assessed WMI and gait velocity [188-191, 193]. A whole brain prospective cohort study (RUN-DMC; $n = 485$) examining the integrity of WMH and the normal-appearing white matter (NAWM) separately, reported significant associations between poor WMI of WMH and the NAWM and slower gait velocity [191]. In contrast, a tractography-based region-of-interest analyses study ($n = 30$) did not find significant associations between microstructural integrity and gait velocity in individuals with two types of parkinsonism or an age-matched control group [193]. The remaining three studies including two employing a ROI approach ($n = 429$ [190] and $n = 16$ [188]) and one using TBSS ($n = 85$ [189]) investigated poor regional WMI and gait velocity.

Aside from gait velocity, three studies from four publications evaluated WMI and quantitative gait characteristics [186, 190, 191, 194]. A cohort study ($n = 484$) using a voxel-wise approach found significant association for integrity between both WMH and the NAWM and cadence and stride width whereas no association was found for stride time variability [191]. Moreover, stride length, double-support percentage, and stride time variability was reported in association for microstructural integrity of WMH but not for areas of the NAWM [191]. Regional correlates were identified for stride length [190], stride width [186, 190, 193] and cadence [190].
2.2.8 White Matter Integrity and Motor-Balance Related Outcomes

2.2.8.1 Cross-sectional Association

Two publications using TBSS and the same study cohort examined WMI and varying measures of postural sway [186, 187]. A significant association was reported between lower WMI and poor postural sway \((n = 25)\) [186]. Upon further investigation, neuroanatomical locations of WMI and poor balance outcomes were also identified [186, 187].

2.2.9 White Matter Integrity and Motor-Composite Outcomes

2.2.9.1 Cross-sectional Associations

One study \((n = 85)\) using TBSS evaluated WMI and SPPB outcomes [189]. Significant findings between poor WMI in the cerebral peduncles were reported in association for lower SPPB score.

Another three studies assessed WMI and TUG scores [191, 194, 195]. A whole brain voxel-wise cohort study reported significant associations between WMI of both WMH and the NAMW and longer TUG completion time (RUN-DMC; \(n = 484\)) [191]. Additionally, a ROI analyses study \((n = 38)\) detected significant associations for poor regional microstructural integrity and TUG completion time in individuals with INPH and PD [195]. In contrast, a whole brain voxel-wise study \((n = 60)\) failed to find significant association between poor WMI and TUG completion time in individuals with INPH, however, significant associations were found for TUG number of steps [194]. Regional correlates of poor WMI in association for TUG number of steps were identified.

Three studies examined WMI and Tinetti outcomes [155, 191, 192]. A voxel-wise approach study \((n = 484)\) reported significant association between poor WMI of WMH and poor Tinetti outcomes but not for WMI of the NAWM [191]. The other two studies including a ROI approach study \((n = 173 [155])\) and a tractography-based ROI study \((n = 65 [192])\) detected significant association between poor WMI in the corpus callosum and poor Tinetti performance.
2.2.10 White Matter Integrity and Adverse Motor Outcomes

No studies evaluated the association between WMI and adverse motor outcomes.

2.3 Discussion

Our systematic review confirmed previous evidence that WMH burden is associated with poor motor performance in gait, balance, composite, and adverse motor outcomes among older adults. We extended this association to clinical samples, established longitudinal associations of WMH progression on motor outcomes and provided quantitative synthesis demonstrating a significant pooled-effect between higher WMH burden and slow gait velocity. More importantly, our results also indicate that microstructural changes to the WMI are associated with poor performance in motor-gait related and motor composite outcomes.

To the authors’ knowledge, this is the first systematic review to provide a comprehensive evaluation of white matter abnormalities suggesting that microstructural alterations that predate the onset of WMH may have a pathological effect on motor performance. There were a large number of studies captured through the database search; however, we only identified a small number of studies examining white matter integrity and motor performance. The studies retrieved did not represent of our predefined outcomes of interest; one study from 2 publications evaluated motor-balance related outcomes and notably, no studies assessed adverse motor outcomes of falls or fractures. Furthermore, all studies investigating WMI were cross-sectional in design impeding our ability to dissociate the causal and temporal course of association.

Previous studies have demonstrated that WMH are associated with an increased risk of stroke, dementia, and death in addition to executive function deficits [88, 114]. Here, we not only confirm the association of WMH on motor outcomes, but we also show compelling evidence of subtle alterations to the white matter microstructure in this association. This is of particular importance for two reasons; firstly, cognitive and motor outcomes are postulated to be interrelated entities, with motor outcomes often preceding the onset of clinically significant cognitive outcomes progressing to neurodegenerative
conditions and dementia syndromes [8, 32, 196]; and secondly, because changes to the white matter microstructure precedes the onset of visible WMH [112, 146, 147]. Taken together, it is plausible to postulate that there is a continuum from disruption in WMI to WMH burden found in the association with age-related motor decline and neurodegeneration. This evidence suggests that white matter abnormalities, as a potential modifiable risk factor, can be a target of early interventions aimed at attenuating physical decline. Future studies are needed to test this hypothesis in light of a few methodological considerations.

Studies employing the use of diffusion-tensor imaging, specifically TBSS and tractography approaches capable of solving voxel and spatial alignment issues, were limited. Two studies from three publications examined diffusion parameters aside from fractional anisotropy to characterize white matter tissue microstructure [189-191]. Moreover, only one study evaluated the microstructural properties of the NAMW and WMH, separately, in association to motor performance [191]. In order to elucidate patterns in white matter alterations leading to physical consequences, these shortcomings need to be addressed.

Anatomical regional correlates of white matter abnormalities in relation to motor outcomes were assessed across a large number of studies. Due to considerable heterogeneity in imaging standards and analysis between studies, no clear patterns of association emerged. Typically, issues of inconsistent terminology and method of classification were common and precluded our ability to synthesize regional correlates.

While the evidence summarized in our review examines structural brain changes, we postulate that patterns in motor performance may also be a result of compensatory strategies of increased activation [197, 198]. Such brain activations are facilitated through the use of functional neuroimaging methods. A recent systematic review examining brain activity during walking found that with aging and in various clinical populations, there were various compensatory mechanisms that aided stable walking [199]. This may explain why clinical symptoms and consequences of white matter abnormalities affect individuals heterogeneously.
2.3.1 Study Highlights and Limitations

Although our study consisted of a comprehensive search strategy examining both visible and subtle white matter changes across healthy and clinical populations, there are several limitations that must be recognized. Firstly, lack of reporting consistency in non-significant results across studies meant that most outcomes could not be meta-analyzed subjecting our review to reporting bias. Secondly, in instances where studies were meta-analyzed the methodologies of different variables varied considerably (e.g., MRI resolution, contrast). Lastly, our stringent definition of motor performance-based outcomes led to the exclusion and underrepresentation of most studies comprising of PD cohorts.

2.4 Conclusion

In conclusion, our research synthesis provides evidence that WMH burden is associated with poor motor performance and adverse motor outcomes, cross-sectionally and longitudinally, in general and clinical samples. Emerging evidence synthesized also supports that early white matter changes, evaluated as WMI, may have a pathological burden on motor performance. Future studies employing DTI techniques are required to understand the role of WMI on motor-balance and adverse motor outcomes, in addition to deciphering the longitudinal association of microstructural changes.
References


47. Doi, T., et al., *Effects of white matter lesions on trunk stability during dual-task walking among older adults with mild cognitive impairment.* Age (Dordr), 2015. 37(6): p. 120.


Chapter 3

3 Moderating Effect of Physical Activity on White Matter Hyperintensities and Quantitative Gait Characteristics

Mobility impairment as manifested by changes in gait characteristics are common in older individuals [1, 2]. These changes have a significant impact on an individual’s functional independence and overall quality of life [1]. Converging evidence highlights the underlying role of white matter hyperintensities (WMH) in association for changes in gait characteristics (see Chapter 2 for review) [3-5]. Although the pathophysiology of WMH is complex, it is postulated that they are associated with cardiovascular risk factors [6]. Therefore, strategies aimed at improving these risk factors may also attenuate the effect of WMH burden on gait characteristics.

Physical activity is a modifiable lifestyle factor with the protective ability to influence brain, cardiovascular and physical functioning [7-9]. Few studies to date have examined the role of physical activity on the association between WMH and gait outcomes [10]. The purpose of this study was to 1) examine the independent association between WMH and gait velocity and stride time variability under single and dual-task conditions in a geriatric clinic sample, and 2) to examine if this relationship is moderated by physical activity.

3.1 Methods

3.1.1 Study Participants

The Gait and Brain Study is an ongoing prospective cohort study initiated to determine whether quantitative gait characteristics can predict cognitive and mobility decline, and progression to dementia among community-dwelling older adults. Recruitment was carried out through geriatric clinics in London, Ontario, which increased the probability of enrolling participants with cognitive impairments. This study comprised a subsample
of cohort members who participated in neuroimaging data collection. Study design and logistics have been detailed in previous publications [11-13]. Additional information can be found at clinicaltrial.gov under study identifier NTC03020381.

After written informed consent was obtained, participants underwent a comprehensive baseline assessment and returned on a biannual basis for follow-up over 3 years and annually for a subsequent 7 years, reaching a total of 10 years of follow-up.

To be included in this analysis, participants needed to complete a neuroimaging session at one of three time-points of during follow-up. Participants were community-living meeting the following inclusion criteria: (1) aged 65 years and older; (2) English speaking; (3) able to ambulate 10 meters independently without the use of a walking aid. Exclusion criteria were: (1) parkinsonism or other neurological condition with residual motor deficit; (2) musculoskeletal disorder affecting lower limbs; (3) use of psychotropic medications (i.e., neuroleptics and/or benzodiazepines); and (4) major depression disorder.

The Gait and Brain Study protocol was approved from the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (see Appendix B). Data collection occurred between December 2012 and May 2017.

3.1.2 Assessment of Clinical and Cognitive Functions

Participants were interviewed on sociodemographic characteristics, comorbidities (i.e., diabetes, hypertension, angina, myocardial infarction, stroke, Parkinson’s disease, chronic lung disease, depression), medications and history of falls. Basic and instrumental activities of daily living were evaluated using the Lawton-Brody Scale [14]. Physical and neurological examination in all participants was carried out by the study clinician.

Global cognitive functioning was assessed using the Mini-Mental State Examination (MMSE) [15] and the Montreal Cognitive Assessment (MoCA) [16]. A comprehensive neuropsychological battery was also administered to assess specific cognitive domains;
executive functions – Trail Making Test (TMT) A and B [17]; verbal episodic memory – Rey Auditory Verbal Learning Test (RAVLT) [18]; attention – Digit Span Test (forward and backward) and attention and working memory – Letter Number Sequence (LNS) [19].

3.1.3 Assessment of Gait

Gait under single and dual-task conditions was assessed using a computerized walkway (GAITRite© Systems, 600 cm long and 65 cm wide; CIR Systems, Havertown, PA USA). Start and end points were marked 1 meter from either end of the walkway to avoid recording acceleration and deceleration phases. For single-task gait testing, participants were asked to ambulate at their “normal pace” wearing comfortable footwear in a well-lit, quiet room. For dual-task gait testing, participants were asked to complete the following cognitive task aloud: (1) counting backwards by one; (2) counting backwards by seven (serial seven); and (3) naming animals. One trial was performed of each dual-task conditions in order to balance and minimize the effects of learning and fatigue.

3.1.4 Assessment of Physical Activity

Physical activity was measured using the Physical Activity Scale for the Elderly (PASE). The PASE is a valid and reliable self-reported measure of physical activity among older adult [20, 21]. It comprises of 10-items examining domains of walking, sport and recreational activities, leisure time activities, housework, and work-related activity during the previous one-week period. The PASE also includes an item assessing sitting activities such as reading, watching TV or doing handcrafts, but it was excluded as it does not reflect physical activity. Total PASE score is calculated by assigning a specific weight for each item based on time spent in each activity (hours per week) or general participant (i.e., yes or no). Higher scores indicate higher levels of physical activity.
3.1.5 Neuroimaging Data Acquisition

Imaging of the brain was performed at Robarts Research Institute Centre for Functional and Metabolic Imaging using a 3.0-T MRI scanner (Siemens, Erlangen, Germany). High resolution images were collected using a standard protocol including 3D T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) sagittal images (acquisition matrix = 256 x 240 x 160, FOV = 240 mm x 256 mm x 192 mm, TR = 2.3 s, TE = 2.91 ms, T1 = 900 ms, flip angle = 9°, average = 1), fluid-attenuated inversion recovery (FLAIR) coronal images (acquisition matrix = 256 x 232, reconstruction to 512 x 464 matrix, FOV = 220 mm x 200 mm, thickness = 4 mm, gap = 0.5 mm, 41 slices, TR 8 s, TE = 120 ms, T1 = 2400 ms, flip angle = 130°, averages = 1).

3.1.6 Neuroimaging Data Processing

White matter hyperintensities were segmented automatically using the lesion growth algorithm [22] as implemented in the Lesion Segmentation Tool (LST) toolbox version 1.2.3 (www.statistical-modelling.de/lst.html) for Statistical Parametric Mapping Version 8 (SPM 8). First, T1 images are segmented into three main tissue classes (cerebrospinal spinal fluid, grey matter and white matter). These tissue classes are then combined with the co-registered FLAIR images to calculate lesion belief maps. Next, through thresholding these lesion belief maps (threshold $\kappa = 0.3$) a binary lesion map is obtained, which is subsequently grown along the voxels that appear as hyperintensities within the FLAIR images resulting in a lesion probability maps. See Appendix C for the flow diagram of the lesion segmentation algorithm.

As intracranial volume (ICV) is an important covariate for volumetric analyses of the brain, estimated ICV was determined using the FreeSurfer software, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). Briefly, FreeSurfer determines ICV from T1 images using an atlas scaling factor derived from registering images to an average template through a full affine transformation (12-parameter) [23]. WMH volume used in the present study was the adjusted volume by ICV, calculated as a percentage [24].
3.1.7 Outcome Measures

Quantitative gait characteristics of gait velocity and stride time variability under single and dual-task conditions (counting, serial seven and naming animals) were the main outcomes of interest. These outcome measures were all modelled as continuous variables.

3.1.8 Predictor Measures

Volumetric measure of WMH burden was the main predictor, as previous studies have demonstrated a relationship with gait outcomes (see Chapter 2 for review). WMH burden was modeled as a continuous and was calculated as a percentage of intracranial volume.

3.1.9 Covariates

Analyses were adjusted for age, sex, cognitive functioning as assessed by the MoCA and vascular risk factors. Vascular burden was attained using a vascular risk factor index comprising of seven items including hypertension, dyslipidemia, diabetes mellitus, history of coronary artery disease, stroke, chronic heart failure and atrial fibrillation. These covariates were determine a priori based on the known influence on physical activity and WMH burden.

3.1.10 Statistical Analysis

Demographic characteristics and scores from gait and cognitive testing were summarized using either means and standard deviations or frequencies and percentage, as appropriate. Participants were stratified according to tertiles using a rank cases approach based on levels of global cognitive functions (MoCA), executive functions (TMT B) and physical activity (PASE) in efforts to better characterize our study sample. Comparisons across stratified groups for continuous outcomes were made using analysis of variance (ANOVA), and where unequal variance was detected, Welch’s Test. Chi-square tests were used for categorical measures. A series of linear regression models were constructed to examine the association between WMH burden and gait velocity and stride time variability under single and dual-task conditions. Because the distribution of WMH
volume and stride time variability was skewed, it was log transformed to normalize distribution. See Appendix D for transformations of non-normally distributed variables.

Moderation analysis examining the interaction between WMH and physical activity was conducted using the PROCESS SPSS Macros version 2.16.3 (Model 1), based on the ordinary least squares analytic framework [25]. WMH volume was entered into the model as a predictor variable and physical activity was entered as the moderator variable. Variables were mean centered prior to model entry. Participant age, sex and MoCA scores were entered as covariates. To test for significant differences in the effect of physical activity on the criterion variables at ±1 SD and mean, a conditional simple slopes analysis was utilized. To further examine the interactions, the Johnson-Neyman technique was used to examine how the relationship between WMH and gait changed across the continuum of physical activity [26].

Statistical significance was set at $p \leq 0.05$ (two-sided). All analyses were conducted using SPSS, version 24 (IBM Corporation, Chicago, IL USA).

3.2 Results

3.2.1 Participant Characteristics

Fifty-nine participants (mean age = 74.24 years ± 5.53; 40.7% women) with MRI were included in this analysis. Briefly, mean MoCA score was 23.58 ± 3.74 (range = 12–30), WMH volume was 34.44 ± 26.2 mL (range = 4.9–110.32 mL) and PASE score was 94.18 ± 41.57 (range = 27.53–205.34). Detailed characteristics of study sample, stratified by global cognitive functioning, executive functioning and physical activity are presented in Table 3.1, 3.2 and 3.3, respectively.

One-way ANOVA comparing participants across MoCA and TMT B stratum indicated that participants across the tertiles differed in MMSE, MoCA, TMT A and B, digit span backwards, RAVLT, LNS, single-task gait velocity, dual-task counting and naming animals gait velocity ($p < 0.05$). Strata of TMT B scores also indicated that participants
across the tertiles differed in age, WMH volume, dual-task serial seven gait velocity, and dual-task counting gait stride time variability ($p < 0.05$). In addition, comparing participants across PASE strata indicated that the tertiles differed in presence of hypertension, vascular risk factors and physical activity scores ($p < 0.05$).
Table 3.1 Baseline characteristics of participants stratified according to tertiles of Montreal Cognitive Assessment scores (n = 59)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full Cohort (n = 59)</th>
<th>Low (n = 18)</th>
<th>Moderate (n = 20)</th>
<th>High (n = 21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>74.24 (5.53)</td>
<td>76.06 (5.72)</td>
<td>74.55 (5.59)</td>
<td>72.38 (4.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>24 (40.7)</td>
<td>6 (33.3)</td>
<td>12 (60)</td>
<td>6 (28.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Education, mean (SD), years</td>
<td>13.75 (2.78)</td>
<td>13.33 (2.68)</td>
<td>13.15 (2.25)</td>
<td>14.67 (3.18)</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>26.91 (4.46)</td>
<td>25.14 (3.93)</td>
<td>27.59 (4.54)</td>
<td>27.79 (4.57)</td>
<td>0.13</td>
</tr>
<tr>
<td>No. of Medications, mean (SD)</td>
<td>7.49 (4.68)</td>
<td>7.78 (4.87)</td>
<td>9 (5.24)</td>
<td>5.81 (3.47)</td>
<td>0.09</td>
</tr>
<tr>
<td>No. of Comorbidities, mean (SD)</td>
<td>5.56 (2.64)</td>
<td>5.83 (2.12)</td>
<td>5.1 (3.16)</td>
<td>5.76 (2.57)</td>
<td>0.64</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (45.8)</td>
<td>8 (44.4)</td>
<td>10 (50)</td>
<td>9 (42.9)</td>
<td>0.89</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (45.8)</td>
<td>9 (50)</td>
<td>8 (40)</td>
<td>10 (47.6)</td>
<td>0.81</td>
</tr>
<tr>
<td>Smoking</td>
<td>28 (47.5)</td>
<td>9 (50)</td>
<td>8 (40)</td>
<td>11 (52.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>21 (35.6)</td>
<td>6 (33.3)</td>
<td>10 (50)</td>
<td>5 (23.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>27.53 (2.52)</td>
<td>25.5 (3.07)</td>
<td>27.85 (1.76)</td>
<td>28.95 (1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MoCA, mean (SD)</td>
<td>23.58 (3.74)</td>
<td>19.28 (2.49)</td>
<td>23.45 (1.05)</td>
<td>27.38 (1.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VRF index, mean (SD)</td>
<td>1.36 (1.17)</td>
<td>1.33 (1.1)</td>
<td>1.5 (1.36)</td>
<td>1.24 (1.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>BP Systolic, mean (SD), mmHg</td>
<td>128.51 (13.16)</td>
<td>124.61 (13.92)</td>
<td>130.6 (12.89)</td>
<td>129.86 (12.65)</td>
<td>0.32</td>
</tr>
<tr>
<td>BP Diastolic, mean (SD), mmHg</td>
<td>74.68 (11.37)</td>
<td>71.22 (8.68)</td>
<td>76.6 (14.25)</td>
<td>75.81 (10.10)</td>
<td>0.3</td>
</tr>
<tr>
<td>PASE, mean (SD)</td>
<td>94.18 (41.57)</td>
<td>91.16 (42.04)</td>
<td>87.18 (47.21)</td>
<td>103.45 (35.29)</td>
<td>0.43</td>
</tr>
<tr>
<td>WMH, mean (SD), mL</td>
<td>36.44 (26.2)</td>
<td>44.99 (28.1)</td>
<td>34.69 (23.5)</td>
<td>30.78 (26.32)</td>
<td>0.23</td>
</tr>
<tr>
<td>Cognition, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A, seconds</td>
<td>44.81 (18.38)</td>
<td>56.61 (21.73)</td>
<td>43.62 (15.15)</td>
<td>35.83 (12.18)</td>
<td>0.004</td>
</tr>
<tr>
<td>TMT B, seconds</td>
<td>142.94 (176.06)</td>
<td>260.05 (286.57)</td>
<td>101.37 (43.92)</td>
<td>82.14 (17.44)</td>
<td>0.02</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>10.58 (2.47)</td>
<td>10.28 (2.19)</td>
<td>10.6 (2.93)</td>
<td>10.81 (2.32)</td>
<td>0.8</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>6.22 (2.36)</td>
<td>5.17 (1.98)</td>
<td>5.7 (2.27)</td>
<td>7.62 (2.13)</td>
<td>0.002</td>
</tr>
<tr>
<td>RAVLT</td>
<td>5.67 (3.52)</td>
<td>4.41 (2.9)</td>
<td>4.35 (3.27)</td>
<td>7.95 (3.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LNS</td>
<td>7.92 (3.14)</td>
<td>6.28 (3.08)</td>
<td>7.75 (3.04)</td>
<td>9.48 (2.58)</td>
<td>0.005</td>
</tr>
<tr>
<td>Gait, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait Velocity, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-task</td>
<td>109.64 (20.28)</td>
<td>99.62 (19.29)</td>
<td>105.61 (17.67)</td>
<td>122.07 (17.64)</td>
<td>0.001</td>
</tr>
<tr>
<td>Test</td>
<td>Single-task</td>
<td>Counting</td>
<td>Serial Sevens</td>
<td>Naming Animals</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>----------</td>
<td>---------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Counting</td>
<td>103.86 (24.64)</td>
<td>90.9 (23.01)</td>
<td>100.13 (21.79)</td>
<td>118.53 (21.66)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Serial Sevens</td>
<td>92.56 (27.1)</td>
<td>84.48 (29.17)^c</td>
<td>87.83 (19.03)</td>
<td>103.61 (29.36)</td>
<td>0.06</td>
</tr>
<tr>
<td>Naming Animals</td>
<td>94.3 (26.62)</td>
<td>84.15 (26.49)</td>
<td>89.43 (21.99)</td>
<td>107.63 (26.39)</td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>

**Stride Time Variability, CoV, %**

<table>
<thead>
<tr>
<th>Test</th>
<th>Single-task</th>
<th>Counting</th>
<th>Serial Sevens</th>
<th>Naming Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-task</td>
<td>2.23 (0.83)</td>
<td>2.32 (0.47)^d</td>
<td>2.38 (1.01)^#</td>
<td>2 (0.84)^#</td>
</tr>
<tr>
<td>Counting</td>
<td>2.97 (1.78)</td>
<td>3.54 (1.77)</td>
<td>3.07 (1.53)</td>
<td>2.39 (1.91)</td>
</tr>
<tr>
<td>Serial Sevens</td>
<td>4.65 (4.45)</td>
<td>6.73 (6.67)^c</td>
<td>3.77 (1.9)</td>
<td>3.81 (3.48)</td>
</tr>
<tr>
<td>Naming Animals</td>
<td>3.4 (1.76)</td>
<td>3.84 (1.96)^c</td>
<td>3.35 (1.94)^f</td>
<td>3.05 (1.37)^g</td>
</tr>
</tbody>
</table>

Note: Statistically significant associations are presented in bold-type font.


^a, Low MoCA scores denotes poor performance in global cognitive functioning.

^b, PASE score excluding items 1 and 10.

^c, Final score is number of words remember out of a list of 15 in trial 6 (delayed recall).

^d, Data available for n = 16.

^e, Data available for n = 17.

^f, Data available for n = 18.

^g, Data available for n = 19.

^h, p-values reported from Welch’s Test for unequal variance.
Table 3.2 Baseline characteristics of participants stratified according to tertiles of Trail Making Test B scores (n = 59)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full Cohort (n = 59)</th>
<th>Low (n = 20)</th>
<th>Moderate (n = 20)</th>
<th>High (n = 19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>74.24 (5.53)</td>
<td>76.75 (5.78)</td>
<td>73.4 (5.34)</td>
<td>72.47 (4.71)</td>
<td>0.04</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>24 (40.7)</td>
<td>8 (40)</td>
<td>6 (30)</td>
<td>10 (52.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>Education, mean (SD), years</td>
<td>13.75 (2.78)</td>
<td>13.55 (2.63)</td>
<td>13.55 (3.05)</td>
<td>14.16 (2.75)</td>
<td>0.74</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>26.91 (4.46)</td>
<td>26.52 (4.2)</td>
<td>27.39 (4.65)</td>
<td>26.82 (4.72)</td>
<td>0.83</td>
</tr>
<tr>
<td>No. of Medications, mean (SD)</td>
<td>7.49 (4.68)</td>
<td>9.5 (4.99)</td>
<td>6.5 (5.42)</td>
<td>6.42 (2.57)</td>
<td>0.06</td>
</tr>
<tr>
<td>No. of Comorbidities, mean (SD)</td>
<td>5.56 (2.64)</td>
<td>5.7 (3.06)</td>
<td>5.65 (2.16)</td>
<td>5.32 (2.75)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>27 (45.8)</td>
<td>9 (45)</td>
<td>7 (35)</td>
<td>11 (57.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>27 (45.8)</td>
<td>8 (40)</td>
<td>7 (35)</td>
<td>12 (63.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>28 (47.5)</td>
<td>8 (40)</td>
<td>12 (60)</td>
<td>8 (42.1)</td>
<td>0.38</td>
</tr>
<tr>
<td>Osteoarthritis, n (%)</td>
<td>21 (35.6)</td>
<td>11 (55)</td>
<td>5 (25)</td>
<td>5 (26.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>27.53 (2.52)</td>
<td>25.95 (3.17)</td>
<td>27.95 (1.85)</td>
<td>28.74 (1.33)</td>
<td>0.004*</td>
</tr>
<tr>
<td>MoCA, mean (SD)</td>
<td>23.58 (3.74)</td>
<td>20.65 (3.63)</td>
<td>24.9 (3.14)</td>
<td>25.26 (2.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VRF Index, mean (SD)</td>
<td>1.36 (1.17)</td>
<td>1.2 (1.11)</td>
<td>1.3 (1.45)</td>
<td>1.58 (0.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>BP Systolic, mean (SD), mmHg</td>
<td>128.51 (13.16)</td>
<td>124.85 (12.08)</td>
<td>131.85 (13.29)</td>
<td>128.84 (13.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>BP Diastolic, mean (SD), mmHg</td>
<td>74.68 (11.37)</td>
<td>70.6 (8.36)</td>
<td>77.35 (12.84)</td>
<td>76.16 (11.84)</td>
<td>0.14</td>
</tr>
<tr>
<td>PASE, mean (SD)</td>
<td>94.18 (41.57)</td>
<td>89.58 (36.4)</td>
<td>100.07 (42.5)</td>
<td>92.83 (46.91)</td>
<td>0.72</td>
</tr>
<tr>
<td>WMH, mean (SD), mL</td>
<td>36.44 (26.2)</td>
<td>47.63 (28.27)</td>
<td>38.79 (28.3)</td>
<td>22.18 (12.76)</td>
<td>0.001*</td>
</tr>
<tr>
<td>TMT A, seconds</td>
<td>44.81 (18.38)</td>
<td>58.05 (22.51)</td>
<td>40.61 (9.6)</td>
<td>35.29 (12.08)</td>
<td>0.002*</td>
</tr>
<tr>
<td>TMT B, seconds</td>
<td>142.94 (176.06)</td>
<td>263.01 (266.69)</td>
<td>94.42 (8.11)</td>
<td>67.61 (10.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>10.58 (2.47)</td>
<td>9.9 (2.34)</td>
<td>11.1 (2.51)</td>
<td>10.74 (2.54)</td>
<td>0.3</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>6.22 (2.36)</td>
<td>4.9 (1.71)</td>
<td>6.25 (2.12)</td>
<td>7.58 (2.48)</td>
<td>0.001</td>
</tr>
<tr>
<td>RAVLT*</td>
<td>5.67 (3.52)</td>
<td>3.63 (2.69)</td>
<td>6.5 (2.98)</td>
<td>6.84 (4)</td>
<td>0.006</td>
</tr>
<tr>
<td>LNS</td>
<td>7.92 (3.14)</td>
<td>5.55 (2.68)</td>
<td>8.7 (2.99)</td>
<td>9.58 (2.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gait, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait Velocity, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-task</td>
<td>109.64 (20.28)</td>
<td>95.9 (19.23)</td>
<td>119.23 (17.55)</td>
<td>114.02 (16.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Counting</td>
<td>103.86 (24.64)</td>
<td>85.81 (21.24)</td>
<td>114.34 (19.43)</td>
<td>111.84 (23.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serial Sevens</td>
<td>92.56 (27.1)</td>
<td>77.9 (24.71)</td>
<td>100.70 (23.41)</td>
<td>98.67 (28.22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Naming Animals</td>
<td>94.3 (26.62)</td>
<td>77.91 (22.92)</td>
<td>102.18 (24.58)</td>
<td>103.26 (25.28)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Stride time variability, CoV, %
<table>
<thead>
<tr>
<th>Task</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-task</td>
<td>2.23 (0.83)</td>
<td>2.34 (0.63)</td>
<td>2.14 (0.79)</td>
<td>2.21 (1.04)</td>
<td>0.76</td>
</tr>
<tr>
<td>Counting</td>
<td>2.97 (1.78)</td>
<td>3.78 (1.73)</td>
<td>2.69 (1.36)</td>
<td>2.43 (1.99)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Serial Sevens</td>
<td>4.65 (4.45)</td>
<td>6.44 (6.32)</td>
<td>3.16 (2.28)</td>
<td>4.44 (3.36)</td>
<td>0.08</td>
</tr>
<tr>
<td>Naming Animals</td>
<td>3.4 (1.76)</td>
<td>3.57 (2.07)</td>
<td>3.37 (1.66)</td>
<td>3.26 (1.6)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Note: Statistically significant associations are presented in bold-type font.


a, Low TMT B scores denotes poor performance in executive functioning.
b, PASE score excluding items 1 and 10.
c, Final score is number of words remember out of a list of 15 in trial 6 (delayed recall).
d, Data available for *n* = 17.
e, Data available for *n* = 18.
f, Data available for *n* = 19.
g, *p*-values reported from Welch’s Test for unequal variance.
Table 3.3 Baseline characteristics of participants stratified according to tertiles of Physical Activity Scale for the Elderly scores (n = 59)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full Cohort (n = 59)</th>
<th>Low (n = 19)</th>
<th>Moderate (n = 20)</th>
<th>High (n = 20)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>74.24 (5.53)</td>
<td>75.84 (6.36)</td>
<td>74.1 (5.15)</td>
<td>72.85 (4.89)</td>
<td>0.24</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>24 (40.7)</td>
<td>9 (45)</td>
<td>9 (45)</td>
<td>6 (30)</td>
<td>0.48</td>
</tr>
<tr>
<td>Education, mean (SD), years</td>
<td>13.75 (2.78)</td>
<td>13.63 (2.59)</td>
<td>14 (3.13)</td>
<td>13.6 (2.72)</td>
<td>0.88</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>26.91 (4.46)</td>
<td>27.25 (5.07)</td>
<td>27.18 (4.68)</td>
<td>26.33 (3.73)</td>
<td>0.78</td>
</tr>
<tr>
<td>No. of Medication, mean (SD)</td>
<td>7.49 (4.68)</td>
<td>7.95 (2.95)</td>
<td>7 (5.18)</td>
<td>7.55 (5.61)</td>
<td>0.82</td>
</tr>
<tr>
<td>No. of Comorbidities, mean (SD)</td>
<td>5.56 (2.64)</td>
<td>5.95 (2.78)</td>
<td>5.1 (3.04)</td>
<td>5.65 (2.08)</td>
<td>0.6</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (45.8)</td>
<td>13 (68.4)</td>
<td>8 (40)</td>
<td>6 (30)</td>
<td>0.045</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (45.8)</td>
<td>11 (57.9)</td>
<td>6 (30)</td>
<td>10 (5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Smoking</td>
<td>28 (47.5)</td>
<td>10 (52.6)</td>
<td>9 (45)</td>
<td>9 (45)</td>
<td>0.86</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>21 (35.6)</td>
<td>8 (42.1)</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>0.73</td>
</tr>
<tr>
<td>MMSE, mean (SD)</td>
<td>27.53 (2.52)</td>
<td>27.58 (2.04)</td>
<td>27.5 (2.46)</td>
<td>27.5 (3.07)</td>
<td>0.99</td>
</tr>
<tr>
<td>MoCA, mean (SD)</td>
<td>23.58 (3.74)</td>
<td>23.11 (3.38)</td>
<td>23.6 (4.41)</td>
<td>24 (3.55)</td>
<td>0.76</td>
</tr>
<tr>
<td>VRF Index, mean (SD)</td>
<td>1.36 (1.17)</td>
<td>1.84 (1.26)</td>
<td>1 (0.97)</td>
<td>1.25 (1.16)</td>
<td>0.07</td>
</tr>
<tr>
<td>BP Systolic, mean (SD), mmHg</td>
<td>128.51 (4.46)</td>
<td>131.68 (19.24)</td>
<td>126.65 (7.61)</td>
<td>127.35 (10.25)</td>
<td>0.58*</td>
</tr>
<tr>
<td>BP Diastolic, mean (SD), mmHg</td>
<td>74.68 (11.37)</td>
<td>77.21 (14.38)</td>
<td>72.45 (8.12)</td>
<td>74.5 (11)</td>
<td>0.43</td>
</tr>
<tr>
<td>PASE, mean (SD)</td>
<td>94.18 (41.57)</td>
<td>48.98 (12.94)</td>
<td>91.44 (15.57)</td>
<td>139.88 (25)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WMH, mean (SD), mL</td>
<td>36.44 (26.2)</td>
<td>46.38 (32.17)</td>
<td>30.63 (21.70)</td>
<td>32.81 (22.28)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cognition, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A, seconds</td>
<td>44.81 (18.38)</td>
<td>43.55 (16.83)</td>
<td>47.81 (22.39)</td>
<td>43.01 (15.71)</td>
<td>0.67</td>
</tr>
<tr>
<td>TMT B, seconds</td>
<td>142.94 (176.06)</td>
<td>104.91 (51.87)</td>
<td>166.41 (207.83)</td>
<td>155.59 (216.07)</td>
<td>0.52</td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>10.58 (2.47)</td>
<td>10.21 (1.99)</td>
<td>10.2 (2.44)</td>
<td>11.3 (2.85)</td>
<td>0.28</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>6.22 (2.36)</td>
<td>5.68 (1.16)</td>
<td>6.65 (3.01)</td>
<td>6.3 (2.47)</td>
<td>0.32</td>
</tr>
<tr>
<td>RAVLTc</td>
<td>5.67 (3.52)</td>
<td>5.26 (3.28)</td>
<td>5.85 (4.16)</td>
<td>5.89 (3.16)†</td>
<td>0.83</td>
</tr>
<tr>
<td>LNS</td>
<td>7.92 (3.14)</td>
<td>7.79 (1.9)</td>
<td>7.75 (3.84)</td>
<td>8.2 (3.43)</td>
<td>0.89†</td>
</tr>
<tr>
<td>Gait, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait Velocity, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-task</td>
<td>109.65 (20.28)</td>
<td>102.64 (19.99)</td>
<td>109.17 (21.41)</td>
<td>116.76 (17.78)</td>
<td>0.09</td>
</tr>
<tr>
<td>Counting</td>
<td>103.86 (24.64)</td>
<td>94.09 (25.87)</td>
<td>104.97 (23.97)</td>
<td>112.05 (21.87)</td>
<td>0.07</td>
</tr>
<tr>
<td>Serial Sevens</td>
<td>92.56 (27.1)</td>
<td>82.88 (26.32)</td>
<td>95.77 (28.25)</td>
<td>98.87 (25.25)‡</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>94.3 (26.62)</td>
<td>85.16 (24.29)</td>
<td>95.16 (28.62)</td>
<td>102.12 (25.22)</td>
<td>0.14</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Stride Time Variability, CoV, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-task</td>
<td>2.23 (0.83)</td>
<td>2.48 (0.9)\text{e}</td>
<td>2.07 (0.75)</td>
<td>2.16 (0.83)\text{e}</td>
<td>0.29</td>
</tr>
<tr>
<td>Counting</td>
<td>2.97 (1.78)</td>
<td>3.7 (2.04)</td>
<td>2.63 (1.55)</td>
<td>2.63 (1.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Serial Sevens</td>
<td>4.65 (4.45)</td>
<td>4.64 (4.23)</td>
<td>4.94 (5.09)</td>
<td>4.36 (4.14)\text{e}</td>
<td>0.92</td>
</tr>
<tr>
<td>Naming Animals</td>
<td>3.4 (1.76)</td>
<td>4.12 (1.71)\text{e}</td>
<td>2.9 (1.31)\text{f}</td>
<td>3.27 (2.03)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Note: Statistically significant associations are presented in bold-type font.


a, Low PASE scores denotes low levels of self-reported physical activity.

b, PASE score excluding items 1 and 10.

c, Final score is number of words remember out of a list of 15 in trial 6 (delayed recall)

d, Data available for $n = 16$.

e, Data available for $n = 17$.

f, Data available for $n = 18$.

\text{g}, Data available for $n = 19$.

h, Data available for $n = 20$.

i, $p$-values reported from Welch’s Test for unequal variance.
3.2.2 Association between White Matter Hyperintensities and Gait

Multiple linear regression analyses were used to test if WMH volume predicted gait velocity under single and dual task conditions, after controlling for covariates of age, sex, MoCA and vascular risk factor (see Table 3.4). In unadjusted models, WMH was significantly associated with single and dual-task gait velocity. After adjusting for age, sex and MoCA, only single-task gait velocity remained significant (standardized $\beta = -0.32$, 95% CI = -17.8, -1.76, $p = 0.018$). In the final model including vascular risk factors, the effect of WMH on single-task gait velocity was no longer significant (standardized $\beta = -0.23$, 95%CI -14.73, 0.8, $p = 0.08$).

There were no significant associations between measures of WMH and stride time variability under single and dual-task conditions (see Table 3.5).
Table 3.4: Linear regression models for the association between white matter hyperintensities and gait velocity under single and dual-task conditions

<table>
<thead>
<tr>
<th></th>
<th>Single-task</th>
<th>Counting</th>
<th>Serial 7</th>
<th>Naming animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
<td>β</td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.42  <strong>0.001</strong></td>
<td>-19.79, -5.23</td>
<td>0.1 <strong>0.01</strong></td>
<td>-20.92, -2.49</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.32 <strong>0.02</strong></td>
<td>-17.8, -1.76</td>
<td>-0.17  0.2</td>
<td>-16.04, 3.35</td>
</tr>
<tr>
<td>Model 3</td>
<td>-0.23 <strong>0.08</strong></td>
<td>-14.73, 0.8</td>
<td>-0.09  0.48</td>
<td>-12.94, 6.18</td>
</tr>
</tbody>
</table>

Model 1: unadjusted.
Model 2: age, sex, and MoCA.
Model 3: model 2 plus adjustment for vascular risk factors.
Values are standardized β (95% CI).
Note: Statistically significant associations are presented in bold-type font. WMH are calculated as a percentage of intracranial volume and log-transformed.
Table 3.5: Linear regression models for the association between white matter hyperintensities and stride time variability under single and dual-task conditions

<table>
<thead>
<tr>
<th></th>
<th>Single-task</th>
<th>Counting</th>
<th>Serial 7</th>
<th>Naming animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
<td>β</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.22</td>
<td>0.1</td>
<td>-0.03, 0.27</td>
<td>0.22</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.21</td>
<td>0.2</td>
<td>-0.62, 0.29</td>
<td>0.21</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.18</td>
<td>0.3</td>
<td>-0.09, 0.28</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Model 1: unadjusted.
Model 2: age, sex, and MoCA.
Model 3: model 2 plus adjustment for vascular risk factors.

Values are standardized β (95% CI).

Note: Statistically significant associations are presented in bold-type font. WMH are calculated as a percentage of intracranial volume and log-transformed.
3.2.3 Moderation of Physical Activity on White Matter Hyperintensities and Gait

For our moderation analysis, the overall model was significant ($F (6, 52) = 6.12, p = 0.001$) and accounted for 36.36% of the variance in gait velocity, see Table 3.6. There was a significant association for MoCA scores ($b = 1.56, p = 0.03$), entered into the model as a covariate, and gait velocity but not for age ($b = -0.44, p = 0.4$) and sex ($b = -4.67, p = 0.34$). Results also indicated that there was significant main effect of WMH volume ($b = -9.12, p = 0.01$), but not PASE ($b = 0.09, p = 0.12$). Further, the interaction term, which accounted for 1% of the variance in gait velocity ($F (1, 52) = 6.12, p = 0.39$) was not significant.

Figure 3.1 illustrates the model-based estimations of the simple slopes regression line showing the relation between WMH volume and gait velocity at three levels of the moderator (PASE scores): mean and ±1 SD from the mean of the PASE. Results indicated that WMH burden was significantly associated with gait speed in participants with low (-1 SD; $t = -2.54, p = 0.01, b = -11.63$) and moderate (mean; $t = -2.92, p = 0.01, b = -9.12$) levels of physical activity, but not for those with high (+1 SD; $t = -1.7, p = 0.1, b = -6.61$) levels of physical activity, see Table 3.7. Further inspection using the Johnson-Neyman technique showed that increases in WMH volume negatively predicted gait velocity when PASE scores were ≤ 127, which included 81.36% of our sample. However, when PASE scores were > 127, WMH volume no longer predicted gait velocity.
Table 3.6 Linear regression models with main and moderating effect for white matter hyperintensities and physical activity with single-task gait velocity

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Effect [95% CI]</th>
<th>SE$_b$</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Age</td>
<td>-0.44 [-1.47, 0.59]</td>
<td>0.51</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex</td>
<td>-4.67 [-14.34, 4.99]</td>
<td>4.82</td>
<td>0.34</td>
</tr>
<tr>
<td>MoCA</td>
<td>1.56 [0.18, 2.94]</td>
<td>0.69</td>
<td>0.03</td>
</tr>
<tr>
<td>WMH</td>
<td>-9.12 [-15.38, -2.86]</td>
<td>3.12</td>
<td>0.01</td>
</tr>
<tr>
<td>PASE</td>
<td>0.09 [-0.02, 0.2]</td>
<td>0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>WMH x PASE</td>
<td>0.06 [-0.08, 0.2]</td>
<td>0.07</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Abbreviations: b, coefficient. MoCA, Montreal Cognitive Assessment. PASE, Physical Activity for the Elderly. SE, standard error. WMH, white matter hyperintensities.*

*Note: Statistically significant associations are presented in bold-type font. WMH are calculated as a percentage of intracranial volume.*
Figure 3.1 Conditional association between white matter hyperintensities and usual gait velocity at different levels of the Physical Activity Scale for the Elderly.

Table 3.7 Conditional effects of physical activity on the association between white matter hyperintensities and single task gait velocity

<table>
<thead>
<tr>
<th>Physical Activity</th>
<th>( b ) [95% CI]</th>
<th>( SE_b )</th>
<th>( P )-value</th>
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</thead>
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<tr>
<td>One SD below mean</td>
<td>-11.63 [-20.81, -2.45]</td>
<td>4.57</td>
<td>0.01</td>
</tr>
<tr>
<td>At the mean</td>
<td>-9.12 [-15.38, -2.86]</td>
<td>3.12</td>
<td>0.01</td>
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<tr>
<td>One SD above mean</td>
<td>-6.61 [-14.41, 1.19]</td>
<td>3.39</td>
<td>0.1</td>
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</table>

Note: Statistically significant associations are presented in bold-type font.

Abbreviations: \( b \), coefficient. CI, confidence interval.
3.3 Discussion

In our study, we found that higher WMH burden was independently associated with slower single-task gait velocity, but not with measures of stride time variability or dual-task gait velocities, in a well-characterized geriatric clinic sample. In addition, while our moderation analysis did not show overall significance, the results of the simple slopes analyses provide evidence to suggest that low and moderate levels of physical activity modified the association between WMH burden and gait velocity. More specifically, this association was only significant when participants had PASE scores that were \( \leq 127 \). These results indicate that physical activity may play a role in attenuating the effect of WMH burden on gait performance in older individuals.

White matter pathways are a central component of frontal subcortical networks proposed to underlie gait control and cognitive functions. Previous studies have demonstrated that WMH burden are associated with slower gait velocity, a finding that was confirmed in our sample [27, 28]. Moreover, the significant effect of WMH on single-task gait velocity was attenuated when vascular risk factors were included as covariates. Noteworthy, however, WMH did not show significant associations with gait velocity under dual-task conditions findings that were also in agreement with the extant literature [29-31].

In efforts to explain our non-significant findings under dual-task conditions, we postulate that WMH impact gait velocity under single and dual task conditions via different pathways. The underlying mechanisms of gait performance under dual-task conditions are not completely understood, although this association is increasingly supported by convergent evidence for the role of executive functions [32]. In a study by Zheng and colleagues [33], it was shown that the association between WMH and a functional test (i.e. choice stepping reaction time) under dual-task conditions was mediated through neuropsychological functioning. Another study extending on these findings proposed a theoretical pathway through which WMH may negatively impact gait performance. The two main proposed pathways were: (1) the direct locomotor pathway, in which WMH disrupts mobility-related pathways; and (2) the indirect locomotor pathway, in which WMH disrupts circuits responsible for cognitive functions leading to impaired mobility.
Furthermore, this study found that when examining the direct pathway, WMH explained a significant 72% of the variance in gait velocity and the indirect pathway through executive functions, but not global cognition, explained a significant 19% of the variance in gait velocity [34].

Considering the aforementioned, it is plausible that taxing an individual’s attention resources while walking deviates from the direct to the indirect pathway given the shared and added cognitive component. In addition, we speculate that the specific regional location of WMH, in particular, damage to frontal areas of the brain may impact dual-task performance. Previous functional neuroimaging studies have confirmed this association by demonstrating increased activation under dual-task conditions within prefrontal brain regions [35]. Further, different pathologies can result in different changes to the brain and activity making it difficult to draw generalizable conclusions. Future studies should aim to elucidate pathways of WMH impact on gait among healthy individuals as well as on the spectrum of neurodegeneration.

In contrast to the effect on gait velocity, we did not report significant results for the associations between WMH and stride time variability. Although gait variability is posited to be more sensitive to fall risk when compared to other gait parameters, there is a paucity of studies investigating this association. To the best of our knowledge, only one prior study has assessed the relationship between WMH and stride time variability [3]. This prospective cohort study in non-demented elderly individuals reported a significant positive association between WMH and stride time variability \( (n = 431; \beta = 0.13, p < 0.05) \) [3]. An alternative explanation can be related to lack of power due to our limited sample size of 59 older adults. Notwithstanding, other studies examining additional quantitative measures of gait variability have produced equivocal results (see Chapter 2) warranting further exploration of the literature [3, 36-38].

Several studies have examined neuroimaging markers necessary for the maintenance of gait stability. A recent study by Annweiler and colleagues [39] reported associations between higher stride time variability and greater temporal volume, a proxy for temporal lobe atrophy including the hippocampus. This study aligns with other studies suggesting
that stride-to-stride fluctuations may be dependent on hippocampal involvement. A community-based sample of individuals aged 70 years and older, reported an inverse association between hippocampal metabolism and stride length variability [40]. Another study in a well-characterized community-dwelling sample reported a significant association between lower grey matter integrity in the hippocampus and step length variability [41]. Considered together, our results along with these studies support that gait variability, a proxy for the efficiency of higher-level motor control may also be supported by cortical grey matter.

While understanding the effect of WMH contributing to decreased gait velocity is important in preventing and treating motor impairments, lifestyle strategies may also offer protective benefits in later life. Although our study did not demonstrate an overall moderation effect of physical activity on the association between WMH and gait velocity, we demonstrated that there was a threshold effect. That is, in our study the magnitude of the PASE score sufficient to modify the association was ≤ 127. Hence, our findings underscore the importance of physical activity having protective effects against WMH burden and gait, which is supported by the cognitive reserve hypothesis [42]. In addition, we speculate that the emergence of a threshold may be in regards to the physical activity scale used. Even though the PASE is a valid and reliable self-reported tool to assess physical activity, its precision may be limited compared to objective measures [20, 21].

Cognitive reserve is a concept that has been proposed to account for individual differences in trajectories of cognitive decline [42]. Defined as the ability of the brain to optimize performance through recruitment of brain networks, cognitive reserve reflects the capacity of the brain to offset symptoms of dementia [42]. We speculate that physical activity is a neuroprotective strategy as it reduces the loss of brain mass and strengthens compensatory functions. In fact, there are numerous studies showing that physical exercise can reverse atrophy in certain areas of the brain that are vulnerable to the aging process and can also increase brain activation although there is a paucity of study examining motor reserve [43, 44].
Furthermore, our findings of low and moderate level of physical activity moderating the association between WMH and gait velocity provides additional support for physical activity as a neuroprotective strategy. Further, it is possible that the PASE may not be representative of the types of activities that have previously been demonstrated to elicit changes at a neural and behavioural level. For example, in this study the physical activity scale asked individuals to report the duration and frequency of engaging in leisure time and household activity. The items pertaining to household activity include; light or heavy housework, home repairs, lawn work, outdoor gardening and caring for another person. These items are also assigned a higher weight in comparison to leisure time activities, yielding a higher score. Further, the literature supports that physical activity in the form of aerobic exercise presents many benefits to older individuals [8, 9]. Thus, future studies should aim to use more objective measures of physical activity.

An alternative approach to using more objective measurements of physical activity may be to test the efficacy to physical exercise in slowing the progression of WMH and the subsequent impact on gait. In such instances, WMH may be used as a surrogate marker in exercise intervention trials to assess intervention efficacy. To date, one randomized controlled trial has adopted this approach. In this study, researchers examined whether resistance-training twice weekly over 12 months in community-dwelling older women aged 65–75 reduced WMH progression, and whether WMH progression was associated with gait velocity [45]. Findings from this study suggest that resistance training slowed WMH progression and it was also associated with maintenance of gait velocity [45]. As a result, modifiable lifestyle strategies may represent an accessible alternative to pharmacological approaches to mitigate WMH burden in this population, however more randomized controlled trials are warranted to strengthen this evidence and to determine the most effective strategies.

3.3.1 Limitations

The cross-sectional nature of our study precludes us to infer causality. Studies that are longitudinal, either observational or interventional, may offer insights into a causal relationship. Our measure of physical activity was self-reported, which may present
issues related to participant bias. Additionally, even though we employed a quantitative approach to delineating WMH, this method was only capable of yielding a value pertaining to total WMH burden and could not infer whether white matter damage extended to areas of the normal-appearing white matter, or the exact location of affected pathways. Lastly, our sample size was relatively small, and may have contributed to the lack of significant findings especially on gait parameters of stride time variability.

3.4 Conclusion

In conclusion, our study demonstrated that WMH are associated with slowing gait velocity, and that this association is modified by physical activity, even though this association is threshold dependent. This suggests that the effects of WMH burden may be attenuated by modifiable lifestyle intervention strategies such as physical exercise. Further studies aimed at determining whether physical exercise has an impact on WMH burden and gait are needed to confirm this association.
References


30. Doi, T., et al., *Effects of white matter lesions on trunk stability during dual-task walking among older adults with mild cognitive impairment*. Age (Dordr), 2015. 37(6): p. 120.


## Appendices

**Appendix A: Search Strategy**

<table>
<thead>
<tr>
<th>CONCEPT</th>
<th>EMBASE</th>
<th>MEDLINE (OVID)</th>
<th>PUBMED</th>
<th>KEYWORDS</th>
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<td><strong>WHITE MATTER CHANGES</strong></td>
<td>Leukoaraiosis/ OR White matter lesion/ OR Leukoencephalopathy/ OR Diffusion Tensor Imaging/</td>
<td>Leukoaraiosis/ OR Leukoencephalopathies/ OR Diffusion Tensor Imaging/</td>
<td>“Leukoaraiosis” [MeSH] OR “Leukoencephalopathies” [MeSH] OR “Diffusion Tensor Imaging”</td>
<td>Leukoaraios* OR Leucoaraios* OR White matter lesion* OR White matter hyperintensit* OR white matter change* OR White matter disease* OR Leukoencephalopath* OR White matter integrity OR White matter microstructure or Diffusion Tensor Imaging</td>
</tr>
<tr>
<td><strong>MOBILITY</strong></td>
<td>Physical mobility/ OR Gait/ OR Balance impairment/ OR exp Falling/ OR Fracture/</td>
<td>Mobility Limitation/ OR Gait/ OR Postural balance/ OR Accidental falls/ OR Fractures, Bone/</td>
<td>“Mobility Limitation” [MeSH] OR “Gait” [MeSH] OR “Postural Balance” [MeSH] OR “Accidental Falls” [MeSH] OR “Fractures, Bone” [MeSH]</td>
<td>Mobility OR Mobility Limitation* OR Gait OR Balance OR Postural Instability OR Postural Sway OR Fracture* OR Fall*</td>
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<td>Aged/ OR Geriatrics/</td>
<td>Aged/ OR “Aged, 80 and over”/</td>
<td>“Aged” [MeSH] OR “Aged, 80 and over” [MeSH]</td>
<td>Older adult* OR Elderly OR Geriatric*</td>
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<td><strong>RECORDS FOUND</strong></td>
<td>572</td>
<td>154</td>
<td>588</td>
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Appendix B: Research Ethic Board Study Approval

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Manuel Montero Odasso
Department & Institution: Schulich School of Medicine and Dentistry/Geriatric Medicine, St. Joseph's Health Care London

Review Type: Full Board
HSREB File Number: 7162
Study Title: Gait Variability as Predictor of Cognitive Decline and Risk of Falls in MCI: A Cohort Study (REB #17200)
Sponsor: Canadian Institutes of Health Research

HSREB Amendment Approval Date: May 15, 2017
HSREB Expiry Date: June 15, 2017

Documents Approved and/or Received for Information:

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<td>2017/05/03</td>
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<td>LOIC (Annual Follow-Up) - CLEAN</td>
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The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB
Appendix C: Conceptual Overview of the Lesion Segmentation Algorithm

The flow diagram of the lesion segmentation algorithm is shown. Preprocessing with the standard software of SPM8 and VBM8 is illustrated in the gray box. At first, the individual native T1 image is used to generate a partial volume estimate (PVE) label. To
this end, some normalization is necessary. To surpass smoothing of the individual images by warping, the algorithm operates in native space exclusively. Thus, preprocessing includes the coregistration of FLAIR images to T1 images, PVE label estimation but output in native space, as well as inverse warping of the white matter (WM) tissue probability map (TPMWM) to native space by the use of the inverse deformation matrix derived from PVE label estimation. Next, FLAIR intensity distribution is calculated for each of the three tissue classes to detect FLAIR-hyperintense outliers which are further weighed according to their spatial probability of being WM resulting in belief maps (BWM react-text: BCSF react-text: 2540, BCSF react-text: 2543, BGM react-text: 2546). Now, the three lesion belief maps are summed up (B react-text: 2548). The binary version (threshold $\kappa$ react-text: 2550 = react-text: 2551 = react-text: 2552) of the GM lesion belief map is used as initial lesion map (Linit react-text: 2557). Finally, the lesion growth model expands the Linit react-text: 2561, a conservative assumption for lesions, toward the lesion belief map (B react-text: 2563), a liberal assumption for lesions (see text for details).
Appendix D: Outcome Distributions

White matter hyperintensities:

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<th>Untransformed Distribution</th>
<th>Transformed Distribution</th>
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<td>White matter hyperintensities volume:</td>
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![Histogram](image1)

![Histogram](image2)
Physical activity:

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![Histogram](image)

- Mean: 93.12
- SD: 30.82
- Shapiro-Wilk: 0.000
Gait characteristics under single-task conditions:

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<td><strong>Gait velocity (units):</strong></td>
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<td><img src="image4.png" alt="Histogram" /></td>
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</tbody>
</table>

- **Untransformed Distribution**
  - Normal
  - Mean = 0.73
  - S.D. = 0.2
  - N = 100

- **Transformed Distribution**
  - Normal
  - Mean = 0.79
  - S.D. = 0.2
  - N = 100
Gait characteristics under dual-task counting gait condition:

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<tr>
<td>Gait velocity (units):</td>
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![Histogram](image1.png)

- **Histogram**
  - Normal
  - Mean = 1.23
  - SD = 0.3

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![Histogram](image2.png)

- **Histogram**
  - Normal
  - Mean = 0.85
  - SD = 0.2

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Dual-task cost stride time variability (CoV):

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Gait characteristics under dual-task serial seven gait condition:

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Dual-task cost stride time variability (CoV):

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Gait characteristics under dual-task naming animals gait condition:

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Dual-task cost stride time variability (CoV):

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- Kinesiology Graduate Travel Award (2017)
- Western Graduate Research Scholarship (2015-2017)
- Queen Elizabeth II Aiming for the Top Scholarship (2011-2012)

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